Dysssenergia cerebellaris myoclonica—primary atrophy of the dentate system: a contribution to the pathology and symptomatology of the cerebellum. J Ramsay Hunt MD (of New York). Brain 1922; 44: 490–538. With Progressive familial myoclonic epilepsy in three families: its clinical features and pathological basis. By D.G.F. Harriman and J.H.D. Millar with an appendix on the genetic aspects by A.C. Stevenson. (From the Department of Neurology, the Royal Victoria Hospital, Belfast, the Institute of Pathology, Queen's University, Belfast, and the Department of Neuro-pathology, The School of Medicine, Leeds) Brain 1955; 78: 325–49

Writing in 1914 and expanding on his presentation to the American Neurological Association from May 5th of that year, (James) Ramsay Hunt (1872–1937) first described three cases of progressive tremor of the extremities apparent during muscular activity and associated with dystonia, adiadochokinesis, asthenia and hypotonia (see Brain 1914; 37: 247–68). No less violent than examples of Huntington’s chorea, the movement differs in that the patients are entirely still at rest. Lacking pathological verification, Ramsay Hunt concludes that the disorder results from a defect of the ‘cerebellar mechanism presiding over the control and regulation of muscle movements’. By 1921, Dr Ramsay Hunt has recognized that ‘dyssynergia cerebellaris progressiva’ may also be associated with myoclonus and epilepsy. Now, his aim is to demonstrate that the cerebellar component arises from damage to the dentate nuclei of the cerebellum. He describes four cases.

A telegraphist, aged 30, is admitted under the care of Dr Pearce Bailey (1865–1922) at the Neurological Institute in New York. Over the previous 13 years he has experienced stereotyped episodes starting with spasm of the right arm and leg followed by unconsciousness, and with generalized convulsions occurring three or four times per year. Two years later, he starts to experience generalized myoclonic jerks; these are present most days on waking and reduced by alcohol intake. After 5 years he develops generalized tremor and speech disturbance. Examination shows dysarthria, hypotonia (but not the ‘Stewart-Holmes sign’ of cerebellar deficit in which the affected individual is unable to check a movement after passive resistance is suddenly released, the ‘rebound phenomenon’) and intention tremor of the extremities; this is ‘appendicular rather than trunkal…[and] similar in all respects to that observed in multiple sclerosis’, and associated with dystonia and adiadochokinesis. He cannot maintain posture of the limbs. Power, sensation and the reflexes are normal. He has violent myoclonic jerks of the face, extremities and trunk—exacerbated by any voluntary movement—while, with the intention tremor, make for a very grave disturbance of muscular coordination and the ability to stand and walk. Dr (Glen J) Doolittle (nk) of the Craig Colony for Epileptics introduces a girl, aged 19 years, who 12 years earlier has developed jerks and shaking of her arms, legs, trunk and face induced by movement. Generalized convulsions start at the age of 10, occurring about six times per year. Although difficult to separate from the myoclonus, over the previous 5 years she has shown a coarse atactic tremor with jerky, irregular, explosive speech. Examination confirms the myoclonus, which interrupts all voluntary movements, and standing and walking. She has intention tremor—appendicular and trunkal, in her case—adiadochokinesis and dysmetria. Her speech shows scanning dysarthria. Despite hypotonia, again the Stewart-Holmes sign is absent. Apart from evidence for impaired intelligence, the Binet-Simon test rating her at 9 years, examination is otherwise normal. Dr (Arthur Lee) Shaw (1883–1928), also of the Craig Colony for Epilepsy, introduces a man now aged 38 who has developed generalized epilepsy at 12 years of age followed by myoclonic jerks, worse in the mornings and especially severe before each convulsion. These are infrequent and it is because of severe myoclonus that he seeks institutional care, and is often confined to bed in his cottage through jerks that make it impossible for him to get about or feed himself. On examination, he is clumsy but not obviously atactic. His speech is scanning and ‘of cerebellar type’ and there is intention tremor, dyssynergia, dysmetria and adiadochokinesis (see Fig. 1). All movements are likely to precipitate myoclonus. He has neither hypotonia nor the Stewart-Holmes sign. Most obviously in this patient, ‘the myoclonus-epilepsy is such a formidable condition and causes so severe a disturbance of motility that it rather tends to mask the cerebellar dyssynergia’. The fourth case, seen in private practice, has developed increasingly frequent nocturnal convulsions now with myoclonus that has also gradually grown worse so that on bad days she cannot stand and remains confined to bed. Increased myoclonus often presages a convulsion.

