
John Morgan-Hughes (1932–2012) was an enigmatic figure who eschewed academic title and preferment but nonetheless made many important discoveries as a pioneer in biochemical aspects of neurological disease, and through his work on mitochondrial cytopathies. Although he remained a part-time consultant neurologist with a private practice and district general hospital sessions in Bedford, UK, he was arguably the most brilliant of the clinician scientists active in research that managed the transition, under the leadership of Roger Gilliatt (1922–91), from excellence in clinical neurology to engagement with emerging disciplines that started to illuminate the scientific basis of neurology. In several respects, Morgan-Hughes represented the type of academic for whom (Sir Francis) Walshe (1885–1973) had argued in a polemic memorandum that, whilst challenging the need for academic investment in the affairs of Queen Square, at the same time extolled the virtues of investing in neurochemistry and abandoning physiology if that Institute was to remain a force in national neurology. Morgan-Hughes obtained a first class honours degree in natural sciences from Trinity College, Cambridge (1954); worked as senior house officer at Queen Square (1961); spent a formative year as an MRC funded international post-doctoral fellow with Dr King Engel at the National Institutes of Health (Bethesda; 1966); and was then appointed as a consultant neurologist at Queen Square (1968–97). In 1987, with Ian Holt and Anita Harding (1952–95), Morgan-Hughes showed that mitochondrial DNA deletions detectable only in DNA extracted from skeletal muscle can cause human neurological disease (Deletions of muscle mitochondrial DNA in patients with mitochondrial myopathies. Nature 1988; 331: 717–19); and, with the demonstration of heteroplasmy, established a new concept in medicine. Between 1970 and 1999, Morgan-Hughes published 18 original articles in Brain: 11 on mitochondrial disease; four on other disorders of muscle; and three on peripheral nerve or related topics.

By the early 1970s, cases had been described with muscle weakness present from birth or with later onset in whom were present various morphological abnormalities of mitochondria; and from which began to emerge a syndrome characterized by progressive ptosis with external ophthalmoplegia. In his first contribution to the subject published in Brain, John Morgan-Hughes and W.G.P. (William George Parker) Mair (1913–2002) add four examples of this disorder with histochemical and ultrastructural changes confined to muscle mitochondria. A 61-year-old engine driver with a family history of deafness develops progressive fatigable weakness of the legs, then the arms, and subsequently his eyelids, with blurred vision—features that are all confirmed on examination. Over 20 years, a 38-year-old man develops ptoses with progressive visual failure and more recent fatigable weakness of the limbs with signs of oculoskeletal myopathy and retinitis pigmentosa. A man aged 55 has a history over several decades of ptoses, external ophthalmoplegia and bulbar weakness with subsequent fatigable involvement of the limbs. A woman of 53 describes a short history of weakness affecting the eyelids, bulbar musculature and limbs with evidence on examination for oculopharyngeal myopathy.

In his career, John Morgan-Hughes looked at more than 12 000 muscle biopsies of which samples taken from the triceps of these four cases were amongst the earliest.

‘The most striking abnormality was the presence of scattered muscle fibres containing excessive accumulations of sarcoplasmic material…dark red in colour with the modified Gomori trichrome stain…confined to the subsarcolemmal regions…or forming a coarse reticular or punctate pattern which extended over the whole cross-sectional area of the fibre’ (Fig. 1).

With histological stains, the abnormal deposits are shown to contain succinic dehydrogenase, diphosphopyridine nucleotide (DPNH) tetrazolium reductase, menadione linked α-glycerophosphate dehydrogenase, and excess lipid. Less marked staining is present for phosphofructokinase, cytochrome oxidase and lactate dehydrogenase. Conversely, acid phosphatase, non-specific esterase and phosphorylase are absent. These fibres, comprising either type I or II in
individual cases, appear in clumps but vary considerably in number between cases. Ultrastructual studies show aggregates of mitochondria, under the plasma membrane and around the nuclei, with local accumulation of glycogen in all muscle fibres (Fig. 2). Many contain laminated inclusions lying within the cristae, some with elongated endings like drumsticks (Fig. 3).

