Handbook of Clinical Neurology, Vol. 95 (3rd series)
History of Neurology
S. Finger, F. Boller, K.L. Tyler, Editors

Chapter 33

The history of movement disorders

DOUGLAS J. LANSKA *
Veterans Affairs Medical Center, Tomah, WI, USA, and
University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

THE BASAL GANGLIA AND DISORDERS OF MOVEMENT

Distinction between cortex, white matter, and subcortical nuclei

The distinction between cortex, white matter, and subcortical nuclei was appreciated by Andreas Vesalius (1514–1564) and Francisco Piccolomini (1520–1604) in the 16th century (Vesalius, 1542; Piccolomini, 1630; Goetz et al., 200 la), and a century later British physician Thomas Willis (1621–1675) implicated the corpus striatum in motor function: "When I opened a number of cadavers of patients who had died from a long paralysis . . . I always found the striate bodies more softened than any other part; also discolored like the dregs in an olive press, and the striae much obliterated" (Willis, 1664, as cited in Schiller, 1967, p. 526). Later Willis elaborated: "[When] the Animal Spirits . . . direct themselves thence into the Corpora Striata, and origins of the Nerves, they actuate all the moving parts, and as often as there is occasion, convey to them the Instincts of setting upon motions" (Willis, 1685, p. 413).

Willis' concept that the corpus striatum is the seat of motor power was pre-eminent for approximately 200 years, and this misconception later formed the basis of mid-19th-century localizations of several movement disorders to the striatum. Thus, for example, striatal dysfunction was implicated in chorea by British physician William Broadbent (1835–1907) (Broadbent, 1869) and British neurologist John Hughlings Jackson (1835–1911) (Jackson, 1868/1932/1996, p. 238), and in athetosis by American neurologist William Hammond (1828–1900) (Hammond, 1871)–localizations that would prove essentially correct, though somewhat seredipitously. It was only with electrophysiologic stimulation studies by German physiologists Gustav Fritsch (1838–1927) and Eduard Hitzig (1838–1907) on the cerebral cortex of dogs (Fritsch and Hitzig, 1870/1960), British physiologist David Ferrier's (1843–1928) stimulation and ablation experiments on rabbits, cats, dogs and primates begun in 1873 (Ferrier, 1876), and Jackson's careful clinical and clinical-pathologic studies in people (late 1860s and early 1870s) that the role of the motor cortex was appreciated, so that by 1876 Jackson could consider the "motor centers in Hitzig and Ferrier's region . . . higher in degree of evolution that the corpus striatum" (Jackson, 1876/1932/1996, vol. 1, pp. 150–151).

By the late 19th century a number of movement disorders were fairly well described clinically, including several forms of tremor, Parkinson's disease, Sydenham's chorea, Huntington's chorea, post-hemiplegic choreoathetosis, several forms of dystonia (including writer's cramp, torticollis, and dystonia musculorum deformans), and Gilles de la Tourette's syndrome. These disorders were puzzling, though, because in most cases pathologic studies had yet to identify a clear pathologic correlate of the clinical disease.

In 1888, in his classic text, *A Manual of Diseases of the Nervous System*, British neurologist William Gowers (1845–1915) was not sure how to classify such movement disorders and lumped them under "general and functional diseases of the nervous system," noting that in general there were

> *no constant changes to be seen [in the brain] with the naked eye . . . but microscopical changes have been discovered in some of them with sufficient frequency to make it certain that there is far more than a mere disturbance of function, and it cannot be doubted that most of these maladies depend upon alteration in the nutrition of the nerve-elements, although these may not yet have been*

*Correspondence to: Douglas J. Lanska MD, VA Medical Center, 500 E Veterans St., Tomah, WI 54660, USA. E-mail: douglaslanska@med.va.gov, Tel: +1-608-372-1772, Fax: +1-608-372-1240.

> *found, and perhaps cannot be detected without more means of investigation that we at present possess. (Gowers, 1888, p. 547)*

Seventy years later, Canadian neurologist Andre Barbeau (1931–1986) noted progress and offered hope, but was frustrated with the limited understanding of etiology and pathophysiology as well as the inadequacies of available treatments for movement disorders:

> *But what of the results? Many are improved that a few years ago would have been miserable, many are permitted a more active life and are forever grateful . . . but none are cured! The cause and exact pathology of the various diseases grouped under the extra pyramidal system remain mysteries almost as deep as in the days of Sydenham and Parkinson. Many clinical varieties have been observed, many pathological studies carried out, but the suffering humanity still goes on twisting, shaking, writhing, jumping and jerking when it does not want to. (Barbeau, 1958, pp. 486–487)*

Models of basal ganglia function

Dramatic and rapid progress is now being made in understanding how the basal ganglia function to influence movement; how various structural, neurochemical, and other derangements of basal ganglia circuits produce different movement disorders; and how pharmacological and surgical treatments act to correct or improve some of the features of movement disorders. In particular, since the late 1980s a series of increasingly sophisticated conceptual models of basal ganglia function (e.g., Alexander and DeLong, 1986; Albin et al., 1989b; DeLong, 1990; Bergman et al., 1990; Wichmann and DeLong, 1998; Mink, 2003), supported and guided by experiments with animal models of disease and by clinical experience with human patients (e.g., Smith and Parent, 1988; Albin et al., 1989a; Bergman et al., 1990, 1994), have provided sufficient insight into disease mechanisms to guide the development of novel pharmacological and surgical therapies, particularly pallidotomy and deep brain stimulation for Parkinson's disease, but also somewhat for other forms of movement disorders. They have also served to guide research efforts with animal models or with human subjects (with sophisticated neuroimaging or during surgery) that have helped to elaborate or correct portions of these models.

These models of basal ganglia function initially focused particularly on the balance of firing rates (rather than temporal or spatial pattern of firing) in various basal ganglia nuclei or projection systems. By 1990, the motor portion of the basal ganglia-thalamocortical circuits was felt to represent "a re-entrant pathway through which influences emanating from specific areas of cortex are returned to certain of those same areas after intermediate processing within the basal ganglia and thalamus" (DeLong, 1990, p. 281). Cortical and nigral projections (i.e., input) to the basal ganglia motor circuit terminate primarily in the putamen, whereas motor output from the basal ganglia is directed primarily from the internal segment of the globus pallidus to the thalamus (ventral tier and mediodorsal nuclei) and to the substantia nigra pars reticulate in the brainstem. Within the basal ganglia are two important projection systems: a "direct pathway" from the putamen directly to the motor portions of the internal segment of the globus pallidus and the pars reticulate of the substantia nigra; and an "indirect pathway" passing from the putamen through intermediate nuclei (i.e., sequentially the external segment of the globus pallidus and then the subthalamic nucleus) before being directed to the basal ganglia output nuclei (i.e., the internal segment of the globus pallidus).

DeLong (1990, p. 281) and others proposed that "the direct pathway effectively provides positive feedback to the precentral motor fields, . . . [whereas] activity conducted along the indirect pathway appears to provide negative feedback to the precentral motor fields . . . Thus, in general it appears that enhanced conduction through the indirect pathway leads to hypokinesia (by increasing pallidothalamic inhibition), whereas reduced conduction through the direct pathway results in hyperkinesias (by reduction of pallidothalamic inhibition)." In a later synthesis, Wichman and DeLong (1998, p. 225) concluded that "In general, hypokinetic disorders such as Parkinson's disease are associated with increased basal ganglia output, whereas hyperkinetic movement disorders such as Huntington's disease are associated with decreased output."

While helpful, even the modelers themselves soon recognized that "these models are only a first draft of basal ganglia function under normal and diseased conditions" (Wichman and DeLong, 1998, p. 232), with significant residual discrepancies and inadequacies that await resolution (Wichman and DeLong, 1998; Obeso et al., 2000). For example, these models essentially considered all hyperkinetic movement disorders to result from a reduction of inhibitory basal ganglia output, particularly to the thalamus, and as such were unable to adequately explain how different forms of hyperkinetic movements occur (Mink, 2003). These models also left many other observations unexplained, including the lack of dyskinesias after pallidotomy, lack of parkinsonism after thalamotomy, failure of lesions of the external segment of the globus pallidus to abolish drug-induced dyskinesias (Wichman and DeLong, 1998), and failure to explain why different

clinical features of movements disorders (e.g., tremor, rigidity, bradykinesia, gait dysfunction, and postural instability in Parkinson's disease) present to different degrees in some patients or respond differently to pharmacological or surgical procedures (Obeso et al., 2000). More complex models that address some of the earlier model deficiencies have subsequently been proposed (Mink, 2003), but remain largely untested and have had limited application to treatment.

TREMOR

Distinction of rest and action tremors

In the second century, Galen (c. 130–200 AD) used the term *tremor* to refer to "involuntary alternating up-and-down motion of the limbs," occurring during action and resulting from partial "weakness of the force that supports and moves the body" (Sider and McVaugh, 1979; Koehler and Keyser, 1997). Galen distringuished tremor from *palpitation*, an "unnatural expansion and collapse" occurring at rest (Sider and McVaugh, 1979; Koehler and Keyser, 1997). Later, in the 17th and 18th centuries, Franciscus de la Boë (Sylvius; 1614–1672), Gerard van Sweiten (1700–1772), and others further distinguished involuntary movements during action and at rest (de la Boë, 1663; Molina-Negro and Hardy, 1975; Koehler and Keyser, 1997).

British physician James Parkinson (1755–1824) provided the first clear clinical description of a specific rest tremor in his treatise on the "shaking palsy" in 1817 (Parkinson, 1817). His report received some, albeit limited, recognition (Schiller, 1986; Keppel Hesselink, 1996; Louis, 1997) until later in the 19th century, when French neurologist Jean Martin Charcot (1825–1893) labeled the condition "Parkinson's disease", and distinguished the tremor of Parkinson's disease from the kinetic "intentional" (intention) tremor seen in multiple sclerosis (Charcot and Vulpian, 1861; Charcot, 1877b, 1887/1987, 1889; Goetz, 1986; Schiller, 1986; Goetz et al., 1995, 2001b, 2001f; Keppel Hesselink, 1996; Lanska, 2000b). Charcot noted that in patients with multiple sclerosis tremor is not present at rest, but only with activity, and that the tremor amplitude increases with effort. In contrast, the tremor of Parkinson's disease is present both at rest and during activity, and the amplitude does not increase with action (Fig. 33.1).

The characteristics of different rest and action tremors were more fully elaborated in the late-19th and 20th centuries by a number of authors using more sophisticated recording devices and other technologies (Fig. 33.2) (Lanska, 2000b). Although overlapping tremor frequencies for different types of tremor precluded tremor recording devices from becoming a definitive

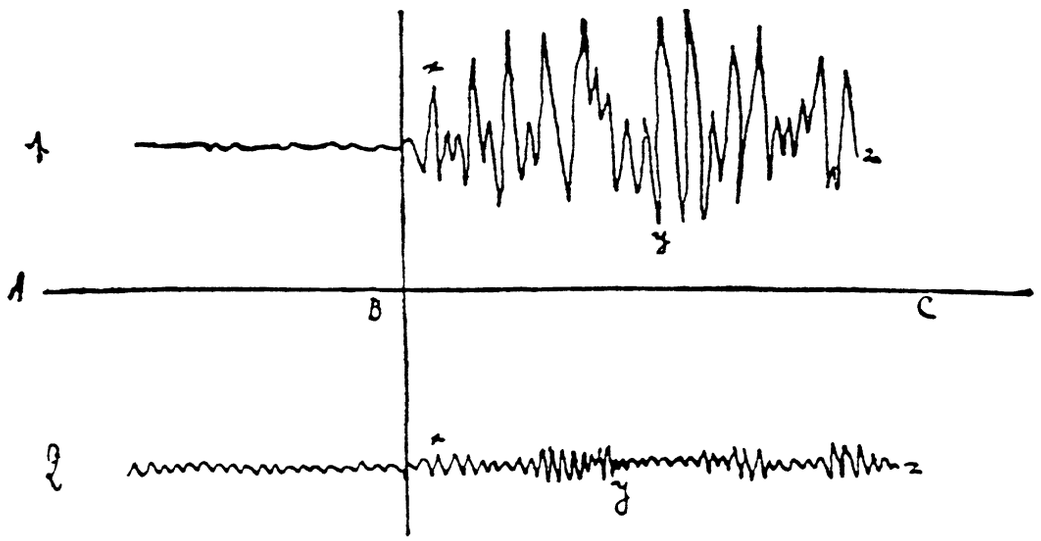

Fig. 33.1. Charcot's semi-diagrammatic graphic representations of tremor based on tracings (Charcot, 1887, 1889): "No. 1 [top curve] represents the intentional tremor of disseminated sclerosis (i.e., multiple sclerosis). The line AB indicates the state of repose. The point B represents the moment of commencing the voluntary movement; BC represents the duration of the movement, and the trembling is represented by the wavy line xyz, of which each oscillation is larger the farther we get from B . . . No. 2 in the figure represents the tremors of paralysis agitans (i.e., Parkinson's disease). You see at once on looking at this diagram how the two tracings differ in the portion BC. The segment under the line AB represents the time of repose. It is cut up by little waves corresponding to the continuous trembling. At point B voluntary movement commences. From this point the components of the wavy line xyz are a little longer and more irregular than in the period of repose, but they are never so much so as in disseminated sclerosis" (Charcot, 1889). Charcot's graphical recording method, upon which this diagram was based, is not described, but in other circumstances he relied on various pneumatic tambour-like mechanisms (Charcot, 1877a, 1889).