Dr Ramsay Hunt observes an attack of myoclonus in which she experiences a sudden release of the muscular mechanisms that underlie the posture of standing, and suffers a severe laceration of the scalp in falling. Against this background, she has become clumsy with intention tremor and uncertainty of articulation. Memory and mood are also affected. Examination confirms frequent movement-induced myoclonus that may ‘throw her about in rather a bizarre manner’. She is slightly dysarthric and atactic...
with dysmetria and adiodokokinesis, hypotonic but with no Stewart-Holmes sign. No one of these cases has a family history and Dr Ramsay Hunt's starting position is to assume the chance occurrence in each of two independent nervous disorders—cerebellar dyssynergia and myoclonus. But since the seat of myoclonus is unknown might there be a closer connection?

Now Dr Ramsay Hunt describes two cases of cerebellar dyssynergia and myoclonus-epilepsy apparently in association with Freidreich's ataxia. A man aged 36, admitted to the Montefiore Home and Hospital, develops convulsions in his early 20s followed by increasingly severe myoclonic jerks which he considers to be aggravated by bright light. Soon after, his balance deteriorates, coordination of the arms is impaired, and his speech becomes indistinct. His memory is poor and affect altered. Later, the patient becomes weak in the extremities and is unable to stand or walk. On examination he is thrown about violently by myoclonus that follows any attempt to move or speak and, as a consequence, becomes physically restricted and socially reclusive. Indeed, he must be tethered to the bed or chair with a sheet in order to remain steady; even so, his wheelchair lurches around the room in response to the movements. He has marked intention tremor, dysmetria and adiodokokinesis. He is hypotonic and the Stewart-Holmes sign is present. Unlike the first four cases described, this patient is also severely wasted and weak in the extremities, with altered deep and superficial sensation and reduced or absent tendon reflexes. His twin brother is also affected. He has developed altered speech, ataxia and intention tremor of the extremities but with the illness dominated by myoclonic jerks—'jumps and starts' of the limbs, face or trunk—albeit less severe than those affecting his brother. The seizures consist of momentary loss of tone with brief unconsciousness (‘static epilepsy’) but no florid generalized convulsions. Examination confirms dysarthria, movement-induced myoclonus, gait ataxia and intention tremor but, despite hypotonia and presence of the Stewart-Holmes sign, no wasting or weakness of the limbs. Sensation is preserved although the tendon reflexes are absent. The opportunity arises for histological examination of the more severely affected twin (Case 5). The autopsy is performed by Dr (Joseph Haim) Globus (1885–1952) from the Montefiore Home and Hospital, with additional investigations arranged by Dr (Frederick) Tilney (1876–1938) of Columbia University.

After a detailed description of essentially normal findings in most organs, Dr Globus concentrates on the central nervous system. There is degeneration of the posterior cord throughout its length, involving especially the column of (Friedrich) Goll (1829–1903) more than that of (Friedrich) Burdach (1776–1847) extending into the medulla oblongata up to the nuclei of these tracts. The ventral and dorsal cerebellar tracts [direct cerebellar and (Sir William) Gowers (1845–1915) tracts] are atrophic with sparing of the direct and crossed pyramidal and spinothalamic tracts. (Jacob Augustus Lockhart) Clarke’s (1817–80) column is also degenerate. The posterior roots and dorsal horns are involved, the anterior nerve roots spared. The blood vessels are normal and inflammation is absent. Within the pons and midbrain, the superior cerebellar peduncles connecting the dentate nuclei to the red nucleus are atrophied throughout their course but with sparing of the rubro-spinal tract (see Fig. 2); the cerebellum and efferent fibres connecting the frontal and parieto-occipital cortex to the pons and cerebellum via the middle cerebellar peduncle are unaffected. But the most striking abnormality is selective loss of nerve cells in the dentate nuclei of the cerebellum, affecting one-third to one-half, with morphological abnormalities in those neurons that have survived. Dr Ramsay Hunt concludes that the spinal cord shows the features of Freidreich's ataxia and the cerebellum has a special form of disease, 'primary atrophy of the efferent dentate system'. But how does this explain the 'dyssynergia cerebellaris progressiva' (progressive cerebellar tremor)?

