On the classification, natural history and treatment of the myopathies, by John N. Walton and F.J. Nattrass (From the Department of Medicine, King’s College, University of Durham and the Royal Victoria Infirmary, Newcastle upon Tyne). Brain 1954: 77; 169–231.

Writing in an era when the classification of neurological disease required astute clinical description supplemented, when available, by pathological examination, and long before different disorders could be defined on the basis of genetic mutations, John Walton and Professor Nattrass use 105 cases of muscle disease to propose an entirely new classification for the muscular dystrophies. First, they set out their stall with a searching historical review, sifting wheat from the chaff in the early descriptions and categorisations. Starting with Aran in 1850 and Meyron in 1852, the difference gradually emerged between familial disorders having ‘granular degeneration of the voluntary muscles’ and sporadic cases of muscular atrophy resulting from ‘changes in the grey matter of the spinal cord’. Perhaps, this distinction was not so clear to Dr Duchenne (de Boulogne) in his original account of pseudo-hypertrophic muscular paralysis of children in 1868, or to Sir William Gowers in 1879; and not until Erb brought clarity to the myopathic nature of Duchenne’s and Gower’s cases in 1884 was a juvenile scapulohumeral-type separated, paving the way for Landouzy and Dejerine to identify the facioscapulohumeral variant, also in 1884. Walton and Nattrass do not ignore several other pioneers contributing to this early history; and they are careful to register the key phenotypes, especially including those characterised by progressive external ophthalmoplegia, or by myotonia, and the metabolic and endocrine myopathies, as each was newly described. In a prescient concluding statement to this historical synthesis, Walton and Nattrass anticipate the critical issue: ‘the great majority of cases are genetic in origin, though the exact pathogenesis of the muscle wasting remains a mystery… the mode of inheritance of the various forms is not fully understood… (due to) the lack of any general agreement concerning classification of the myopathies’.

First, they need to sort the 18 conditions already described and competing for nosological independence. Several are so rare as not to be worth considering further in the attempt to define broad groups ‘into which the majority of cases can be classified’. One way forward is to separate myopathic and myotonic disorders, even though there is overlap—ocular involvement and similar muscle histology occurring in each. Now begins the work of reviewing in more detail the previous descriptions, and so whittling down this collection into discrete and manageable entities. Clearly exercised by the large series of Kiloh and Nevin from 1951—as it turns out, an example of mitochondrial cytopathy—and toying with the idea of accommodating these cases in the general category of ‘myopathy’, eventually Walton and Nattrass put ocular myopathy aside. The distal myopathy of Gowers also survives their critical appraisal and stands as a discrete entity, as do the cases of congenital myopathy. Generous to some previous classifiers, Walton and Nattrass are frankly dismissive of others: ‘the classification, or lack of classification, attempted by Milhorat and Wolff and by the authors of many of the papers they reviewed is to be deplored as being likely to obscure both the patterns of inheritance and the distinctive clinical pictures of the various types of myopathy’.

Walton and Nattrass do not shirk from criticising the monumental efforts of Julia Bell who, based at the Galton Laboratory in London, wrote The Treasury of Human Inheritance between 1909 and 1958, including in Vol. IV, parts 4 and 5, 1228 cases of myopathy taken from the literature and 113 from case-records of the National Hospital, Queen Square. Her classification proposes pseudohypertrophic, atrophic and facial categories. But is the sample representative? Similarly, Tyler and Wintrobe’s classification of cases as ‘childhood or facioscapulohumeral’ also seems to suffer from selective case material. Leivson, reporting Danish material, also takes himself down blind alleys of classification. Light first appears with the synthesis of Irish cases by Stevenson in 1953 who has realized that the disorder described by Duchenne only affects young boys, and hence is a sex-linked recessive condition, whereas all other forms are autosomal limb-girdle muscular dystrophies inherited as dominant or recessive traits.

But, despite some merits, no one of these prior systems is entirely satisfactory, and Walton and Nattrass start to fashion...
their own preferred classification incorporating: clinical features at onset and during the evolution; mode of inheritance, based—unlike Julia Bell—on a population-based sample; and careful evaluation of at-risk individuals in each pedigree. Since pseudohypertrophy is non-specific, ‘Duchenne-type muscular dystrophy’ is a preferred designation for the group of cases that, according to Walton and Nattrass, may also include late onset and more benign examples, and (allowing for transmission by a surviving affected male) the very occasional female who has inherited the recessive trait from each parent. The most unsatisfactory aspect of the earlier Danish and Irish classifications, and that of Julia Bell, is ambiguity with respect to facial involvement. Walton and Nattrass propose that all such cases should be separated for good clinical and genetic reasons and referred to as ‘facioscapulohumeral muscular dystrophy’. Apart from the congenital, ocular and distal cases this leaves the residue of autosomal conditions as ‘limb-girdle muscular dystrophies’. Walton and Nattrass distance themselves from any similarity between their proposals and Julia Bell’s classification by pointing out her insistence that all three phenotypes might arise from defects of the ‘same main gene’. Rather, they anticipate genetic heterogeneity. On the classification of myotonic disorders, Walton and Nattrass have less to say. Too few cases—other than dystrophia myotonica—have been encountered in north-east England. Their hunch is that these constitute a single disorder with phenocopies (as with Bell on the myopathic muscular dystrophies). They do not like the previously suggested designation as ‘Thomsen’s disease’, preferring the concept of a ‘myotonic syndrome’.