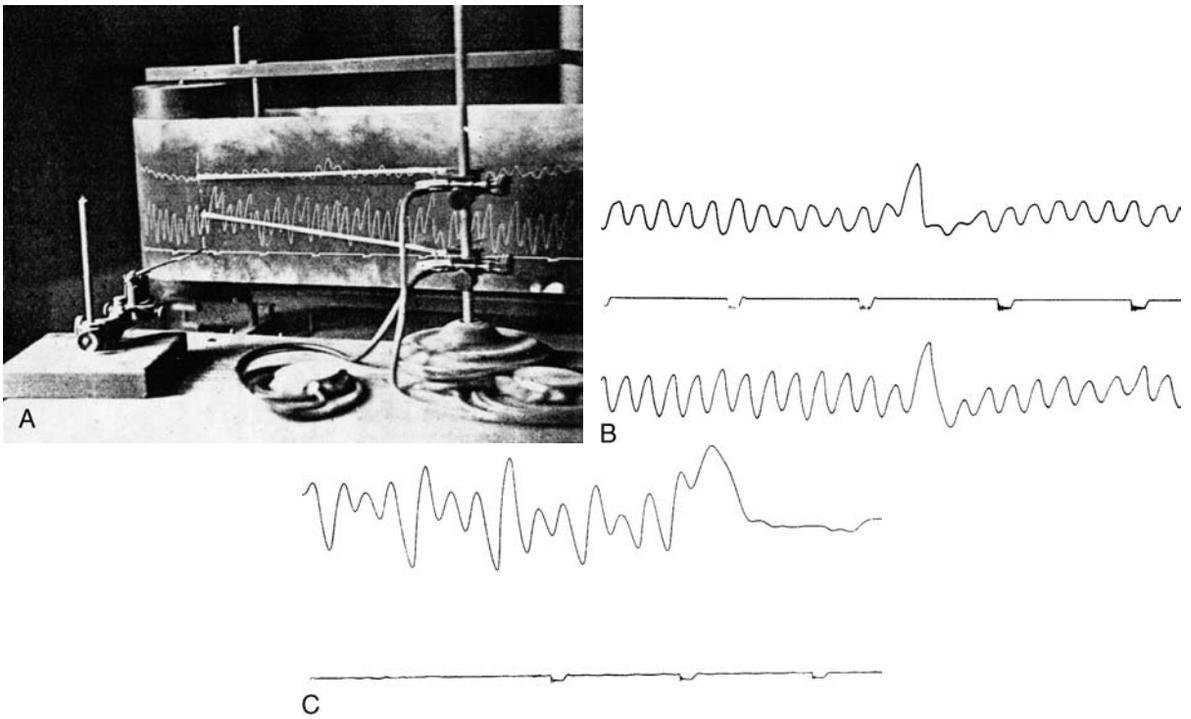

Fig. 33.2. American physician Augustus Eshner used a tambour recording apparatus for some studies, including those requiring "simultaneous observations of the two sides of the body or of two or more different parts" (A) (Eschner, 1897). For example (B), the use of two tambours allowed simultaneous recording from both hands in a patient with Parkinson's disease (upper curve is the left hand, lower curve is the right hand, and middle line marks time in seconds); the tracings demonstrate a synchronous tremor in the two hands at about 5.5 hertz. Eschner was also able to demonstrate (C) suppression of a rest tremor with action (i.e., finger extension) in a patient with Parkinson's disease (left portion of the tracing shows a tremor at rest and the far right portion without tremor is during action). Prior to action, the tremor had a frequency of approximately 4.7 hertz. The tracings in B and C are the negatives of the originals made on smoked paper.

diagnostic tool, graphical recordings did allow 19th-century investigators to demonstrate: (1) tremor frequency varies as a function of weight and elastic properties in different body parts; (2) tremor amplitude and frequency are inversely related; and (3) the tremor of Parkinson's disease is a relatively low frequency rest tremor, suppressed by action, and generally synchronous in symmetric body parts, but varying in amplitude and frequency over time (Eschner, 1897; Lanska, 2000b; Lanska et al., 2001a). (Fig. 33.2)

Physiologic tremor

As early as 1610, Italian physicist and astronomer Galileo Galilei (1564–1642) recognized that cardioballistic and respiratory movements contributed to the shaking of the magnified image in a hand-held telescope: ". . . the instrument must be held firm, and hence it is good, to escape the shaking of the hand that arises from motion in the arteries and from breathing, to fix the tube in some stable place . . ." (Galilei, 1610/1978, p. 147). In 1897, American physician Augustus Eschner (1862–1949) offered several ways of demonstrating physiologic tremor in healthy individuals, including holding a glass of water and viewing the surface, or using a mechanical recording apparatus. Eschner (1897, p. 306) noted that: "[Small amplitude physiologic tremors should be expected] . . . as every muscular movement is made up of a series of alternate contractions and relaxations, occurring ordinarily with such frequency as to escape detection with the unaided eye." Eschner considered uneven integration of individual muscle twitches to be the basis of physiologic tremor, but he ignored other possible components, including rhythmic bursts of discharges from central generators, oscillatory feedback systems, resonant properties of the moving parts, postural adjustments, and cardioballistic and respiratory movements (Lanska, 2000b).

Essential tremor

In the late-19th century, physicians began to recognize familial forms of postural action tremors. In 1887,

American neurologist Charles Dana (1852–1935) described a familial postural tremor:

> *The affection in question consists of a fine tremor, constantly present in typical cases during waking hours, voluntarily controlled for a brief time, affecting nearly all the voluntary muscles, chronic, beginning at very early life, not progressive, not shortening life, not accompanied with paralysis or any other disturbances of nervous function . . . It begins in infancy or childhood, sometimes being brought out by an infectious fever . . . . The upper extremities are most noticeably affected, but it may involve the head, neck, eye, laryngeal, or, in fine, any of the voluntary muscles. It ceases during sleep, and can be inhibited temporarily by the will. Everything that produces excitement or nervousness increases the tremor. It may be barely noticeable, except under some excitement, or the influence of alcohol or tobacco. It does not interfere with delicate coordination. It neither stops nor increases on ordinary voluntary movements. (Dana, 1887, pp. 386–387, 392)*

Although Dana's description of familial tremor has generally been accepted as an early description of hereditary essential tremor, the condition (1) reportedly *increased* under the influence of alcohol; (2) did not interfere with fine manual tasks; and (3) was *not* likely hereditary given the large reported pedigree, with almost all individuals affected (e.g., with 41 of 42 individuals in two successive generations affected, and with the sole exception an obligate carrier under an autosomal dominant mode of hereditary transmission) (Lanska, 2002).

There was considerable interest in hereditary neurologic disorders in the late-19th century, especially following Friedreich's (1863) work on hereditary ataxia, and Huntington's (1872) report of hereditary chorea. Yet there was no understanding at this time of Mendelian genetics, and most investigators considered any familial disorder as "hereditary." Hereditary conditions were not understood in anything resembling the modern sense until Mendel's laws were simultaneously rediscovered and made known by DeVries, Correns, and Tschermak von Seyenegg in 1900 (Mendel, 1865; Correns, 1900; De Vries, 1900; Tschermak von Seyenegg, 1900).

Multigenerational familial tremors having characteristics of autosomal dominant transmission were recognized in the early-20th century (e.g., Mitchell, 1903; Critchley, 1949), but clear recognition of autosomal dominant transmission of essential tremor did not occur until the middle of the 20th century (Critchley, 1949; Davis and Kunkle, 1951; Jager and King, 1955; Larsson and Sjögren, 1960). Since the late 1990s, essential tremor loci have been identified on several chromosomes: 3q13 (familial essential tremor 1), 2p24.1 (familial essential tremor 2), and 6p23. However, some pedigrees consistent with autosomal dominant essential tremor have excluded known genetic loci as a cause, supporting genetic heterogeneity (Ma et al., 2006). Twin studies and segregation analysis have further suggested that essential tremor may require interaction of environmental and genetic factors (Louis et al., 2001; Ma et al., 2006). Au4

British neurologist MacDonald Critchley (1900–1997) noted that "Some patients find that a heavy dose of spirits will temporarily check the tremor and this factor has appeared only too often to have served as an excuse for habits of intemperance" (Critchley, 1949, pp. 117–118). Davis and Kunkle (1951, p. 815) similarly reported, "Treatment with Phenobarbital apparently offers some symptomatic benefit, but this may be largely nonspecific, i.e., without altering the basic mechanism of the tremor. Although alcohol has been found beneficial by some patients, its prescribed use is unwarranted, for this may lead to excessive drinking."

Beneficial effects of propranolol were documented in the 1970s (Dupont et al., 1973; Winkler and Young, 1974) and the utility of primidone was documented in the 1980s (O'Brien et al., 1981; Findley et al., 1985). These two medications remain the best available drugs (Zesiewicz et al., 2005), but surgery is increasingly recognized as efficacious for tremor refractory to drug therapy (Hassler and Reichert, 1954). Thalamotomy is associated with significant potential complications, particularly if performed bilaterally (Goldman et al., 1992; Shahzadi et al., 1994; Jancovic et al., 1995), so thalamic stimulation has been increasingly used (Limousin et al., 1999; Pahwa et al., 1999; Schuurman et al., 2000). Au5

PARKINSON'S DISEASE

Parkinson's disease is of fundamental importance to the history of movement disorders, because of its common occurrence, the dramatic progress that has been made in understanding and treating the condition, and the insights this progress has provided for understanding the anatomy and function of the basal ganglia.

Clinical description

The first clear clinical description of Parkinson's disease was the monograph titled *An Essay on the Shaking Palsy* by British general practitioner James Parkinson in 1817 (Parkinson, 1817). Parkinson gave a short account of six subjects, some of whom he had never examined, but only saw on the neighborhood

streets or when making his medical rounds. He noted the tremulous involuntary shaking at rest, the asymmetric onset, the slowed movements, the flexed posture, and the festinating gait:

> *Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being unimpaired . . . The first symptoms perceived are, a slight sense of weakness, with a proneness to trembling in some particular part; sometimes in the head, but most commonly in one of the hands and arms . . . [As] the malady proceeds . . . [the] propensity to lean forward becomes invincible, and the patient is thereby forced to step on the toes and fore part of the feet, whilst the upper part of the body is thrown so far forward as to render it difficult to avoid falling on the face. In some cases, when this state of the malady is attained, the patient . . . [is] irresistibly impelled to take much quicker and shorter steps, and thereby to adopt unwillingly a running pace . . . The power of conveying the food to the mouth is at length so much impeded that he is obliged to consent to be fed by others . . . As the disease proceeds towards its last stage, the trunk is almost permanently bowed, the muscular power is more decidedly diminished, and the tremulous agitation becomes violent. The patient walks now with great difficulty, and unable any longer to support himself with his stick, he dares not venture on this exercise, unless assisted by an attendant . . . His words are now scarcely intelligible; and he is not only no longer able to feed himself, . . . the food is with difficulty retained in the mouth until masticated; and then as difficultly swallowed. Now also . . . another very unpleasant circumstance occurs: the saliva fails of being directed to the back part of the fauces, and hence is continually draining from the mouth . . . As the debility increases and the influence of the will over the muscles fades away, the tremulous agitation becomes more vehement . . . The chin is almost immoveably bent down upon the sternum. The slops with which he is attempted to be fed, with the saliva, are continually trickling from the mouth. The power of articulation is lost . . . [At] the last, constant sleepiness, with slight delirium, and other marks of extreme exhaustion, announce the wished-for release. (Parkinson, 1817, pp. 1–9)*

In his classroom lectures at the Salpêtrière over 50 years later, Jean-Martin Charcot lauded Parkinson's clear and succinct clinical descriptions and suggested the eponym of "Parkinson's disease." Charcot rejected the earlier designation of "paralysis agitans," correctly noting that Parkinson's disease patients are not particularly weak and do not necessarily have tremor (Charcot and Vulpian, 1861; Charcot, 1877b; Goetz, 1986; Schiller, 1986; Goetz et al., 1995, 2001b; Keppel Hesselink, 1996). Charcot distinguished bradykinesia as a cardinal feature of the illness, separate from rigidity. Charcot and his students described the clinical spectrum of this disease, noting both tremorous and rigid/akinetic forms. Charcot believed strongly that Parkinson's disease patients have no head tremor, and that any apparent tremor is a secondary oscillation resulting from trunk or extremity tremors. He demonstrated this with the use of a simple device: a head band to which was attached a long rod with a feather at the end: when patients with Parkinson's disease sat or stood, the feather oscillated prominently, but if the trunk or arm was supported or moved, the head tremor immediately ceased.

One of the best 19th-century descriptions of Parkinson's disease was given by Gowers (1888) (Fig. 33.3), although he incorrectly reported weakness as a feature of the disease:

Fig. 33.3. In 1888, British neurologist William Gowers published one of the best neurology textbooks of the 19th century, a two-volume textbook titled A Manual of Diseases of the Nervous System. Among the many excellent illustrations and meticulous and vivid descriptions were those concerning the clinical features of paralysis agitans (Parkinson's disease).

The aspect of the patient is very characteristic. The head is bent forward, and the expression of the face is anxious and fixed, unchanged by any play of emotion. The arms are slightly flexed at all joints from muscular rigidity, and (the hands especially) are in constant rhythmical movement, which continues when the limbs are at rest so far as the will is concerned. The tremor is usually more marked on one side than the other. Voluntary movements are performed slowly and with little power. The patient often walks with short quick steps, leaning forward as if about to run . . . The tremor is an alternating contraction in opposing muscles, causing a rhythmical movement of the parts to which they are attached. It is usually greatest in the hands and fingers, partly from the contraction of the forearm-muscles, partly from that in the interossei; the latter causes a movement of the fingers at the metacarpo-phalangeal joints similar to that by which Orientals beat their small drums. This movement may be chiefly in the thumb and forefinger, which may move as in the act of rolling a small object between their tips . . . Usually the head is free from tremor except such as may be communicated to it from the distant oscillation. It does not, however, always escape, as some [e.g., Charcot] have asserted . . . The great characteristic of the tremor of paralysis agitans is, as Parkinson pointed out, that it continues during rest. The hands go on moving when they are resting on the patient's knee, and the legs when he is sitting. A voluntary movement may stop the tremor for a few seconds, sometimes for many, but it recommences and accompanies the movement . . . The loss of power varies much in degree. At first slight, it gradually increases, and is usually greatest in the part in which the tremor developed first and most. The patient may ultimately be unable even to move the index of the dynamometer, or to rise from his seat. But the paralysis is never absolute, – some power always persists. Voluntary movement is not only feeble; it is also slow . . . This seems to be, in part at least, the result of muscular rigidity, which causes a resistance to passive movement. Another effect of the rigidity is to impress certain characteristic postures on the limbs. These are determined by the fact that the rigidity preponderates in certain muscles, chiefly the flexors. The arms are flexed at the elbow-joints, sometimes slightly, sometimes almost at a right angle. The wrists are usually slightly extended. The position of the fingers varies . . . often they are flexed at the metacarpo-phalangeal joints and extended at the others, from preponderant contraction of the interossei . . . (Gowers, 1888, pp. 591–597)

Pathology

In 1893, Blocq and Marinescu reported a 38-year-old woman with hemiparetic parkinonism who was found at autopsy to have a tuberculoma of the right cerebral peduncle that had destroyed the substantia nigra (Blocq and Marinescu, 1893).Brissaud (1895) relied heavily on this case when suggesting that the substantia nigra might be the site of the lesion in Parkinson's disease. In 1912 and 1913, Freiderich (or Fritz or later Frederic) Lewy (later spelled Lewey; 1885–1950) described serpentine or elongated eosinophilic intracytoplasmic *Kugeln* (i.e., "balls") in the dorsal motor nucleus of the vagus nerve and in the substantia innominata of patients with Parkinson's disease (Lewy, 1913; Sweeney et al., 1997; Schiller, 2000; Holdorff, 2002).