In their discussion Morgan-Hughes and Mair rehearse the history of descriptions for progressive ptosis with external ophthalmoplegia including the paper by Kiloh and Nevin [Progressive dystrophy of the external ocular muscles (ocular myopathy) Brain 1951; 74: 115–43; and see Brain 2008; 131: 311–13]; and extension of the phenotype to include retinal abnormalities, deafness, ataxia, peripheral neuropathy and heart block. But with mitochondrial abnormalities also described in conditions having altogether different clinical features, and some lacking external ophthalmoplegia,

‘it seems clear…that proliferation of muscle mitochondria with the formation of paracrystalline inclusions represents a non-specific reaction to a variety of different metabolic defects…[although] mitochondrial abnormalities…represent the major pathological change in the extracranial and skeletal muscles of some patients who present with progressive ptosis and external ophthalmoplegia’.

By 1982, the concept of mitochondrial disorders affecting muscle and the nervous system has broadened to include various encephalopathies with onset in childhood manifesting as mental retardation, movement disorder and other motor deficits, visual failure, epilepsy and the features of oculoskeletal myopathy sometimes with neuropathy. Associated with these protein manifestations of mitochondrial disease are raised lactate and pyruvate, and deficiencies involving the pyruvate dehydrogenase complex, cytochrome b, cytochrome c oxidase and impaired nicotinamide adenine dinucleotide (NADH) oxidation. Now Morgan-Hughes and colleagues describe two cases with mitochondrial encephalomyopathy in whom defects at different points in the respiratory electron transport chain are demonstrated in samples of muscle even though myopathy is not prominent in either patient. A 46-year-old man presents with a long history of visual failure and poor cognitive development together with episodic motor impairment and confusion. Electrophysiological studies indicate impaired retinal rod and cone function. There is brain atrophy on computerized tomography; and evidence for cardiomyopathy. Later he deteriorates with inability to stand, rigidity, involuntary...
movements, incontinence and further cognitive impairment. Fasting pyruvate and lactate levels are normal (0.8 and 0.063 mmol/l, respectively). In her early 30’s, an Indian woman, now aged 48 years, develops jerking movements of her arms, ataxia, deafness and slight muscle weakness; and, later, she becomes confused with cognitive impairment. Examination shows retinal pigmentation and neurological abnormalities consistent with these symptoms. She also has evidence for impaired retinal rod and cone function. Investigations show an intermittent increase in fasting serum lactate (up to 3.1 mmol/l) rising considerably after exercise (to 9.5 mmol/l), and in her CSF (up to 4.7 mmol/l). Brain imaging shows cerebral atrophy with basal ganglia calcification. Despite some improvement on corticosteroids, she dies suddenly whilst at home.

In both cases, muscle biopsies are obtained and subjected to detailed biochemical analysis. Case 1 has typical, mainly type I, ‘ragged red’ fibres and atrophic angulated type 2B muscle fibres. Much the same appearances are present in Case 2. In both patients, electron microscopy shows an excess of mitochondria, some swollen with glycogen, and many containing ‘parking lot’ paracrystalline inclusions gathered between the inner and outer mitochondrial membranes or between individual cristae (Fig. 4). The markedly depressed mitochondrial respiration, varying with substrate and in the presence of materials feeding into different stages in the respiratory electron transport chain, suggests that the rate-limiting step in Case 1 lies on the substrate side of the coenzyme-Q/cytochrome b complex—a conclusion supported by spectral analysis of the mitochondrial cytochromes. More specifically, this is considered to lie in the NADH-dehydrogenase/ coenzyme-Q segment of the respiratory chain involving one of the non-haem iron sulphur proteins (Fig. 5). Matters are somewhat different in Case 2:

1. the findings indicated that the terminal part of the electron transport chain from cytochrome c through cytochrome aa3 to oxygen was functionally intact and that the step giving rise to the low rates of oxygen uptake with NAD-linked substrates and with succinate involved the CoQ-cytochrome c segment…the patient’s mitochondria contained less than 0.17nmol of reducible cytochrome b/mg mitochondrial protein.