Against this background, their 105 cases represent complete ascertainment, using sound epidemiological principles, of prevalent cases in Northumberland and Durham: 48 are Duchenne-type (3 out of 48 being female), 18 limb-girdle, 15 facioscapulohumeral, 2 distal and 1 ocular muscular dystrophies: 21 have the myotonic syndrome of whom 15 are examples of dystrophia myotonica and 6 myotonia congenita; a few are consigned to the ‘borderland of myopathy’, and others to a category of childhood onset with recovery.

The 48 patients with Duchenne-type muscular dystrophy usually present at <4 years although, as described, onset has occurred after the age of 8 years in 11—the oldest being aged 26: the pelvic muscles are first affected with characteristic gait disturbance and calf pseudohypertrophy; only later is there

Fig. 2 The characteristic ‘pout’ of the lips in facioscapulohumeral muscular dystrophy.

Fig. 3 Inability to close the eyes in facioscapulohumeral muscular dystrophy.

Fig. 4 Advanced muscular wasting with remarkably good functional capacity in a case of limb-girdle dystrophy.

Fig. 5 Generalized muscular hypertrophy in a girl aged 13 with ‘myotonia congenita’.

Fig. 6 At the age of 25 years, there is bilateral ptosis, symmetrical impairment of ocular movement (the strabismus is concomitant in type) and weakness of facial muscles and of sternomastoids; the proximal limb muscles remain hypertrophied.
selective involvement of the upper limb and shoulder-girdle musculature; the reflexes are depressed but with relative preservation of the ankle jerks; the course is progressive but disease duration of >10 years observed in 23, 13 of whom are still ambulant; there is an impression of mental backwardness in 16; death results from inanition or respiratory involvement (Fig. 1). Onset in the facioscapulohumeral cases is at any time during the first 30 years, usually with ‘pouting lips’, a myopathic facies and drooping shoulders (Figs 2 and 3); after 20–30 years, but not invariably, the disorder progresses to involve the trunk and pelvic girdle but is rarely disabling; although the pattern of muscle involvement eventually mimics that seen in Duchenne-type muscular dystrophy, there is no pseudohypertrophy, and the prognosis is very different. The limb-girdle form begins in the second or third decade, either in the arms or pelvic girdle, eventually spreading to the other, and vice versa, within 20 years. In time, significant disability becomes apparent (Fig. 4). Of the rarities, distal myopathy begins in the 3rd decade and progresses rapidly; and little can be said about ocular myopathy-based on a single case. On the myotonic syndrome, Walton and Nattrass list as typical features muscle stiffness and difficulty walking due to myotonia and peripheral myopathy at onset, usually in young adults, and followed by weakness of the neck and facial muscles with frontal baldness and testicular atrophy, cataract and mental defect—the prominence and evolution of the myotonia differing between myotonic dystrophy and myotonia congenita (Figs 5 and 6); abnormalities of the electrocardiogram are more frequent in the myotonic syndrome than in Duchenne-type muscular dystrophy but, overall, the prognosis is not so bad.

It may seem ambitious of Walton and Nattrass to consider treatments in individuals affected by these genetically determined disorders. Their account opens with a catalogue of failed remedies that includes insulin, resection of the nerve to the carotid sinus and—inevitably—corticotrophin and cortisone. They have treated 98 of their patients with \( \alpha \)-tocopherol (in three different formulations of vitamin E), wheat-germ oil, nicotanamide or placebo, under conditions that precisely conform to protocols for randomized and single-blind trials, using groups of c20 cases (98 in total) assigned to each treatment and with objective outcome measurements made at baseline and 6 months. But no treatment effects are observed. Nor does best management in the form of physiotherapy, massage or electrical therapy appear to help. A positive attitude and sensible levels of physical activity are to be encouraged.

With an introduction extending to 21 pages, and a highly informative 126 line summary (blessedly free from abbreviations), this is a paper in the best tradition of definitive Brain clinical series, offering a new synthesis for an old problem. John Walton had already completed work for an MD thesis on subarachnoid haemorrhage, and was committed to a career in neurology through the influence of Henry Miller, when, as a research assistant in the department of medicine, he began this first excursion into the neurology of muscle disease with Professor Nattrass. Their involvement was at the instigation of Dr (subsequently Dame) Albertine Winner from the Ministry of Health who needed a team to study childhood muscle disease at the request of several anxious parents. Fifty-three years later, John Walton recalls being on the road in Northumberland in his Ford Prefect (BPY 871!) assessing these cases, and modestly points out that subsequent work refined the details of their classification: the Becker type of muscular dystrophy was not well appreciated; their explanation for females with Duchenne muscular dystrophy would now be different; the myotonias are not phenocopies of one disease; and, although mentioned, the prior description by Edward Meyron of Duchenne-type muscular dystrophy may have deserved more emphasis. But it was the industry, organization and clinical ‘savvy’ of Dr Walton, and the guiding hand of Professor Nattrass, that suggested a classification for the muscular dystrophies, of which Jonathan Jarry and colleagues now provide a new example that not only has survived but itself enabled the neurogenetics of muscle disease to proceed rapidly because an inspired phenotypic classification, accurately predicting true heterogeneity, was already in place.

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