In 1919, Trétiakoff first described the presence of these *corps de Lewy* (i.e., "Lewy bodies"), as he referred to them, in the substantia nigra, and proposed that they represented a pathology specific to Parkinson's disease (Trétiakoff, 1919, 1921). Trétiakoff studied the substantia nigra in nine cases of Parkinson's disease, one case of hemiparkinsonism, and three cases of postencephalitic parkinsonism, and found pathologic changes (i.e., depigmentation, neuronal loss, and gliosis) in the substantia nigra in all of them. Subsequently some investigators confirmed nigral pathology in Parkinson's disease, while the Vogts and other authorities instead emphasized pathological changes in the striatum (Vogt and Vogt, 1920). In 1938, Hassler found that some cell groups within the zona compacta of the substantia nigra were severely affected (Hassler, 1938). In 1953, Greenfield and Bosanquet at the National Hospital, Queen Square, London, provided the most complete pathologic analysis of Parkinson's disease, confirmed the selective loss of the ventrolateral cell groups within the zona compacta of the substantia nigra, and emphasized the nigral lesion and the Lewy body as features of Parkinson's disease (Greenfield and Bosanquet, 1953; Goetz et al., 2001b).

Empiric pharmacotherapy with anticholinergic alkaloids

Belladona alkaloids were empirically identified as helpful in Parkinson's disease in the latter half of the 19th century. Charcot noted that the anticholinergic alkaloid hyoscyamine (the levorotatory form of atropine) was modestly beneficial for the tremor of Parkinson's

disease, as reported in the doctoral thesis of his German student Ordenstein in 1867 (Foley, 2003). In 1887, Wilhelm Erb successfully introduced scopolamine (initially somewhat confusingly called "hyoscine") (Foley, 2003). Similar preparations were used for generations with at best modest success. Synthetic centrally-acting anticholinergic medications were introduced in the 1950s and were soon adopted because they were associated with fewer systemic side effects (Corbin, 1949; Dorshay and Constable, 1949).

Surgical treatment

Because of the inadequacies of available pharmacotherapies, various neurosurgical approaches were also tried to address Parkinson's disease and other movement disorders, beginning very crudely at the end of the 19th century and expanding into a more modern approach in the 1930s through the 1960s. Initially neurosurgeons focused on lesioning the corticospinal pathways, but such efforts merely traded tremor and bradykinesia for paralysis.

Beginning around 1939, Meyers examined the effects of lesions in the caudate nucleus, globus pallidus, and ansa lenticularis, demonstrating that parkinsonian tremor and rigidity could be improved surgically without impairing consciousness or producing weakness or spasticity, although the surgical morbidity and morbidity were prohibitively high (Meyers, 1940). Stereotactic techniques were introduced into human neurosurgery in 1947 (Spiegel et al., 1947), and beginning in the 1950s stereotactic lesions to treat the symptoms of Parkinson's disease were made variously in the ventrolateral thalamus, globus pallidus, and the emerging ansa lenticular fibers, although by the early 1960s most surgeons were lesioning only the thalamus (Gildenberg, 1998). However, by the end of the 1960s, neurosurgical approaches to the treatment of Parkinson's disease were suddenly eclipsed and largely abandoned with the general availability of L-DOPA.

With the general availability of computed tomography in the 1980s, and with growing recognition of the limitations of medical treatments, earlier stereotactic neurosurgical ablation procedures were revisited and improved, particularly stereotactic pallidotomy (Laitinen et al., 1992a, b; Gildenberg, 1998; Speelman and Bosch, 1998).

Since the late 1980s, an important role of the subthalamic nucleus in Parkinson's disease has been identified, allowing targeted therapies that modulate subthalamic nucleus activity to be effectively used for Parkinson's disease (Smith and Parent, 1988; Guridi and Obeso, 2001; Hamani et al., 2003; Haméleers et al., 2006); initial beneficial results in animal models (Bergman et al., 1990; Aziz et al., 1991; Benazzous et al., 1993) were subsequently confirmed in humans with Parkinson's disease (Limousin et al., 1995, 1998; Krack et al., 2003).

In 1987, Alim Louis Benabid, Pierre Pollak, and colleagues at the University of Grenoble in France pioneered the use of non-destructive and reversible high-frequency electrical stimulation of deep brain nuclei with implanted electrodes (Benabid et al., 1987). This deep brain stimulation approach was applied first to the Vim (ventralis intermedius) nucleus of the thalamus and was found to be effective in controlling disabling tremor (Benabid et al., 1991, 1994; Siegfried, 1994; Siegfried and Lippitz, 1994). Deep brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus has fewer reported adverse effects that ablative procedures, and has been found to be more globally effective than thalamotomy or thalamic stimulation in addressing rigidity, tremor, bradykinesia, motor fluctuations, and dyskinesias in patients with Parkinson's disease; nevertheless, deep brain stimulation cannot prevent the progression of Parkinson's disease, nor does it alleviate associated problems with cognition, speech, or balance.

Neurochemistry and the L-DOPA story

Important biochemical developments began in the 1950s that paved the way for rational therapeutics, including the recognition by Montagu (1957) that dopamine is present in the mammalian brain, the report by Arvid Carlsson and colleagues that racemic DOPA (D,L 3-4 dihydroxyphenylalanine), a dopamine precursor, antagonizes the sedative and bradykinetic effects of reserpine in rabbits and mice (Carlsson et al., 1957), and the demonstration that dopamine is localized primarily within the neostriaum (Bertler and Rosenberg, 1959; Carlsson, 1959; Sano et al., 1959; Foley, 2000). Based on the distribution of dopamine in the brain with concentration in the basal ganglia, the production of parkinsonism and brain catecholamine depletion by reserpine, and restoration of normal function by administration of the dopamine precursor DOPA, Carlsson and colleagues proposed that depletion of dopamine will induce parkinsonism and that treatment with L-DOPA will reverse the syndrome by restoring brain dopamine levels (Carlsson et al., 1959; Carlsson, 2003), work for which Carlsson was later awarded the Nobel Prize in Physiology or Medicine in 2000 (Carlsson, 2003). In 1960, Degwitz and colleagues demonstrated that L-DOPA reversed the sedation of reserpine in humans (Degwitz et al., 1960), confirming Carlsson and colleagues' earlier report in animals. In 1961, Ehringer and Hornykiewicz documented the dramatic loss of dopamine in the striatum of brains

from patients dying with post-encephalitic and idiopathic Parkinson's disease (Ehringer and Hornykiewicz, 1961).

In 1962, following this series of neurochemical discoveries and especially with the understanding that dopamine is depleted in the striatum, Birkmayer and Hornykiewicz (1962) reported dramatic reduction of akinesia and improvement in speech and gait in Parkinson's disease patients using intravenous L-DOPA, and Barbeau et al. (1962) reported similar results with small oral doses of racemic DOPA. Birkmayer and Hornykiewicz's description of what they called the "L-DOPA-Effekt" still vividly conveys the dramatic improvement observed:

> *The effect of a single i.v. administration of L-DOPA was, in short, a complete abolition or substantial relief of akinesia. Bed-ridden patients who were unable to sit up; patients who could not stand up when seated; and patients who when standing could not start walking, performed after L-DOPA all these activities with ease. They walked around with normal associated movements and they even could run and jump. The voiceless, aphonic speech, blurred by pallilalia and unclear articulation, became forceful and clear as in a normal person. For short periods of time the patients were able to perform motor activities which could not be prompted to any comparable degree by any other drug. (Birkmayer and Hornykiewicz, 1962; Horniekiewicz, 2001, p. 859)*

Unfortunately, subsequent reports of the efficacy of DOPA were at best inconsistent—a small placebo-controlled trial demonstrated no convincing benefit for L-DOPA treatment (McGreer and Zeldowitz, 1964), and a double-blind trial found no significant difference between L-DOPA and placebo (Fehling, 1966) – so in short order the initially reported beneficial effects of DOPA were largely discounted. With hindsight these negative results reflected a combination of small doses of medication and problems of study design (including very small sample sizes and inadequate controls).

Cotzias and colleagues nevertheless persevered with DOPA as a treatment for Parkinson's disease and, in 1967, reported the successful use of high-dose oral racemic DOPA in an open trial (Cotzias et al., 1967). Using doses from 4 to 16 grams of racemic DOPA daily, Cotzias et al. (1967, p. 375) noted "complete sustained disappearance or marked amelioration" of symptoms in half of their 16 patients, with a clear dose-response relationship, and with manageable side effects (transient nausea, faintness, occasional vomiting, and dyskinesias). Cotzias et al. (1969) later showed that the benefits of L-DOPA are sustainable for extended periods, and side effects could be managed or prevented by slow dose escalation or with co-administration of a peripheral dopa-decarboxylase inhibitor. These findings were later confirmed in double-blind trials with L-DOPA alone (Yahr et al., 1969) or in combination with a dopa-decarboxylase inhibitor (Calne et al., 1971). In 1975, Lloyd and colleagues showed that dopamine levels in the striatum are an order of magnitude higher in the striatum of Parkinson's disease patients treated with L-DOPA than in untreated patients, are greater in good responders than poor responders, and are related to the time before death of the last dose (Lloyd et al., 1975). Subsequent progress has included development of long-acting levodopa preparations and inhibitors of catechol-O-methyltransferase (COMT), the enzyme responsible for most of the peripheral degradation of L-DOPA.

Beginning in the mid-1960s, a previously unsuspected nigrostriatal dopaminergic neuronal projection was demonstrated first in the rat (Anden et al., 1964, 1965), and shortly thereafter unilateral lesions of the substantia nigra were shown to deplete striatal dopamine ipsilaterally in monkeys (Poirer and Sourkes, 1965; Goldstein et al., 1966). The nigrostriatal projection had escaped previous notice because the fibers were too small and thinly myelinated to be shown by classic histologic techniques. Degeneration of neurons in the pars compacta of the substantia nigra in Parkinson's disease was then understood to cause depletion of striatal dopamine as a result of degeneration of the nigrostriatal projections, neatly explaining various pathologic and neurochemical observations, and finally settling the lingering controversy of whether it is the substantia nigra or the striatum that is affected in Parkinson's disease (they *both* were!).

Dopamine agonists

Shortly after the advent of L-DOPA therapy for Parkinson's disease, it became apparent that chronic therapy was associated with development of motor fluctuations, dyskinesias, and loss of efficacy in some patients. These changes were thought to be due in part to loss of the presynaptic pigmented neurons in the substantia nigra, which normally function to convert L-DOPA to dopamine, which is then transported and released onto post-synaptic receptors in the striatum. It was hoped that the limitations of L-DOPA might be overcome by development of dopamine agonists that could directly stimulate striatal neurons.

Apomorphine was the first dopamine agonist, synthesized from morphine in the 19th century. In 1951, Schwab and colleagues noted that apomorphine injection could cause a marked temporary improvement

in Parkinson's disease patients (Schwab et al., 1951), and in 1965 Ernst recognized the structural similarity of apomorphine and dopamine (Ernst, 1965). In 1970, in light of the side effects increasingly recognized with L-DOPA, Cotzias and colleagues re-evaluated apomorphine in Parkinson's disease and reported significant anti-parkinsonian effects (Cotzias et al., 1970), but toxicity and the need for parenteral administration limited its usefulness. Later attempts with oral apomorphine (Cotzias et al., 1976) were also abandoned, because of the development of dose-dependent azotemia with long-term therapy. Only recently has apomorphine been revisited in the treatment of Parkinson's disease.

Most subsequent dopamine agonists were synthetic derivatives of ergot, the first of which was bromocriptine. In the late 1960s, bromocriptine was originally tested in humans as a potential prolactin inhibitor. Subsequently, dopamine was found to be an inhibitor of prolactin release, and bromocriptine was found to have dopaminergic properties in rats (Corrodi et al., 1973). In 1974, Calne and colleagues reported the beneficial effects of bromocriptine in Parkinson's disease in a double-blind trial (Calne et al., 1974). Patients with severe dyskinesia or motor fluctuations benefited from adding bromocriptine while reducing the dose of L-DOPA.

Kebabian and Calne (1979) later used the pharmacologic properties of bromocriptine to propose that there are at least two kinds of dopamine receptors, termed D1 and D2, and that parkinsonism results at least in part from inadequate transmission at D2 receptors. These two types of receptors are now known to exert their biological actions by coupling to and activating different molecular switches called G-protein complexes, so named because they react with GTP in order to transduce extracellular "first messenger" signals identified by a specific extracellular receptor to amplified intracellular "second messenger" signals (Gilman, 1997; Rodbell, 1997): specifically extracellular dopamine (the first messenger) acts on D1 receptors (the discriminator) through a G-protein complex (the transducer) to *activate* adenylyl cyclase (the amplifier) and increase production of intracellular cAMP (the second messenger), whereas extracellular dopamine acts on D2 receptors through a G-protein complex to *inhibit* adenylyl cyclase and decrease cAMP production.

Five types of dopamine receptors are now recognized: D1 and D5 receptors are members of the D1-like family of receptors, whereas D2, D3, and D4 receptors are members of the D2-like family. These receptor types have overlapping but distinct localizations within the central nervous system, but the D1 and D2 receptors are the predominant receptor types within the nigrostriatal system, and both are highly expressed in the striatum (Lahti et al., 1995). The human genes for all of these receptor types have been cloned.

Genetics and molecular biology

Throughout much of the 20th century, Parkinson's disease was suspected to be a "non-genetic" disorder, in part because extended pedigrees of familial Parkinson's disease were not available, in part because exogenous factors (e.g., neuroleptic medications and later MPTP) were identified that produced forms of parkinsonism clinically similar to that of Parkinson's disease, and in part on the basis of twin studies that were interpreted as excluding a significant genetic etiology for Parkinson's disease. However, by 1990 a re-evaluation, including a meta-analysis of twin studies, suggested that genetic factors could be important to the pathogenesis of at least some forms of Parkinson's disease (Johnson et al., 1990).