First, he rehearses the functional anatomy of the cerebellar peduncles: the inferior conveying information from the spinal cord via the nuclei of Goll and Burdach and the lower cranial nerve nuclei; the middle connecting the frontal and occipital cortex to the ipsilateral pontine nuclei and then through a crossed tract to the opposite cerebellar hemisphere; and the superior peduncle conveying impulses arising in the intrinsic nuclei of the cerebellum, especially the dentate, to the opposite red nucleus and thalamus. Dr Ramsay Hunt distinguishes the neodentate system that has expanded with development of the cerebral cortex and cerebellar hemisphere from the paleodentate, which connects components of the older cerebellum and vermis. He notes that cerebellar atrophy is often combined with spinal cord degeneration as in the disorder described by (Pierre) Marie (1853–1940), and the...
non-familial olivo-ponto-cerebellar degeneration of (Jules) Dejerine (1849–1917) and (André Antoine Henri) Thomas (1867–1963) in which the damage targets the olive and its cerebellar connections, the pontine nuclei and fibres of the middle cerebellar peduncle and cerebellar cortex, sparing the intrinsic nuclei and the superior cerebellar peduncle. In the familial disorder described by (Sir Gordon) Holmes (1876–1965), it is the olive and olivo-cerebellar tract and the cerebellar cortex that bear the brunt of the disease. Le Jonne (nk) and (Jean) Lhermitte (1877–1959) have distinguished a form of olivo-rubro-cerebellar atrophy in which the olive and its connections, the intrinsic cerebellar nuclei, superior cerebellar peduncles and red nucleus are all involved. And André-Thomas describes a disorder characterized by loss of cerebellar cortical Purkinje cells.

‘At the present time we may recognise therefore the following pathological types of cerebellar atrophy. The cerebellar cortical type of André-Thomas, the olivo-ponto-cerebellar type of Déjerine and Thomas; the olivo-cerebellar type of Holmes, and the olivo-rubro-cerebellar type of Le Jonne and Lhermitte. To these various types I would add the primary atrophy of the dentate system... the dyssynergia is, therefore, of the appendicular rather than the axial type. In this respect differing from the massive truncal involvement of many other forms of cerebellar atrophy’.

(Sir David) Ferrier (1843–1928) and (William Aldren) Turner (1864–1945) have shown experimentally that lesions of the efferent superior cerebellar peduncular pathway reproduce the intention tremor exhibited by Dr Ramsay Hunt’s cases. It is the selective affection of neodentate cerebellar functions that explains the characteristic involvement of appendicular rather than axial structures.

Modern concepts, ‘under the leadership of (Joseph) Babinski (1857–1932),’ consider the cerebellum to be the organ that regulates synergies of movement but there is much that is not explained by this unitary formulation of cerebellar disease as dyssynergia. Movement has a kinetic component (motion) and a static one (tone and posture); ultimately the former is dependent on activity of anisotropic discs and the latter on the sarcoplasm of the muscle fibres each having differences in structure, innervations, mode of contractility and metabolism. Fixation of the muscle fibres each having differences in structure, innervations, mode of contractility and metabolism. Fixation of the sarcoplasm converts the contractile muscle fibre from its kinetic to a static mechanism. ‘Every movement starts from posture, is accompanied by posture, and terminates in posture, posture following movement like a shadow’. The cerebellum is the integrating organ for posture, or static movement. Dr Ramsay Hunt disaggregates movement into reflex, automatic and isolated-synergic components each having its kinetic and static components. The cerebellum integrates information from the periphery and cortex and exerts effects on spinal mechanisms and skeletal muscle that subserves posture. The older parts of the cerebellum are concerned with ‘paleostatic’ automatic postures of the trunk and axial musculature; and the dentate nuclei orchestrate ‘neostatic’ postures of the limbs, together determining the secondary postures on which conscious movements depend for their stability.

‘I would regard the cerebellum as a central ganglionic station for the coordination and control of static or posture synergies in contradistinction to kinetic or motion synergies which are localized in their respective kinetic spheres (rolandic and striatal).’ And he concludes that loss of synergy for posture, be that paleostatic or neostatic, is the basis for cerebellar symptoms explained on the basis of altered postural control and resulting in scanning speech, cerebellar ataxia, intention tremor, hypermetria, adiadochokinesis and nystagmus. Although the primary atrophy of the dentate explains the neostatic appendicular symptoms, what is the significance of the myoclonus and epilepsy that so affected these patients in life? It is similar to the disorder described by (Heinrich) Unverricht (1853–1912) although not familial other than in the two twins. Whilst coincidence is the most parsimonious explanation, sudden breaks in postural control dependent on cerebellar dysfunction—the so-called ‘static seizures’—might explain the movements. The disorder he wishes to designate as primary atrophy of the dentate system is comparable to the form of progressive pallidal atrophy manifesting as paralysis agitans that he has already described (see Brain 1917; 40: 58–148). Primary atrophy of the pallidal system is a disorder of the kinetic mechanism, manifesting as paralysis agitans; primary atrophy of the dentate nuclei is a disorder of the static mechanism in which activity of muscle sarcoplasm is impaired giving rise to the symptomatology of dyssynergia cerebellaris.