The shift in [spectral] wavelength of reduced cytochrome b from 562nm to 559 nm would suggest that in addition to an absolute deficiency of reducible cytochrome b, there may have been an abnormality in its molecular structure or an alteration in its membrane environment’ (Fig. 5).

The reader does not need persuading that understanding mitochondrial disorders and resolving their classification requires biochemical characterization in each patient and, ultimately, genetic analysis. On this basis, Morgan-Hughes and his colleagues propose a classification listing 19 disorders in the categories of defects of mitochondrial substrate transport or utilization, and those of the respiratory chain or energy conservation and transduction. Each has a likely but not fully predictable phenotype. The two cases now reported add to the evidence for clinical and biochemical heterogeneity; but quite why the progressive course is marked by additional clinical fluctuations, not all related to activity that could reasonably be expected to tip the cell into a state whereby it is unable to meet energy demands, is less clear.

Four years later, working with Richard Petty and Anita Harding, John Morgan-Hughes wishes to summarize his team’s experience of disorders in which the hallmark is the ragged red fibre seen with modified Gomori trichrome stain containing peripheral and
inter-myofibrillar accumulations of abnormal mitochondria. But despite the designation of symptom complexes of the mitochondrial encephalomyopathies into the Kearns-Sayre syndrome, MELAS (Mitochondrial myopathy, Encephalopathy, Lactic Acidosis, and Stroke-like episodes) and MERFF (Myoclonic Epilepsy with Ragged Red Fibres), studies of mitochondrial metabolism sit awkwardly with conditions dubbed by such eponyms and acronyms. The authors draw on the experience of 66 cases studied between 1969 and 1984 (including those described above) selected from 2000 muscle biopsies carried out over that period in which, based on sampling 400–600 fibres from three areas chosen at random, >4% of muscle fibres show peripheral mitochondrial accumulations. The organization of the paper is reminiscent of the many case series that Anita Harding, in particular, perfected at the time: we read of sex ratio (1.3F:M); age-at-onset (birth to 68 years); age-at-assessment (14 to 75 years); and clinical presentation (ptosis, 54%; oculoskeletal phenotype, 20%; seizures or ataxia, 53%, mild in 32%; exercise related weakness of the limbs, 23%; and encephalopathy with multisystem involvement, 5%). With the emerging discipline of neurogenetics that Harding pioneered at the National Hospital, having trained with Cedric Carter (1917–84), a family history is noted in 13 (20%) cases derived from 10 pedigrees; but with no consistent patterns of inheritance. Now the authors move on to an account of prevalent clinical features: pigmentary retinopathy (36%) with severe visual failure in those showing loss of retinal pigment epithelium or the appearances of retinitis pigmentosa; ptosis, often asymmetrical, and external ophthalmoplegia (79%) usually combined with muscle weakness (74%: Fig. 6); fatigable muscle weakness alone, always of the arms and often also affecting the legs but without involvement of the eyes (21%); dementia (20%), rarely severe; ataxia (41%), severe in a minority; involuntary movements, usually chorea (11%: Fig. 7); reduced reflexes (21%) or peripheral sensory loss (17%); pyramidal signs (24%); deafness (26%); and short stature (20% of those with onset in childhood). Creatine kinase is usually not raised (74%); electrophysiological studies show myopathic (62%) or neuropathic (31%) changes but with only a minority having clinical evidence for neuropathy. Resting lactate levels are raised in 15 (30%) of 50 cases studied; but most show an abnormal and prolonged elevation on exercise. Mitochondrial accumulations are present in between 4% and 68% of muscle fibres examined, being more likely in cases with fatigue. The majority of patients with pigmentary retinopathy show abnormal rod and cone function. With the introduction of computerized tomography, 51% are shown to have evidence for cerebral or cerebellar atrophy, some also with focal lesions, vascular in appearance, and basal ganglia calcification. Cardiac conduction defects are present in 17% of all patients. Coming at the problem of classification both from the position of defined biochemical abnormalities and clinical phenotype, most cases (55%) have chronic progressive external ophthalmoplegia with muscle weakness, sometimes with retinopathy, ataxia, deafness, seizures and pyramidal signs; others manifest proximal fatigable limb weakness (18%) with normal eye movements and no retinopathy; and the rest have encephalopathy of varying severity (27%) invariably with ataxia as one component and usually including retinopathy, visual failure and deafness—this category predictably carrying the least favorable prognosis. But these clinical groupings give no insight into the underlying biochemical defect: complex I abnormalities alone (18 of 33 cases) sometimes with carnitine deficiency (3 of 18 cases); complex III abnormalities (n = 9; of whom three have cytochrome b deficiency); complex III and IV, with cytochrome b and aa3 deficiency (n = 1); complex V (mitochondrial ATPase) with carnitine deficiency (n = 1); and four in whom no abnormality can be identified. Abnormalities either of complex I or III might be present in any one of the three groups of patients