In 1990, Lawrence Golbe, Roger Duvoisin, and colleagues reported an autosomal dominant form of Parkinson's disease in two large kindreds originating in the village of Contursi in the Salerno province of Italy (Golbe et al., 1990); the disease in this kindred was characterized by often early onset and rapid progression, a lower frequency of tremor, responsiveness to L-DOPA, and pathologic findings typical of Parkinson's disease with Lewy bodies. In 1996, Mihael Polymeropoulos and colleagues at the US National Institutes of Health established linkage of Parkinson's disease in the Contursi kindred to chromosome 4q21-23 (Polymeropoulos et al., 1996), an area to which the alpha-synuclein gene had been mapped (Chen et al., 1995). Shortly thereafter, Polymeropoulos et al. (1997) showed that disease in this family and several Greek kindreds resulted from a mutation in the alpha-synuclein gene (PARK1). Alpha-synuclein—a small protein only 144 amino acids long—had been recognized in human brains in the mid 1990s (Ueda et al., 1993; Campion et al., 1995), and was known to be concentrated in presynaptic nerve terminals (Jakes et al., 1994).

Following recognition that familial Parkinson's disease could result from mutations in the alpha-synuclein gene, synuclein was rapidly shown to be the major fibrillar component of Lewy bodies and Lewy neuritis in both sporadic Parkinson's disease and dementia with Lewy bodies (Spillantini et al., 1997; Giasson et al., 2000). Subsequent studies have shown that mutated alpha-synuclein does not fold properly, resists proteasome degradation, and tends to form insoluble aggregates. Although mutations in the alpha-synuclein gene are very rare and represent less than 1% of the worldwide burden of Parkinson's disease, these developments triggered intense interest and rapid progress in understanding the pathogenesis of Parkinson's disease.

In 1998, only a year after the discovery of the alpha-synuclein mutation, Japanese researches reported mutations in a separate gene (PARK2) on chromosome

6q25.2-q27, whose protein product was designated "parkin" (Kitada et al., 1998), in Japanese families with early-onset parkinsonism segregating as an autosomal recessive trait (Matsumine et al., 1997). Other previously reported families with juvenile-onset parkinsonism (Ishikawa and Miyatake, 1995), were also then reported to have mutations in the PARK2 gene (Hayashi et al., 2000). Patients affected by mutations in PARK2 were found to have a wide range in age of onset, with slow progression, generally symmetric involvement, dystonia at onset, hyperreflexia, a good response to L-DOPA, and dyskinesias during treatment (Lucking et al., 2000; Kann et al., 2002; Pramstaller et al., 2005). Some patients were later found to present at an older age with clinical features indistinguishable from idiopathic Parkinson's disease (Pramstaller et al., 2005). Although initially reported to lack Lewy bodies, subsequent studies have shown that alpha-synuclein positive Lewy bodies can be present in the substantia nigra and locus ceruleus of patients dying with parkin-associated parkinsonism (Pramstaller et al., 2005). Mutations in the PARK2 gene are now the most frequent known genetic cause of parkinsonism.

In 1998, Kitada and colleagues suggested that parkin may interfere with ubiquitin-mediated protein degradation and cause the death of nigral neurons (Kitada et al., 1998).

The ubiquitin-proteasome proteolytic system had been elucidated, beginning in the late 1970s, largely through the efforts of Aaron Ciechanover and Avram Hershko of Technion-Israel Institute of Technology and Irwin Rose of the University of California-Irvine, work for which the three received the 2004 Nobel Prize in chemistry (Ciechanover, 2005; Hershko, 2005; Rose, 2005). In this "garbage disposal" system, a very small (76 amino acids long), highly evolutionarily conserved protein called ubiquitin is activated by the ubiquitin-activating enzyme (E1), then transferred to a ubiquitin-carrier protein called ubiquitin-conjugating enzyme (E2), which transfers the activated ubiquitin to a ubiquitin-protein ligase (E3), which in turn attaches the ubiquitin to a protein to be degraded. Repetitive conjugation of ubiquitin moieties produces a poly-ubiquitin chain, a tagging process dramatically termed "the kiss of death," which marks the protein for recognition by the proteasome, a molecular complex that digests proteins into short peptides and finally into amino acids that are recycled for further protein synthesis.

In 2000, Shimura and colleagues reported that parkin is indeed involved in protein degradation as an ubiquitin-protein ligase (E3), a function lost in autosomal recessive juvenile-onset parkinsonism (Shimura et al., 2000). The following year, Shimura et al. (2001) reported that a particular form of alpha-synuclein is a protein substrate for parkin, an important finding linking these two Parkinson's disease genes by the ubiquitin-proteasome proteolytic system. Mutant parkin fails to attach ubiquitin to misfolded proteins, which then accumulate and cause cell death. Subsequent identification of other genetic forms of parkinsonism have reinforced the importance of this pathway in the pathogenesis of Parkinson's disease.

ENCEPHALITIS LETHARGICA: VON ECONOMO'S ENCEPHALITIS

In 1917 and 1918, Constantin von Economo (1876–1931) described the clinical and pathological findings of 13 cases with an unusual encephalitic condition that had occurred during the winter of 1916–1917, often with profound lethargy or stupor (von Economo, 1917, 1918): Au15

> *It seems strange when sleep appears as a symptom of an illness. "Sleeping sickness" where the phenomenon of people falling asleep while eating or working was first described in two cases in our clinic in Vienna in 1916. Usually headache, nausea, and fever were followed, often the next day, by sleeping, frequently in a most uncomfortable position. One can wake them, but in severe cases, coma can rapidly lead to death. Malfunction of eye muscles, especially oculomotor dysfunction, and ptosis, was common. (von Economo, 1918/2001, as translated by Dickman, 2001, p. 1696)* Au16

He named the condition "encephalitis lethargic" and identified three overlapping clinical subsets of the acute illness: somnolent-ophthalmoplegic, hyperkinetic, and amyostatic-akinetic. He documented the highly variable acute manifestations, which included sleep disturbances, lethargy, neuropsychiatric disorders (e.g., catatonia, obsessive-compulsive disorder), oculomotor abnormalities, and various associated hypo- and hyper-kinetic movement disorders, including rigidity, akinesia, generalized and hemi-chorea, myoclonus, dystonia, opisthotonus, akathisia, and variably superimposed oculogyric crises. Von Economo subsequently studied the evolution, natural history, and sequelae of encephalitis lethargica over several years. He noted that post-encephalitic parkinsonism could develop early with the amyostatic form, or up to several years after apparently complete recovery from other forms of acute encephalitis lethargica (von Economo, 1931). In addition, he emphasized the neuropathological features, including microscopic inflammatory changes, particularly in the grey matter of the midbrain tegmentum and the basal ganglia.

Encephalitis lethargica became a global pandemic affecting more than one million people between

approximately 1916 and 1925. As the epidemic of acute encephalitis waned in the mid-1920s, numerous cases of post-encephalitic parkinsonism were identified, typically with bradyphrenia, generalized rigidity, bent posture, and unsteady gait, but usually without a pill-rolling tremor. Post-encephalitic parkinsonism cases were identified even into the 1930s, but by that time the nosologic distinction between idiopathic Parkinson's disease and post-encephalitic parkinsonism had become confused. There have been no further epidemics of encephalitis lethargica, although rare sporadic cases continue to be reported.

The etiology of encephalitis lethargica remains unknown. Although encephalitis lethargica and influenza both occurred in epidemics between 1918 and 1923, the timing and extent of the outbreaks were dissimilar (Reid et al., 2001). Furthermore, recent studies failed to identify influenza RNA in archived encephalitis lethargica brain specimens, and suggested that the 1918 influenza virus was genetically incapable of neurotropic disease (McCall et al., 2001; Reid et al., 2001). Despite considerable effort, no neurotropic virus has yet been implicated, and some have suggested that encephalitis lethargica was a post-infectious autoimmune disorder similar to Sydenham's chorea (Dale et al., 2003). Au17

DRUG-INDUCED PARKINSONISM

Neuroleptic-induced parkinsonism and associated movement disorders

In the 1950s and 1960s, shortly after the introduction of chlorpromazine and other related tranquilizers ("neuroleptics") (Delay et al., 1952; Hamon et al., 1952; Lehman and Hanrahan, 1954), a variety of immediate and late (tardive) drug effects were recognized that included various abnormal involuntary movements, including akathisia, tremor, akinesia, parkinsonism, choreoathetosis, dystonia, and dyskinesias (Hall et al., 1956; Schonecker, 1957; Ayd, 1961; Faurbye et al., 1964). Acute dystonia, akathisia, and drug-induced parkinsonism – with prominent bradykinesia, and also rigidity, postural instability, and tremor – were recognized in as many as 10–20% of patients (Freyhan, 1957; Ayd, 1961). Akathisia – a term coined by Haškovec (1901) to refer to individuals unable to remain seated as a result of hysteria or neurasthenia – was adopted to label features of motor restlessness occurring as a side effect of antipsychotic drugs (Steck, 1954; Kruse, 1960; Ayd, 1961); although early descriptions described motor restlessness, later accounts emphasized a subjective internal discomfort and a need to move to relieve this uncomfortable sensation (Chien et al., 1967; Van Putten, 1975).

Tardive dyskinesia – a term introduced by Faurbye and colleagues in 1964 – was recognized as an involuntary, repetitive, and choreic or stereotypic movement disorder that persisted even after the offending drug was stopped (Schonecker, 1957; Uhrbrand and Faurbye, 1960; Faurbye et al., 1964); most prominent were involuntary patterned buccolingual masticatory movements with lip smacking, puckering, chewing, tongue movements, grimacing, and other facial movements.

MPTP

In 1982, Langston and colleagues identified a group of drug addicts who had developed parkinsonism after mistakenly self-injecting a toxin called MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), a reaction product of the illicit synthesis of a meperidine analogue (Langston et al., 1983; Langston and Palfeman, 1995). Au18 The addicts rapidly developed permanent parkinsonian signs, including tremor, bradykinesia, rigidity, and postural instability. A similar case had been reported in 1979, but the role of MPTP was not clarified at that time, in part because administration of MPTP to rats, rabbits, and guinea pigs failed to produce a motor deficit (Davis et al., 1979).

In 1983, Burns and colleagues demonstrated that MPTP could induce parkinsonism in monkeys (Burns et al., 1983), with stooped posture, tremor, rigidity, and bradykinesia, which were reversed temporarily by administration of L-DOPA. When the brains of these monkeys were examined they were found to have histologic similarity to Parkinson's disease, with destruction of neurons in the pars compacta of the substantia nigra and marked depletion of dopamine in the striatum (Mitchell et al., 1985; Forno et al., 1986). It was soon discovered that MPTP is converted *in vivo* to MPP + (1-methyl-4-phenylpyridium) by monoamine oxidase type B (Markey et al., 1984), a conversion that is necessary (although not sufficient) for manifestation of the toxic effects of MPTP in animals. Pretreatment with monoamine oxidase inhibitors prevented both the accumulation of MPP + and the toxic effects of MPTP (Heikkila et al., 1984; Langston et al., 1984; Markey et al., 1984). The discovery of the selective neurotoxic properties of MPTP established a useful animal model, greatly accelerated basic research, and supported theories that an environmental toxin could contribute to the multifactorial causes of Parkinson's disease.

ATYPICAL PARKINSONISM

In addition to Parkinson's disease, a number of other neurodegenerative conditions have hypokinesia as a major clinical feature. Separation of these conditions

from Parkinson's disease ultimately led to important anatomical and physiological discoveries concerning basal ganglia function (Goetz et al., 2001g).

Wilson's disease

In 1911, British neurologist Kinnier Wilson (1878–1937) of the National Hospital, Queen Square, London, presented a thesis entitled, "Progressive lenticular degeneration: a familial nervous disease associated with cirrhosis of the liver" (Wilson, 1911). Wilson reviewed the clinical and pathologic features of 12 cases, including four he had seen and studied himself, two from the records of the National Hospital, and six previously published. Wilson concluded:

> *Progressive lenticular degeneration may be defined as a disease which occurs apparently only in young people, which is often familial, but not congenital or hereditary; it is essentially and chiefly a disease of the extra-pyramidal motor sysem, and is characterized by involuntary movements, usually of the nature of tremor, dysarthria or anarthria, dysphagia, muscular weakness, spasticity or hypertonicity, and contractures, with progressive emaciation; with these may be associated emotionalism and certain symptoms of a mental nature. It is progressive and, after a longer or shorter period, fatal. Pathologically it is characterized predominantly by bilateral degeneration of the lenticular nucleus, and in addition cirrhosis of the liver is constantly found, the latter morbid condition not giving rise to symptoms during the lifetime of the patient. (Wilson, 1912b, p. 1116)*

Wilson's thesis was awarded a gold medal by the University of Edinburgh in 1911 (Wilson, 1911), and his definitive publication of 213 pages in *Brain* in 1912 occupied the entire issue (Wilson, 1912a). His findings were also published in shorter accounts in several languages (Wilson, 1912b, c, 1914). Though the first to describe the condition in detail, Wilson acknowledged earlier works by Westphal (1883) and Strümpel (1898) on "pseudosclerosis" (a 19th-century label for a clinical condition with tremor resembling that seen in multiple sclerosis but distinguished by the lack of ocular signs), and Gowers on familial "tetanoid chorea" (Gowers, 1888), associated ultimately with cirrhosis of the liver (Gowers, 1906).

The full clinical spectrum of Wilson's disease was not appreciated for many years. Unappreciated by Wilson, in 1902 Bernard Kayser (1869–1954) had described ring-like deposition of greenish pigment in a patient suffering from pseudosclerosis (Kayser, 1902), a finding reinforced by Bruno Fleischer (1874–1965) in 1903, who recognized the ring as a marker for a neuropsychiatric disorder associated with cirrhosis (Fleischer, 1903; Dening and Berrios, 1990). In 1916, Bramwell suggested that Wilson's disease could present with liver pathology (Bramwell, 1916), a finding ultimately confirmed by Uzman et al. (1956). By the early 1960s, it was clear that while other tissues, including kidney and bone, could also be affected (Bearn, 1957), before puberty Wilson's disease generally presents with liver disease, whereas after puberty neurological presentations are typical (Walshe, 1962).