Thirty-four years later, D.G.F. (Denis) Harriman (nk) and J.H.D. (Harold) Millar (1917–92) acknowledge that myoclonus may be a feature of epilepsy ‘as a minor phenomenon, short-lived and arousing little curiosity’. But when it dominates the clinical picture and increases in frequency and severity, it becomes part of the autosomal recessive syndrome first defined by Unverricht (Die myoclonie. 1891 p. 128) and (Herman Bernard) Lundborg (1868–1943); Medizinisch-biologische Familienforschungen innerhalb eines 2232-köpfigen Bauerenge-schlechtes in Schweden. 1913. 2 vol: pp. 520 and 220 with seven maps, 10 plates and 50 tables of pedigrees) in which the myoclonus, provoked by stimulus, is almost constant. Although some cases have cytoplasmic amyloid inclusion bodies, as described by (Gonzalo Rodríguez) Lafora (1886–1971), the pathological basis for the condition is confusing. The authors from Belfast and Leeds describe eight cases from three separate families, with one autopsy that does demonstrate Lafora bodies. TWS, the child of a first cousin marriage, dies aged 24 after an illness lasting 10 years characterized by generalized epilepsy and later developing ataxia, anarthis, dementia and myoclonus so that institutional care at Purdysburn Mental Hospital becomes necessary for the last 4 years of life. His brother, SS, develops epilepsy and an altered mental state requiring institutional care and later exhibits increasingly severe myoclonus. In a second pedigree, TM has a 15 year history of severe myoclonus and generalized epilepsy followed by dysarthria, ataxia, dementia and incontinence leaving him bed-bound for several years. Much the same pattern characterizes the illness of JM, his brother, aged 20 years. BM, the third affected brother in this family, suffers epilepsy from the age of nine, soon followed by myoclonus. EM, from a third affected family, lives in a part of rural County Donegal where intermarriage is common and half of the inhabitants have the same surname. She does not present until aged 19 but then has occasional seizures and increasingly severe myoclonus with dysarthria and ataxia so that she is chair-bound for more than a decade at the time of
her death aged 48 years. Her sister, CM, also has a long history of occasional seizures with increasingly severe myoclonus and dysarthria but remains independent into her mid-40s. The third affected sister, EB, has experienced much the same sequence of events despite a somewhat shorter clinical course. In most cases the myoclonus is accompanied by bilateral synchronous sharp cortical spikes on the electroencephalogram that increase with photic stimulation. Unaffected siblings within Family B show no electroencephalographic abnormalities. Jerking movements of the arm and leg, respectively, follow these discharges within only 15–25 ms suggesting to the authors that the myoclonus is of brainstem origin spreading from there to the cortex and cord. Since any movement is likely to induce these jerks, it is difficult to separate the myoclonus from an independent underlying disorder of articulation and coordination. And whereas Ramsay Hunt has distinguished the cerebellar deficits arising from primary atrophy of the dentate system of the cerebellum from the myoclonus, ‘in our cases the cerebellar-like signs were present when the myoclonus was apparent, and increased when the myoclonus was severe; in fact it seemed as if the myoclonus was primarily responsible for signs usually attributed to cerebellar disease’. That is the authors preferred interpretation of their patients’ severe dysarthria and inability to walk. The illness passes through epileptic, myoclonic and, after some years, a terminal or marantic stage in which mental deterioration and behavioural disturbance are prominent.

Autopsy is performed in case TWS from Family A (see Figs 3 and 4). This shows numerous intracellular amyloid bodies, containing an acid mucopolysaccharide and staining with the periodic acid–Schiff technique, in association with nerve cell bodies, axons and dendrites throughout layers II–V of the cerebral cortex but sparing the white matter; some inclusions are extracellular and appear to have been released from degenerate neurons. A large number of nerve cells contain lipofuscin. There are reactive changes in microglia and astrocytes. Whilst amyloid bodies are present in the brainstem, medulla and spinal cord, the dentate nuclei of the cerebellum and the substantia nigra are especially affected. Similar inclusions are present in the heart and liver suggesting that the disorder results from a genetic or abiotrophic abnormality of carbohydrate metabolism. Others have reported Lafora bodies in some but not all cases of Unverricht-Lundborg disease and these may also be found in altogether different disorders. But taking involvement of the dentate nuclei as a core feature of familial myoclonic epilepsy, cases segregate into those with Lafora bodies; examples with lipoid inclusions; and a heterogeneous group showing degeneration of the dentate and substantia nigra without inclusions, which is where the disorder described by Ramsay Hunt properly belongs. Evidence for recessive inheritance is apparent in all three groups. Pursuing their observations on the timing of cortical discharges and the electromyographic signatures of the involuntary movements, Harriman and Millar now conclude that the dentate lesion is directly responsible for myoclonus.

Against this background, the spectrum of the phenotype seen in progressive myoclonus epilepsy syndromes and knowledge on the underlying genetic architecture and disease mechanisms involved continues to expand, as papers by Elizabeth Stogmann et al. (see page 1155) and Lysa Boisse´ Lomax and colleagues (see page 1146) in the current issue make clear.

Alastair Compston
Cambridge