![Figure 5](https://academic.oup.com/brain/article-abstract/137/2/640/284614) Scheme of respiratory chain to show the site of the proposed lesion in each case. FAD = flavin adenosine dinucleotide-linked succinic dehydrogenase. FMN = flavin mononucleotide-linked NADH dehydrogenase. (Fe-S) = non-haem iron sulphur proteins. Q = coenzyme Q: b6, b1, c1, c, aa3 = mitochondrial cytochromes. TMPD = tetramethyl phenylenediamine. I, II and III = coupling sites. From Morgan-Hughes et al. (1982).
defined clinically; and severity is unpredictable and extremely variable in the context of both these common biochemical defects.

There follows a careful catalogue of other case series listing clinical features from which emerges most clearly definition of the Kearns-Sayre syndrome. But, despite some additional symptoms and signs, this diagnosis can only be made in 9 of 30 cases reported by Richard Petty and colleagues with onset of progressive external ophthalmoplegia before the age of 20 years, or (occasionally) amongst the 21 with onset as adults. Four of these nine are studied in detail showing defects of complex I \((n = 2)\); an abnormality of complex V with secondary carnitine deficiency \((n = 1)\); and a defect of oxygen uptake that cannot be further characterized \((n = 1)\).

‘Thus the concept of the Kearns-Sayre syndrome is not supported by our clinical or biochemical data from a predominantly adult population. It is probable that this syndrome, however striking clinically, is merely a fortuitous combination of some of the more common features seen in patients with mitochondrial myopathy.’

Much the same difficulty arises in assigning the MERFF acronym to their cases—perhaps four cases qualify; and, at best, they have only two examples of MELAS. At the time, and despite Anita Harding’s expertise, the authors can do no more than note that the solution to imprecise mapping of clinical and biochemical features in these cases may eventually be resolved by genetic analyses. Most of their cases do not have a family history. They can only speculate that the syndrome of mitochondrial myopathy may result from mutations of either mitochondrial or nuclear DNA resulting both in Mendelian and maternal modes of transmission.

Dying shortly before her 43rd birthday, Anita Harding was denied the many accolades and achievements that her combination of personality and ability would inevitably have yielded; and, in turn, neurology never benefited to the full from the many further contributions and outstanding leadership that she would have provided. She was unable to participate in the discoveries of neurogenetics that modern molecular medicine has made possible; and a generation of neurologists trained since the mid-1990s lost the opportunity of mentorship and supervision by an outstanding clinical neurologist. With John Morgan-Hughes, she was ahead of the game in realizing that the concept of mitochondrial disease might become one of the great discoveries of late-20th century neurology—important not only in understanding muscle disease but also with implications for optic neuropathy, encephalopathy and neurodegeneration as practically every issue of Brain in recent times and four papers in the current issue make clear (see pages 323–379).

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