Understanding that Wilson's disease involved deposition of copper in tissues developed over several decades in the early-20th century. In 1913, Rumpel reported excess hepatic copper in a patient dying of Wilson's disease (Rumpel, 1913), and, in 1922, Siemerling and Oloff described the association of corneal pigmentation ("Kayser-Fleischer rings") with sunflower cataracts and noted the similarity of the cataracts to those developing with a copper-containing foreign body in the eye (Siemerling and Oloff, 1922), but unfortunately these findings were apparently overlooked (Walshe, 2006). Later, Vogt (1929), Haurowitz (1930), Glazebrook (1945), and others reported excess copper in the brain or liver of patients dying of Wilson's disease. In 1948, in an influential paper, Cumings (1948) demonstrated excess copper in both the brain and the liver of patients with Wilson's disease. In the late 1940s, Holmberg and Laurell (1947, 1948) purified and characterized a blue copper-containing plasma glycoprotein they called "caeruloplasmin" (from the Latin *caeruleus*, dark blue), which was demonstrated to have reduced plasma concentrations in patients with Wilson's disease in the early 1950s (Bearn and Kunkel, 1952; Scheinberg and Gitlin, 1952).

A genetic basis for Wilson's disease was suggested by Bramwell (1916) and by Hall (1921) (who also coined the term "hepatolenticular degeneration"), but the autosomal recessive mode of transmission was not established unequivocally until 1960 by Bearn (1960). The gene responsible for Wilson's disease was mapped to chromosome 13 in 1985 (Frydman et al., 1985), and in the early 1990s Wilson's disease was found to be due to mutations in the *ATP7B* gene on the long arm of chromosome 13 (13q14.3), which codes for a 140-kD copper-transporting P-type ATPase (Bull et al., 1993; Petrukhin et al., 1993; Tanzi et al., 1993).

The Wilson's disease gene has close homology with the Menke's disease gene *ATP7A*, and is distinct from the loci for ceruloplasmin on chromosome 3 and the metallothionein cluster on chromosome 16. Loss of function of the Wilson's disease gene product results in excessive intracellular deposition of copper in hepatocytes, hepatic

cellular necrosis, and leakage of copper into the plasma, from whence it is transported to and deposited in other tissues, including brain.

In 1948, Cumings suggested that British anti-lewisite (BAL) might be of value in removing copper from the body and thereby in improving the prognosis of Wilson's disease (Cumings, 1948). BAL is a chelating agent designed during World War II as an antidote to the arsenical vesicant gas "lewisite," which had been developed during World War I (Vilensky et al., 2002; Walshe, 2006). By 1951, Cumings (1951) and Denny Brown and Porter (1951) reported clinical benefit from BAL in patients with Wilson's disease, even though the treatment required repeated painful intramuscular injections and was highly toxic.

Several therapies have superceded BAL in the treatment of Wilson's disease. In 1956, Walshe suggested that penicillamine could be an effective orally administered chelator for copper (Walshe, 1956), a suggestion confirmed by 1960 (Scheinberg and Sternlieb, 1960; Walshe, 1960). Penicillamine rapidly replaced BAL, but within a decade penicillamine was also found to produce several significant immunologically-induced side effects (Walshe, 1968), which led to continued efforts to find safer alternatives (Walshe, 1982, 2003, 2006). In 1961, Schouwink demonstrated that orally-administered zinc could significantly reduce the absorption of copper from the gut (Schouwink, 1961), a finding which was unpublished and initially largely unknown.

Zinc was later shown to be helpful in the long-term management of Wilson's disease patients (Hoogenraad et al., 1979, 1987; Brewer et al., 1983, 1998), although it may not be adequate for initial therapy (Walshe, 2006). Zinc induces the synthesis of intestinal metallothionein, a metal-binding protein in the intestinal mucosa, which effectively binds copper in a complex that cannot be systemically absorbed, and is ultimately excreted in the stool with desquamated intestinal epithelial cells. In 1982, Walshe introduced triethylene tetramine (Trientine) as a substitute chelator for patients intolerant of penicillamine (Walshe, 1982); triethylene tetramine is much safer than penicillamine and does not exhibit the frequent hypersensitivity reactions seen with penicillamine. In the 1970s and 1980s, liver transplantation was introduced and increasingly used for patients with hepatic failure (Groth et al., 1973; Sokol et al., 1985; Rothfus et al., 1988).

Multisystem atrophy (olivo-ponto-cerebellar degeneration)

For decades, the overlapping clinical features and pathologies in individual cases with sporadic olivopontocerebellar atrophy, striatonigral degeneration, and Shy-Drager syndrome have been sources of confusion, burgeoning terminology, and competing nosologies. These disorders are now recognized as forms of multiple system atrophy, an adult-onset sporatic neurodegenerative disease characterized clinically by varying degrees of parkinsonism, cerebellar ataxia, pyramidal signs, and autonomic dysfunction, and characterized pathologically by degeneration in the substantia nigra, putamen, olivary nucleus, pontine nuclei, and cerebellum.

The term "olivo-ponto-cerebellar atrophy" was coined by French neurologists Joseph Jules Dejerine (1849–1917) and André Thomas in 1900, in their report of a 53-year-old patient who developed progressive cerebellar ataxia, masked face, dysarthria, hypertonia, hyperreflexia, and urinary incontinence (Dejerine and Thomas, 1900, 1900/1977). Autopsy at age 55 showed severe degeneration of the basis pontis, inferior olivary nuclei, middle cerebellar peduncles, and less so the inferior cerebellar peduncles, with loss of Purkinje cells particularly in the cerebellar hemispheres.

In 1933, Scherer gave the first clear description of striatonigral degeneration in clinicopathologic studies of four cases, two of whom had severe parkinsonism masking cerebellar signs, and two of whom had predominant cerebellar ataxia (Scherer, 1933a, 1933b; Berciano et al., 1999); in these cases, the severity of parkinsonism correlated with degenerative changes in the substantia nigra and striatum, rather than with the degree of cerebellar degeneration, as had been previously thought (Berciano et al., 1999). In 1964, American neurologist Raymond Adams and Belgian neuropathologist Ludo van Bogaert (1897–1989) introduced the term "striatonigral degeneration" for a sporadic neurodegenerative disorder characterized by parkinsonism plus other neurological findings (e.g., cerebellar dysfunction, choreoathetosis, dystonia, pyramidal, or pseudobulbar signs, etc.) (Adams and van Bogaert, 1964).

In 1960, Shy and Drager described a primary neurodegenerative condition in which autonomic failure occurred in association with other neurological manifestations:

> *The full syndrome comprises the following features: orthostatic hypotension, urinary and rectal incontinence, loss of sweating, iris atrophy, external ocular palsies, rigidity, tremor, loss of associated movements, impotence, the findings of an atonic bladder and loss of the rectal sphincter tone, fasciculations, wasting of distal muscles, evidence of a neuropathic lesion in the electromyogram that suggests involvement of the anterior horn cells, and the finding of a neuropathic lesion in the muscle biopsy. The age of onset is usually in the fifth to the seventh*

decade of life. The disorder appears to be more frequent in the male. Any of the above signs or symptoms may be the presenting ones, and the hypotension may be a relatively late finding. The duration of the illness . . . shows the disorder to be of relatively slow progression (Shy and Drager, 1960, p. 511–512).

Variability in presentation, with components of autonomic, extrapyramidal, and cerebellar features led Graham and Oppenheimer to introduce the term "multiple system atrophy," which was intended to "cover this collection of overlapping progressive, presenile multisystem degenerations" (Graham and Oppenheimer, 1969):

There is a group of progressive neurological conditions, most often arising during middle life, with symptoms and signs of lesions affecting several central nervous structures, more or less symmetrically. These cases are usually sporadic, but sometimes familial. The pathological findings are of cell loss and gliosis in a selection of well-defined structures (including both anatomical "nuclei" such as the putamen, and extensive cellular layers, such as the Purkinje cells of the cerebellum). In different cases, different selections of structures are affected. Some combinations of lesions are commoner than others: thus, familiar names, such as OPCA, have come into use. Nevertheless combinations are encountered which do not correspond with any familiar syndrome. In such cases, unnecessary confusion is caused by inventing new names, of the type "pallido-subthalamico-vestibular atrophy," for unusual syndromes . . . What is needed is a general term to cover this collection of overlapping progressive presenile multisystem degenerations. As the causes of this group of conditions are still unknown, such a general term would merely be a temporary practical convenience . . . What we wish to avoid is the multiplication of names for "disease entities" which in fact are merely the expressions of neuronal atrophy in a variety of overlapping combinations. We therefore propose to use the term multiple system atrophy to cover the whole group. Among the structures at risk in this disease we must include the preganglionic cells of the autonomic system. These may be attacked apparently in isolation . . . or in combination with other structures . . . (Graham and Oppenheimer, 1969, pp. 32–33)

In 1989, Papp and colleagues reported that oligodendroglia in multiple system atrophy contain argyrophilic, tubulofilamentous inclusions in the cytoplasm, which were called "glial cytoplasmic inclusions" (Papp et al., 1989). Glial cytoplasmic inclusions are not membrane bound and are composed ultrastructurally of filaments and granular material. This important discovery helped to define multiple system atrophy as a clinicopathological entity and drew attention to the prominent role of the oligodendrocyte in the pathogenesis of the disorder (Papp and Lantos, 1992; Lantos, 1998). Glial cytoplasmic inclusions were subsequently shown to be highly immunoreactive for ubiquitin and alpha-synuclein (Arima et al., 1998; Spillantini et al., 1998; Tu et al., 1998; Wakabayashi et al., 1998). The recognition that multiple system atrophy has inclusions composed of alpha-synuclein provided an unexpected molecular link between multiple system atrophy and Lewy body diseases, such as Parkinson's disease and Lewy body dementia. Collectively these disorders are now considered "synucleinopathies."

Progressive supranuclear palsy

"Progressive supranuclear palsy" is the descriptive name applied by neurologist J. Clifford Richardson (1909–1986) for an unusual condition he first encountered in the 1950s and later reported in detail in 1963 and 1964 with neurologist John C. Steele (1934–) and neuropathologist Jerzy Olszewski (1913–1964) (Richardson et al., 1963; Olszewski et al., 1964; Steele et al., 1964; Steele, 1994).

As reported by Steele and colleagues, their patients had

. . . an unusual progressive neurological disorder with ocular, motor, and mental features. The clinical picture was characterized by supranuclear ophthalmoplegia, particularly of downward gaze, pseudobulbar palsy, dysarthria, dystonic rigidity of the neck and upper trunk, and dementia . . . Commonly the disease started in the sixth decade and led to death within several years . . . Pathological investigation showed the presence of cell loss, gliosis, neurofibrillary tangles, granulovacuolar degeneration and demyelination in various regions of the basal ganglia, brain stem, and cerebellum . . . (Steele et al., 1964, p. 357)

The original appellation "heterogeneous system degeneration" (Richardson et al., 1963; Olszewski et al., 1964) was soon abandoned because the authors were not certain that it was a primary degenerative disease (Steele, 1994). The eponymic designation of "Steele-Richardson-Olszewski syndrome" was first used by Andre Barbeau in 1965 (Barbeau, 1965).

The initial speculation that progressive supranuclear palsy might be a post-infectious disease (based

on similarities with postencephalitic parkinsonism) (Steele et al., 1964) has been discounted (Kristensen, 1985). Likely cases of progressive supranuclear palsy have been retrospectively identified from the era before the occurrence of encephalitis lethargica (Brusa et al., 2004), although one early suspected case (Steele, 1994), reported in 1904 by Posey and in 1905 by Spiller, has since been shown to have had a midbrain neoplasm (Posey, 1904; Spiller, 1905; Siderowf et al., 1998). Attempts to transmit progressive supra- Au19 nuclear to animals by intracerebral inoculation have been unsuccessful (Steele, 1972).

Progressive supranuclear palsy is characterized pathologically by predominant brain stem, diencephalon, and basal ganglia pathology, with neuronal loss, gliosis, and the presence of globose neurofibrillary tangles (i.e., filamentous neuronal inclusions composed of dense aggregates of neurofilaments and associated proteins). The neurofibrillary tangles are composed Au20 predominantly of 15-nm straight filaments (Tomonoga, 1977), which have strong immunoreactivity to the microtubular associated protein tau. The recognition that progressive supranuclear palsy has inclusions composed of tau provided a molecular link between various neurodegenerative disorders with predominant parkinsonism (including corticobasal ganglionic degeneration and frontotemporal dementia and parkinsonism linked to chromosome 17), which are collectively considered among the "tauopathies."

Cortico-basal ganglionic degeneration

In 1967, Rabeiz and colleagues described three cases of what is now called cortico-basal ganglionic degeneration under the appellation of "corticodentatonigral degeneration with neuronal achromasia" – a label which summarized the distribution of neuropathological changes and highlighted one of the microscopic features (Rabeiz et al., 1967). The patients demonstrated progressive neurological deficits in middle age, with manifestations including unilateral or markedly asymmetric motor impairment, with dystonic arm postures, tremulous or jerking movements, dyspraxia, and gait dysfunction. What were later labeled as "alien limb" phenomena were recognized in the initial cases, including "uncontrollable elevation and abduction of the limbs that came on during attempted motor activity. Thus, when the patient attempted to walk, the leg hovered in the air instead of being placed on the ground, causing the patient to fall. Alternatively, when the unaffected right arm was being used in purposive activity, the left arm rose up in its way, greatly hampering the right arm's performance" (Rebeiz et al., 1967, p. 23). Further cases were subsequently described under various labels including corticobasal degeneration (Gibb et al., 1989) and cortico-basal ganglionic degeneration (Riley et al., 1990).

It is now recognized that a variety of movement disorders occur commonly in association with cortico-basal ganglionic degeneration, including parkinsonism (with akinesia, rigidity, postural instability, and falls), limb dystonia, action tremor, and focal reflex myoclonus. Other common clinical features include apraxia, alien limb phenomenon, eyelid and oculomotor abnormalities, dysarthria, and dysphagia, so-called "frontal lobe reflexes" (e.g., grasp), pyramidal tract signs, and cortical sensory loss.

Pathologically, there is asymmetrical cortical atrophy most pronounced in the medial fronto-temporal cortex contralateral to the side of the body most severely affected, with associated marked neuronal loss, extensive fibrillary gliosis, and achromatic ballooned neurons (Rebeiz et al., 1967, 1968; Gibb et al., 1989; Riley et al., Au21 1990). Many surviving neurons are "ballooned" with cytoplasmic swelling, displacement of the nucleus to an eccentric location, cytoplasmic vacuoles of varying sizes, and loss of typical staining of the cytoplasm ("neuronal achromasia"). The substantia nigra pars compacta shows a marked loss of neurons with pigmentary incontinence, melanin-containing macrophages, marked gliosis, and occasional ballooned neurons. Ultrastructurally the ballooned neurons are filled with cytoplasmic aggregates of 10-nm filaments that stain immunohistochemically with phosphorylated neurofilament proteins. Although Rebeitz et al. (1968) emphasized involvement Au22 of cerebellar nuclei, these nuclei have not been prominently affected in subsequent cases.

CHOREOATHETOSIS

Since the Middle Ages, the term chorea (from the Greek word ???e?a for "dance") has been used to Au23 describe both organic and psychological disorders of motor control. In the Middle Ages, epidemics of a psychosomatic "dancing mania" erupted in central Europe coincident with the Black Plague, with St. Vitus among the various saints called upon to intercede, leading to the term "chorea Sancti Viti" (Krack, 1999; Goetz et al., 2001c). Paracelcus (1493–1541) introduced the concept of chorea as an organic medical condition with his tri-part categorization: chorea imaginativa (arising from the imagination), chorea lasciva (arising from sexual desires), and chorea naturalis (organic chorea) (Goetz et al., 2001c).

Sydenham's chorea

In 1686, British physician Thomas Sydenham (1624–1689) applied the term Saint Vitus' dance to his description of childhood chorea (Sydenham, 1686;

Goetz et al., 2001f). However, in so doing he also added confusion, because after Sydenham the term St. Vitus dance could mean either organic chorea (aka Sydenham's chorea, chorea minor, or chorea anglorum) or psychogenic chorea (aka chorea major or chorea germanorum).

> *There is a kind of convulsion, which attacks boy and girls from the tenth year to the time of puberty. It first shows itself by limping or unsteadiness in one of the legs, which the patient drags. The hand cannot be steady for a moment. It passes from one position to another by a convulsive movement, however much the patient may strive to the contrary. Before he can raise a cup to his lips, he makes as many gesticulations as a mountebank; since he does not move it in a straight line, but has his hand drawn aside by spasms, until by some good fortune he brings it at last to his mouth. He then gulps it off at once, so suddenly and so greedily as to look as if he were trying to amuse the lookers-on. (Sydenham, 1686, 1848/1979, vol. 2, pp. 257–258)*

Subsequently, a number of observers suggested a relationship between childhood chorea, rheumatic arthritis, and valvular heart disease [e.g., Bouteille (1810), Bright (1831), Sée (1850), Roger (1866)] (reviewed by Jummani and Okun, 2001).

In 1887, William Osler (1849–1919) reviewed and reported clinical and pathologic data on 410 cases of Sydenham's chorea treated at the Infirmary for Nervous Diseases in Philadelphia since 1876 (Osler, 1887). In 1894, while at Johns Hopkins, Osler published a monograph based largely on his earlier studies in Philadelphia, titled *On Chorea and Choreiform Affections* (Osler, 1894), which continues to be among the most widely cited 19th-century American contributions to neurology (Lanska, 2001).

The bulk of Osler's treatise focused on Sydenham's chorea, which he described as "an acute disease of childhood . . . characterized by irregular, involuntary movements, a variable amount of psychical disturbance, and associated very often with arthritis and endocarditis" (Osler, 1894. p. 2). Osler carefully reviewed both the literature and the Philadelphia experience to marshall evidence that Sydenham's chorea is an infectious disorder, which is frequently associated with endocarditis, particularly affecting the mitral valve.

By 1899, a diplococcus had been isolated from the cerebrospinal and pericardial fluids of a child who died with chorea and carditis, and from 1901 to 1903 Poynton and Paine produced irregular movements, arthritis, and carditis in rabbits intravenously injected with diplococci from affected patients (Poynton and Payne, 1913). Development of the antistreptolysin O titer as a marker of antecedent streptococcal pharyngitis in the early 1930s allowed definite proof that all manifestations of rheumatic fever, including Sydenham's chorea, are a sequel to group A streptococcal pharyngitis (Coburn, 1931; Todd, 1932; Taranta and Stollerman, 1956).

By the late 1930s, sulfonamides were demonstrated to prevent recurrences of rheumatic fever (Coburn and Moore, 1939), and in the 1940s prompt administration of penicillin for group A streptococcal pharyngitis was shown to prevent primary (initial) attacks of rheumatic fever (Rammelkamp et al., 1952; Stollerman, 1997). The use of antibiotic prophylaxis for prevention of rheumatic fever led to a marked drop in the incidence of rheumatic fever and its major manifestations, including Sydenham's chorea (Nausieda et al., 1980; Special Writing Group . . ., 1993; Stollerman, 1997).

As early as the 1860s, striatal dysfunction was implicated in childhood chorea by British physicians John Hughlings Jackson and W. H. Broadbent. Jackson concluded that: "It has long seemed to me that embolism . . . of parts in the region of the corpus striatum gives a most satisfactory explanation of the physiology and pathology of cases of chorea" (Jackson, 1868/1932/1996, p. 238). Broadbent claimed that chorea is "a delirium of the sensori-motor ganglia," which (in agreement with Jackson) is caused typically by embolism but which in some cases may be caused by "a morbid condition of the blood" (Broadbent, 1869; Greenfield and Wolfsohn, 1922).

In the early 20th century the embolic theory was discarded because of the "diffuse nature of the encephalitis," the absence of pathology of the cardiac valves in many cases of childhood chorea, and the relative absence of chorea in cases of adult bacterial endocarditis (Greenfield and Wolfsohn, 1922). Instead, several authorities proposed that Sydenham's chorea was a bacterial meningoencephalitis (Poynton and Paine, 1913; Greenfield and Wolfsohn, 1922). However, bacteria were not consistently cultured from brain tissue or cerebrospinal fluid of affected cases, and the process by which an infection would selectively target the corpus striatum was never satisfactorily explained. Sydenham's chorea is now understood to result from an antibody cross-reaction to basal ganglia epitopes following infection with group A β-hemolytic streptococci (Husby et al., 1976).

Huntington's disease

George Huntington's (1850–1916) classic description of adult-onset hereditary chorea in 1872 was preceded by earlier clinical descriptions by Waters in 1841, Lund in the 1860s, and Lyon in 1863 (Waters, 1841; Lyon, 1863;

Browning, 1908a, b; Ørbeck, 1959; reviewed in Lanska, 2000a). Huntington first encountered victims of hereditary chorea at age 8, while accompanying his physician father around East Hampton at the extreme eastern end of Long Island, New York. After his own medical school graduation in 1871, George Huntington incorporated the clinical notes of cases treated previously by his father and grandfather in an essay titled "On chorea," which was edited by his father. Huntington noted the hereditary transmission, the gradual onset of chorea in adulthood, the progressive course, a tendency to insanity and suicide, and lack of response to treatment:

> *The hereditary chorea . . . is confined to certain and fortunately a few families, and has been transmitted to them, an heirloom from generations away back in the dim past. It is spoken of by those in whose veins the seeds of the disease are known to exist, with a kind of horror, and not at all alluded to except through dire necessity, when it is mentioned as "that disorder." It is attended generally by all the symptoms of common chorea, only in an aggravated degree, hardly ever manifesting itself until adult or middle life, and then coming on gradually but surely, increasing by degrees, and often occupying years in its development, until the hapless sufferer is but a quivering wreck of his former self . . . There are three marked peculiarities in this disease: 1. It's hereditary nature. 2. A tendency to insanity and suicide. 3. Its manifesting itself as a grave disease only in adult life . . . When either or both the parents have shown manifestations of the disease, and more especially when these manifestations have been of a serious nature, one or more of the offspring almost invariably suffer from the disease, if they live to adult age. But if by any chance these children go through life without it, the thread is broken and the grandchildren and great-grandchildren of the original shakers may rest assured that they are free from the disease . . . The tendency to insanity, and sometimes that form of insanity which leads to suicide, is marked . . . As the disease progresses the mind becomes more or less impaired, in many amounting to insanity, while in others mind and body both gradually fail until death relieves them of their sufferings . . . Its third peculiarity is its coming on, at least as a grave disease, only in adult life . . . It begins as an ordinary chorea might begin, by the irregular and spasmodic action of certain muscles, as of the face, arms, etc. These movements gradually increase, when muscles hitherto unaffected take on the spasmodic action, until every muscle in the body becomes affected (excepting the involuntary ones), and the poor patient presents a spectacle which is anything but pleasing to witness. I have never known a recovery or even an amelioration of symptoms in this form of chorea; when once it begins it clings to the bitter end. No treatment seems to be of any avail, and indeed nowadays its end is so well known to the sufferer and his friends, that medical advice is seldom sought. It seems at least to be one of the incurables . . . (Huntington, 1872, pp. 320–321).*

Huntington's description of hereditary chorea was considered particularly important, because of his clear and concise wording, and because it demonstrated that hereditary conditions could have their clinical onset in adulthood (Lanska, 2000a). William Osler noted that, "In the history of medicine there are few instances in which a disease has been more accurately, more graphically, or more briefly described" (Osler, 1908, p. 115). By the late 1880s, authors began referring to hereditary chorea as "Huntington's chorea," as did Huntington himself after about 1895 (Lanska, 2000a).

Early neuropathological studies, particularly in the early-20th century, revealed atrophy, neuronal loss, and fibrillary astrocytosis, particularly in the basal ganglia and less consistently in adjacent areas and the neocortex. The gross pathology of Huntington's disease with marked atrophy of the striatum (particularly the head of the caudate and putamen with accompanying dilation of the frontal horns of the lateral ventricles) was recognized by Alzheimer (Alzheimer, 1911). Later studies demonstrated selective loss of gaba-ergic medium-sized spiny projection neurons in the striatum (Vonsattel et al., 1985) with relative sparing of the much smaller population of striatal interneurons, including medium and large aspiny neurons (Dawbarn et al., 1985; Ferrante et al., 1985, 1987). Indirect projections to the external globus pallidus are the first to degenerate (Reiner et al., 1988; Albin et al., 1990, 1992). The degree of clinical disability generally reflects the degree of loss of striatal neurons (Myers et al., 1988). Au27

The distinct clinical profile, midlife onset, and autosomal dominant inheritance pattern made Huntington's disease ideal for investigation by genetic linkage analysis a century after Huntington's description. The initial approach used by Gusella and colleagues was based on the detection of variations (polymorphisms) in the length of DNA fragments resulting from digestion with restriction endonuclease enzymes which recognize

specific nucleotide base sequences (Gusella et al., 1983); the resulting "restriction-fragment length polymorphisms" (RFLPs) from individuals in large Huntington's disease kindreds were hybridized with arbitrary segments of labeled DNA derived from normal genomic DNA. In the decade from 1983 to 1993, Huntington's disease was sequentially linked to an anonymous polymorphic DNA marker, associated with a mutation in the IT15 ("interesting transcript 15") gene on the tip of the short arm of chromosome 4 (in 4p16.3), and with the combined effort of a consortium of researchers from laboratories around the world it was ultimately attributed to an unstable expanded CAG trinucleotide repeat in a gene coding for a large (350-kilodalton) multi-domain protein with multiple functions labeled huntingtin (Gusella et al., 1983, 1985; Zabel et al., 1986; Gilliam et al., 1987; Wasmuth et al., 1988; Hoogeveen et al., 1993; Huntington's Disease Collaborative Research Group, 1993).

As a result of these developments, Huntington's disease was found to be the most common member of a family of neurodegenerative diseases caused by mutations in which a CAG trinucleotide repeat expansion in the protein coding region of a gene produces long segments of polyglutamine (or "polyQ," where "Q" is the single letter code for glutamine) in the encoded protein. PolyQ diseases—including Huntington's disease, dentatorubral-pallidoluysian atrophy (DRPLA), spinal and bulbar muscular atrophy (Kennedy's disease), and several spinocerebellar ataxias—are all dominantly transmitted, typically adult-onset neurodegenerative disorders affecting selected neuronal populations.

Identification of the Huntington's disease gene and the huntingtin protein product triggered a remarkable surge in research and numerous important discoveries of cell function and disease pathogenesis. Within several years, disease course and degree of pathological severity was clearly associated with the magnitude of the trinucleotide repeat expansion (Furtado et al., 1996; Penny et al., 1997). The CAG triplet is normally repeated about 20 times (with non-expanded alleles considered to include less than 27 CAG repeats). Alleles with 27 to 35 CAG repeats are considered "mutable normal alleles," because they are not associated with clinical disease but have potential meiotic instability and so could possibly transmit disease in some offspring (ACMG/ASHG statement, 1998). Pathological effects occur when the length of polyQ exceeds a threshold of 36–40 glutamines (Duyao et al., 1993; Snell et al., 1993; Rubinsztein et al., 1996; ACMG/ASHG statement, 1998). A single copy of the mutant gene invariably causes disease when the number of repeats is 40 or more (complete penetrance), while some but not all individuals develop disease when the number of repeats is between 36 and 39 (reduced penetrance) (Rubinsztein et al., 1996; ACMG/ASHG statement, 1998).

The length of the CAG trinucleotide repeat (and hence of polyQ) is inversely related to the age of onset and directly related to the severity of symptoms: disease onset typically occurs in the fourth or fifth decade of life for CAG repeat expansions of 40–50, but juvenile-onset cases occur in those with more than 60 repeats, and juvenile onset is invariably present in those with more than 100 repeats (Duyao et al., 1993; Stine et al., 1993; Trottier et al., 1994; Brandt et al., 1996; Penny et al., 1997).

Huntington's disease had long been reported to have progressively earlier onset in successive generations, but the cause of this "anticipation" phenomenon was unclear and was suspected by some authors to represent a form of observation or selection bias (e.g., because persons of early onset in previous generations could be "selectively nonreproductive" because of manifestation of the disorder; see Myers et al., 1982), although a variety of genetic mechanisms including imprinting with DNA methylation were also considered (Reik, 1988; Ridley et al., 1988, 1991; Farrer et al., 1992). It was also recognized by the late 1960s that a disproportionate number of cases with early onset (before age 21 years) had inherited the Huntington's disease gene from their fathers (Merritt et al., 1969; Barbeau, 1970).

These curious observations were inexplicable by traditional mechanisms, but after the Huntington's disease gene was identified, both genetic anticipation and the tendency for early-onset cases to be associated with paternal transmission were understood to result from meiotic instability of the Huntington's disease trinucleotide repeat expansion, particularly during spermatogenesis. Indeed, by the 1990s it was recognized that anticipation was a common phenomenon of trinucleotide repeat diseases. The trinucleotide repeat number was found to change in more than 70% of transmissions from parent to offspring, with a tendency toward expansion (Andrew et al., 1993), apparently because the CAG repeats form-stable, hairpin-like structures, which produce mistakes with replication and consequently further expansion of the trinucleotide repeat. This instability of the CAG repeats during meiosis was found more often to result in expansions (and sometimes quite large expansions) during paternal transmission, so that juvenile-onset cases typically inherit the disease from their fathers (Duyao et al., 1993; Snell et al., 1993; Telenius et al., 1993; Zuhlke et al., 1993; Ranen et al., 1995). Thus, anticipation was found to result from a novel mutation process and not from selective gene activation or suppression mechanisms.

The molecular mechanisms responsible for the trinucleotide repeat expansion mutation have not been fully clarified: DNA replication slippage, homolygous recombination, and slippage during dysfunctional DNA damage repair are among the mechanisms proposed. Initial studies suggested that trinucleotide repeat expansion mutations occurred during meiosis, particularly during spermatogenesis (Duyao et al., 1993), but both somatic tissues and gametes were subsequently found to experience trinucleotide repeat mosaicism (Telenius et al., 1994, 1995; Furtado et al., 1996), with the greatest levels of repeat mosaicism detected in brain and sperm (Telenius et al., 1994, 1995). Analysis of sperm from affected patients showed that both the mutation frequency and the mean change in allele size increase with increasing somatic repeat number (Leeflang et al., 1999); the extraordinarily high mutation frequency (82%) was felt consistent with a mutation process occurring throughout germline mitotic divisions, rather than occurring during just a single point in meiosis (Leeflang et al., 1999). Analysis of testicular germ cells subsequently demonstrated that human germ-line trinucleotide repeat expansions could occur before meiosis begins, but some expansions continue to occur during meiosis (Yoon et al., 2003). The expansion mechanism may be augmented in the male germline because of continuous cell division of spermatogonia throughout adult life, which could explain the tendency of trinucleotide repeat length in offsping to increase as a function of the age of the parent (Farrer et al., 1992). It is now believed that germline expansion accounts for the phenomenon of anticipation, and that tissue-specific somatic expansion may contribute to the tissue specificity of pathologic involvement.

Most efforts to understand the pathophysiology of Huntington's disease have been driven by the "gain-of-function" hypothesis in which a novel toxic property of mutated huntingtin is assumed to cause dominantly transmitted neurodegeneration. By 1997 it was recognized that mutant huntingtin with its expanded polyglutamine segment misfolds and aggregates, possibly as self-associating antiparallel β strands ("polar zippers") (Perutz et al., 1994), to form insoluble intranuclear inclusions (Davies et al., 1997; DiFiglia et al., 1997). The discovery of intracellular aggregates of mutant huntingtin supported the concept that neurodegenerative diseases are generally associated with protein misfolding, and suggested further that polyglutamine toxicity might result from its ability to form aggregates (Davies et al., 1997; DiFiglia et al., 1997). It was subsequently demonstrated that nuclear localization is necessary for toxicity (Yang et al., 2002), but it is still not clear (and is indeed contentious) whether nuclear aggregates are themselves toxic, are benign biomarkers, or are effectively neuroprotective (e.g., perhaps representing the cell's attempts to inactivate the toxic expanded protein) (Zoghbi and Orr, 2000).

Several studies using animal models now suggest that soluble protein fragments, rather than insoluble aggregates, are the toxic factors involved. One problem for the gain-of-function hypothesis had been that rare disease homozygotes (i.e., with two mutant alleles) had been identified prior to identification of the Huntington's disease gene, and were found to have a similar age of onset to disease heterozygotes, suggesting that Huntington's disease is a rare "pure dominant" disorder (Wexler et al., 1987); however, because patients homozygous for Huntington's disease receive a "double dose" of any gain-of-function mutation, a greater toxic effect would be anticipated for homozyogotes—an expectation ultimately confirmed in 2003 with a preliminary demonstration that homozygotes have a more severe clinical course (Squitieri et al., 2003).

The pathophysiology of neurodegeneration in Huntington's disease is still not fully understood, but apoptosis (i.e., inappropriate activation of programmed cell death, for example from direct activation of an apoptotic enzymatic cascade, or through loss or lack of transport of anti-apoptotic neurotropic factors, including brain-derived neurotropic factor), transcriptional dysregulation (e.g., due to sequestration of polyglutamine-containing nuclear transcription factors), excitotoxicity (i.e., death of neurons resulting from excess glutamate neurotransmission) (Coyle et al., 1976; McGeer and McGeer, 1976; Olney and de Gubareff, 1978; Beal et al., 1986), and mitochondrial dysfunction (possibly linked to excitotoxicity) are among the mechanisms implicated. Indeed, these putative neurodegenerative processes were either initially investigated or elaborated substantially in models of Huntington's disease, and have since been applied to a range of neurologic disorders. Au28

The recent developments of transgenic mouse, fly, worm, and cellular models of Huntington's disease have contributed greatly to understanding of cellular processes and potential pathogenic mechanisms. Because of such models, there is now increasing evidence that multiple possibly overlapping pathologic mechanisms are involved in Huntington's disease, and in particular both toxic gain-of-function properties of mutated huntingtin and loss of function of wild-type huntingtin are now thought to contribute to neural degeneration.

More than a century after Huntington recognized the futility of treatment for hereditary chorea (Huntington, 1872), there are still no effective therapies to delay onset or slow progression in Huntington's disease.

Athetosis and post-hemiplegic hemichorea

In the first American textbook of neurology, published in 1871, neurologist William Hammond described a condition that he called "athetosis" (from the Greek term for "without fixed position"), "characterized by an inability to retain the fingers and toes in any position in which they may be placed, and by their continual motion" (Hammond, 1871; Lanska et al., 2001b). There were associated "pains in the spasmodically-affected muscles, and especially complex movements of the fingers and toes, with a tendency to distortion," with a slower, sinuous quality compared with chorea, and without any associated weakness (Fig. 33.4).

Hammond speculated that "one probable seat of the morbid process is the corpus striatum," a supposition ultimately supported by the autopsy on the original case that was reported by his son Graeme Hammond in 1890 (Hammond, 1890). There was a lesion involving the posterior thalamus, part of the internal capsule, and the lenticular nucleus (Fig. 33.4). Graeme Hammond "called attention to the fact that the motor tract was not implicated in the lesion, and claimed that this case was further evidence of his theory that athetosis was caused by irritation of the thalamus, the striatum, or the cortex, and not by a lesion of the motor tract" (Hammond, 1890, p. 555).

Despite the confirmation of a proposed clinico-pathological association, athetosis was, and remains,

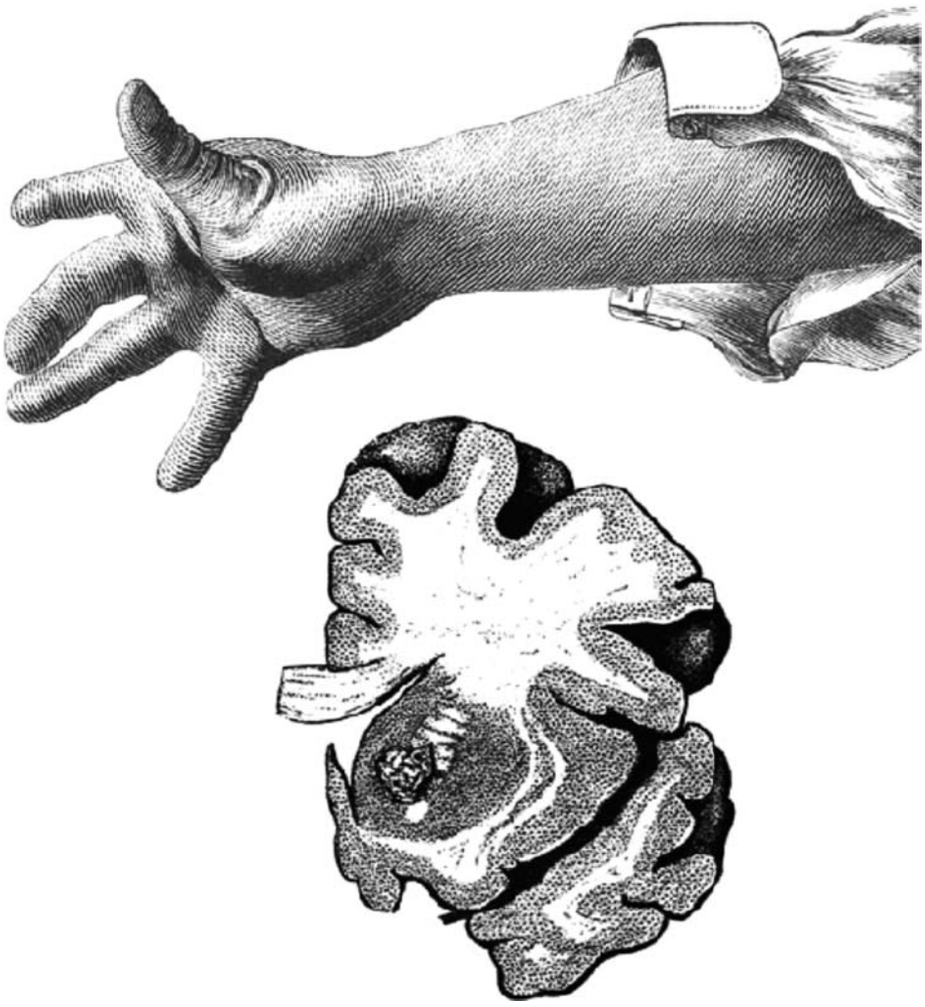

Fig. 33.4. Athetosis. Woodcut of athetosis taken from a photograph as illustrated in William Hammond's Text-book of Nervous Diseases in 1871. Hammond proposed that the responsible lesion would be found in the basal ganglia. The autopsy in 1890 confirmed Hammond's prediction. Hammond's prediction and the subsequent confirmation are often regarded as a landmark in the clinicopathologic correlation of movement disorders, and specifically in the linkage of abnormal movements to pathology of the basal ganglia. However, at the time of Hammonds prediction, the motor centers were thought to be located in the corpus striatum.

controversial, being considered by many late-19th- and 20th-century neurologists as a form of post-hemiplegic chorea or part of a continuum between chorea and dystonia. Silas Weir Mitchell described similar cases under the term "post-paralytic chorea," noting "as there is a post-choreal paralysis, so, also, is there a post-paralytic chorea . . . [In] adults who have had hemiplegia and have entirely recovered power, there is often to be found a choreal disorder, sometimes of the leg and the arm, usually of the hand alone" (Mitchell, 1874, p. 343).

Gowers felt there was considerable clinical overlap between Hammond's athetosis and "post-hemiplegic disorders of movement," and described similar patients in whom the movement disorder followed a sudden hemiplegia with some degree of recovery (Fig. 33.5) (Gowers, 1876, 1888). He argued for athetosis to be placed in a spectrum of "post-hemiplegic disorders of movement," between the irregular "quick, clonic spasm" of chorea and the "slow, cramp-like incoordination" and tonic spasms associated with "spastic contracture" (Gowers, 1876, p. 291). As a result, Gowers was willing to accept athetosis with the proviso that hemiparesis could be associated, depending on the extent of the lesion.

Charcot, on the other hand, dismissed Hammond's athetosis as "simply choreiform movements" (Charcot, 1881, p. 390) or as "only a variety of post-hemiplegic hemichorea" (Charcot, 1881, p. 394), to which Hammond retorted, "I have only to say that the distinction between the two conditions is as well marked as between chorea and disseminated cerebro-spinal sclerosis. In athetosis the movements are slow, apparently determinate, systematic, and uniform; in post-hemiplegic chorea they are irregular, jerking, variable, and quick. Moreover, athetosis is not by any means necessarily post-hemiplegic" (Hammond and Hammond, 1893, p. 324).

Even modern authors have erroneously indicated that Hammond's original cases were examples of a post-hemiplegic movement disorder (Dooling and Adams, 1975; Sharp et al., 1994), but, as emphasized by Hammond, "In the original case there had never

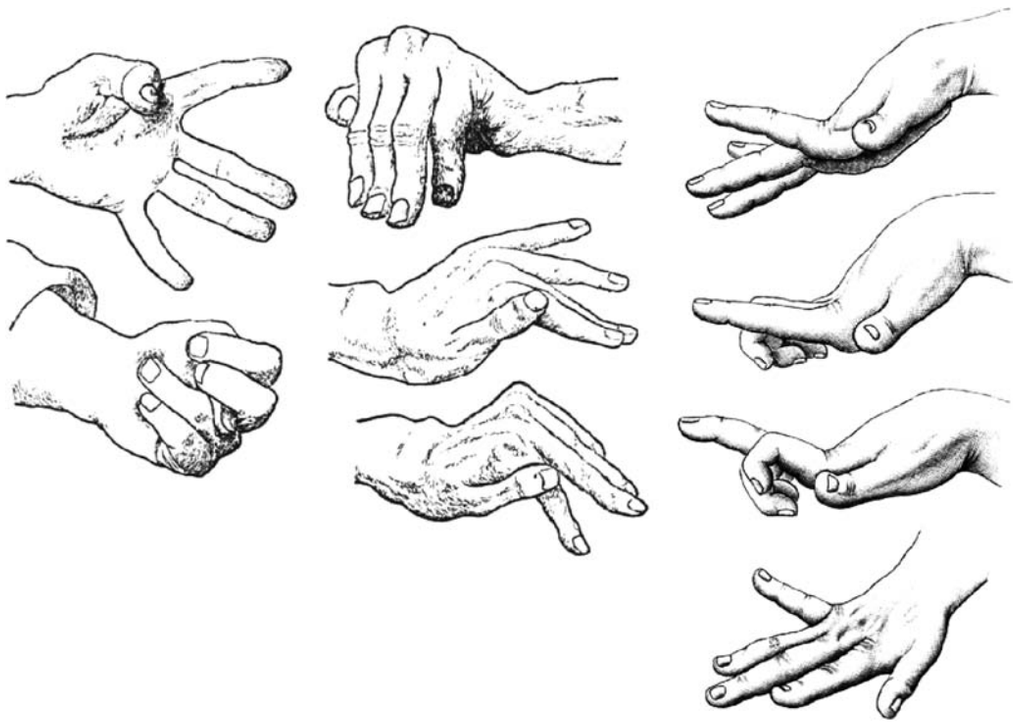

Fig. 33.5. Post-paralytic choreoathetosis was recognized by many eminent late 19th-century neurologists, including Charcot, Gowers, and Mitchell. The left-most column of illustrations from Gowers' textbook show "continuous mobile spasm (athetosis) after slight hemiparesis" in a 24-year-old syphilitic patient who developed left hemiparesis at age 23 and abnormal involuntary movements 4 months later; "The hand was in continuous movement between the two positions shown" (Gowers, 1888, p. 80). The center column of illustrations, also from Gowers' textbook, are some of the postures of the left hand of a 23-year-old man with "post-hemiplegic mobile spasm"; the abnormal movements began 1 year after onset at the time of some improvement in volitional movement (Gowers, 1876, Plate 12; 1888, p. 80). The right-most column of illustrations are other "examples of the position of the fingers in the movements of athetosis (Strümpel)" as shown in the late-19th-century multi-authored American textbook of neurology edited by Francis Dercum (Sinkler, 1895, p. 265).

been hemiplegia, nor was there such a state in the second case, on which [Hammond's] description of the disease was based" (Hammond and Hammond, 1893, p. 324). Hammond's cases both occurred after convulsions and loss of consciousness, and both were associated with some sensory loss. Hammond accepted that hemiplegia could be an antecedent in some cases, but "Where the motor tract is implicated there will be hemiplegia, spastic spasm, and exaggerated reflexes in addition to the athetosis" (Hammond and Hammond, 1893, p. 324).

Many preferred to incorporate athetosis into a broader conceptualization of chorea, noting that some cases included features of both types of abnormal movement, and that both could occur after hemiparesis (Wilson, 1925). However, in 1950, Malcolm Carpenter reviewed the literature and concluded that:

> *Athetosis is a pattern of involuntary dyskinesia which can be distinguished from chorea and is characterized by increases and decreases of tone in irregular sequence in antagonistic muscle groups and slow involuntary movements involving chiefly, but not exclusively, the distal appendicular musculature such that vermicular activity results . . . Hemiathetosis usually develops after hemiparesis, or in association with it, as a consequence of necrotizing cerebrovascular lesions which destroy part of the internal capsule and striatum on the side opposite that of the activity (Carpenter, 1950, p. 900).*

Ballism and the subthalamic nucleus (nucleus luysii)

In 1865, Jules Luys (1828–1897) named the subthalamic nucleus the "accessory band of the superior olives" (*bandelette accessoire des olives supérieures*), terminology that was anatomically incorrect, as noted by Auguste Forel (1848–1931), who instead proposed to rename it Luy's body (or corpus Luysii) (Luys, 1865; Forel, 1877; Parent, 2002; Haméleers et al., 2006).

Several authors in the late-19th century and early-20th century reported cases of hemiballismus—characterized by continuous, non-patterned, vigorous, or even violent, large amplitude, proximally generated involuntary limb movements—but none of these early authors clearly established the subthalamic nucleus as the locus of pathology in hemiballismus. In 1884, Ralph Canfield and James J. Putnam presented one of the earliest such reports in their case of a 59-year-old man with "acute hemiplegic chorea": "The right arm and leg were found to be in violent and constant motion of a distinctly choreic type, but involving the muscles of the larger joints—hip, shoulder, etc.—even more than those of the smaller" (Canfield and Putnam, 1884, p. 220). In describing the location of areas of infracted brain at autopsy, Canfield and Putnam (1884, p. 222) noted that "The only ganglionic matter involved besides the substantia nigra was (probably) the so-called ganglion of Luys," but other brain areas were also involved, and no supportive body of evidence or theoretical framework were available to make a clear clinical-pathologic correlation.

The relationship between a lesion of the subthalamic nucleus and contralateral hemiballismus was first convincingly demonstrated by J. P. Martin in 1927 (Martin, 1927): Martin reviewed the world's literature and noted that 11 of 12 previously reported patients with hemiballismus and available pathology had lesions in the area of the contralateral subthalamic nucleus, including two with lesions restricted to the subthalamic nucleus, plus an additional case reported by Martin had a small hemorrhage nearly limited to the subthalamic nucleus. In 1947, Whittier noted that lesions of the *connections* of the subthalamic nucleus could also produce contralateral hemichorea or hemiballismus in man, a finding reinforced by Martin a decade later when he reported a patient with post-hemiplegic hemichorea-hemiballismus associated with degeneration of efferent connections of the subthalamic nucleus as they passed across the internal capsule in the subthalamic fasciculus en route to the internal segment of the globus pallidus (Whittier, 1947; Martin, 1957).

In 1949, Whittier and Mettler produced experimental hemichorea-hemiballismus in monkeys by lesioning the contralateral subthalamic nucleus (Whittier and Mettler, 1949a, b), an animal model subsequently utilized extensively by Carpenter (Carpenter et al., 1950; Carpenter and Carpenter, 1951; Carpenter, 1955). These studies demonstrated profuse interconnections between the subthalamic nucleus and the pallidum, but no clear descending connections from the subthalamic nucleus, suggesting that the subthalamic nucleus served to modulate the output of the pallidum (Whittier and Mettler, 1949a). Whittier and Mettler (1949b) found that at least 20% of the subthalamic nucleus had to be damaged to produce hemichorea-hemiballismus, although smaller lesions could produce hyperkinetic movements, if the efferent fibers in the subthalamic fasciculus were also involved. Subsequent lesions of the internal segment of the globus pallidus abolished or ameliorated the hemichorea-hemiballismus, a finding which was interpreted (erroneously) as suggesting that the subthalamus normally exerts an inhibitory influence on the pallidum (Whittier and Mettler, 1949b), and which in any case provided an experimental basis for what would later be a useful surgical therapy (Suarez et al., 1997; Slavin et al., 2004).

Throughout the first half of the 20th century, hemiballismus was generally thought to have a poor prognosis, often with progression to death within weeks or months (Whittier and Mettler, 1949), but more recent studies have shown that hemiballismus can have a relatively benign course with spontaneous recovery, or can respond to various pharmacological or surgical therapies (Klawans et al., 1976; Dewey and Jankovic, 1989; Ristic et al., 2002). In addition, with the advent of computed tomography and magnetic resonance imaging, the recognition of both non-stroke causes (particularly for patients under age 55 years) and cases with lesions outside of the subthalamic nucleus has expanded markedly (Dewey and Jankovic, 1989).

As late as the 1980s, the subthalamic nucleus was thought to modulate basal ganglia output via primarily inhibitory (and presumably GABA-ergic) efferents to the pallidum, a seemingly straightforward conclusion generally consistent with previous experimental findings and with the clinical observation that lesions of the subthalamic nucleus seem to release the dramatic movements of hemichorea-hemiballismus. However, since the late 1980s, the neurochemistry and neurophysiology of the subthalamic nucleus have been substantially revised (Smith and Parent, 1988; Albin et al., 1989; Guridi and Obeso, 2001; Hamani et al., 2003; Haméleers et al., 2006).

In 1988, using immunohistochemical methods, Smith and Parent (1988) found that virtually all cell bodies in the subthalamic nucleus of monkeys are, in fact, intensely immunoreactive to glutamate, but not to gamma-aminobutyric acid, as had been expected. This finding, which implied an excitatory rather than inhibitory function for subthalamic nucleus efferents, was soon independently confirmed in cats (Albin et al., 1989). Subsequently, in 1992, Hamada and DeLong demonstrated directly that discharge rates of neurons in both segments of the globus pallidus of monkeys decreased substantially following lesions of the subthalamic nucleus, confirming that the subthalamic nucleus provides excitatory input to both segments of the globus pallidus (Hamada and DeLong, 1992). Since then, the subthalamic nucleus has been increasingly recognized to play an important role in the pathophysiology of both hyperkinetic and hypokinetic movement disorders (Crossman, 1989).

DYSTONIAS

In 1944, Herz provided detailed cinematographic and electromyographic analyses of 15 personal cases of generalized dystonia, as well as an extensive review of more than 100 literature cases, and concluded that dystonic movements are best described as slow, sustained, powerful, and non-patterned contortions of the axial and appendicular muscles, with simultaneous contractions of agonist and antagonist muscles (Herz, 1944a, b, c). Dystonia is now defined as "a syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements, or abnormal postures" (Fahn, 1988). Current classification schemes categorize dystonias by age of onset, parts of the body affected (focal, segmental, multifocal, or generalized), and etiology (primary or secondary) (Fahn, 1988).

Since the original descriptions in the 19th and early-20th centuries, dystonias have repeatedly been interpreted in psychological or psychiatric terms, because of the bizarre contortions exacerbated by voluntary movement, the relief by certain movements or gestures (*geste antagonists*), and failure to identify a neuropathological substrate, particularly for generalized dystonias (Zeman and Dyken, 1967; Zeman, 1970). Only in the late-20th century was an organic framework established with identification of genetic mutations in some families with dystonia (Ozelius et al., 1989, 1997a, b) and with demonstration that the putamen, caudate, and posterior ventral thalamus were often damaged contralateral to hemidystonia (Narbona et al., 1984; Marsen et al., 1985; Pettigrew and Jancovic, 1985).

Therapies for dystonia have focused on both central and peripheral pharmacology, with anti-cholinergic agents long employed with variable and at best modest benefit for neuroleptic-induced dystonia (Winslow et al., 1986; Goff et al., 1991), cranial dystonia (Lang et al., 1982; Nutt et al., 1984), and generalilzed dystonia (Fahn, 1983), and, since the 1980s, with botulinum toxin increasingly used as a treatment for focal dystonia (Elston and Russell, 1985; Mauriello, 1985; Tsui et al., 1985, 1986, 1987; Brin et al., 1987).

Generalized primary tortion dystonia

In 1897, Spanish neurologist Lluis Barraquer i Roviralta (1855–1928) described a patient with generalized dystonia, although he labeled it "athetosis" (Barraquer-Roviralta, 1897; Barraquer-Bordas and Giménez-Roldán, 1988). In 1908, Gustav Schwalbe (1844–1911), under the tutelage of Theodore Ziehen (1862–1950), presented his thesis on dystonic spasms in three siblings with onset between ages 12 to 14 years, which he attributed to a combination of hysteria and a variety of tics—hence his label "tonic cramps with hysterical symptoms" (Schwalbe, 1908; Truong and Fahn, 1988), a designation apparently influenced by Ziehen (1991), who later called this "torsion neurosis". Schwalbe noted the "chronic course, characterized predominantly with tonic, not painful, asymmetrical cramps of variable intensity and duration spreading over the muscles

Au33 of the whole body" (Schwalbe, 1908/1988, as translated by Truong and Fahn, 1988, p. 657).

In his 1911 treatise, Hermann Oppenheim (1858–1919) described four Jewish children with a progressive form of generalized dystonia, which he termed "dystonia musculorum deformans" (Oppenheim, 1911; Goetz et al., 2001i). Oppenheim insisted that dystonia is an organic disease and therefore rejected Ziehen's term "torsion neurosis." Oppenheim introduced the term "dystonia" to reflect his conclusion that the disorder is associated with a generalized abnormality of tone with coexistent hypo- and hyper-tonia: "in addition to an increased tonus of some muscles, one finds hypotonia of most of the others"
Au34 (Oppenheim, 1911/2005, as translated by Grundmann, 2005, p. 682). Oppenheim also suggested an alternative name, "dysbasia lordotica progressive," emphasizing postural deformity and the bizarre gait, which he termed "monkey gait" or "dromedary gait."

Flatau and Sterling (1911) instead emphasized torsion spasms as the major clinical feature: "Since the nature of the disease is still unknown to us we should retain its most outstanding characteristic in the designation. In our opinion this consists in the drawing, twisting spasm which is progressive in these affected children, so we select the designation 'progressive tor-
Au35 sion spasm'" (Flatau and Sterling, 1911/2005, as translated by Grundmann, 2005, p. 683). Because this is not a primary disease of muscles, and because not all patients develop fixed postural deformities, "dystonia" or "torsion dystonia" are now generally preferred over previous designations (Fahn, 1988).

In the late 1950s and 1960s, Wolfgang Zeman and colleagues demonstrated that primary torsion dystonia is a heritable disease (Zeman et al., 1959), and recognized *formes frustes* in families with autosomal dominant transmission (Zeman et al., 1960; Zeman and Dyken, 1967). Roswell Eldridge at the US National Institutes of Health subsequently emphasized autosomal recessive patterns among Ashkenazi Jews (Eldridge, 1970). In the 1980s and 1990s, it became clear that the disorder, though genetically heterogeneous, is usually transmitted as an autosomal dominant trait with reduced penetrance. The first primary dystonia locus, DTY1, was localized to chromosome 9q32-34 in 1989, and in 1997 the genetic mutation was identified as a three-base pair (GAG) deletion in the coding region of the Torsin A gene (Ozelius et al., 1989, 1997a, b). This mutation is responsible for most patients with early-onset primary torsion dystonia. Many other loci have now been identified with different modes of inheritance.

Treatment of primary generalized dystonia is still limited. Some benefits have been demonstrated with high doses of anticholinergic drugs (Burke et al., 1986), sometimes combined with baclofen or other drugs, and with bilateral deep-brain stimulation of the globus pallidus (Vidailhet et al., 2005).

Writer's cramp and other occupational dystonias

Several authors described writer's cramp in the 1830s, including Scottish neuroanatomist and surgeon Charles Bell (1774–1842) and J. H. Kopp (Bell, 1830; Kopp, 1836; Goetz et al., 2001d), and these are often cited as the earliest reports, although reports as early as the mid-18th century have also been recognized (Lewis 1885–1886). In 1864 and 1865, British surgeon Samuel Solly (1805–1871) presented a series of clinical lectures on "scrivener's palsy, or the paralysis of writers" that has been credited with increasing medical recognition of this condition (Solly, 1864, 1865a, b):

> *The disease, as the name implies, shows itself outwardly in a palsy of the writing powers. The muscles cease to obey the mandates of the will. It comes on very insidiously, the first indication often being only a painful feeling in the thumb or forefinger of the writing hand, accompanied with some stiffness; these unnatural sensations subsiding during the hours of rest and sleep, to return with the writer's work on the next day. The loss of power is not sudden, as in a paralytic stroke nor is it a complete paralysis of any group of muscles. The paralysed [sic] scrivener, though he cannot write, can amuse himself in his garden, can shoot, and cut his meat like a Christian at the dinner-table; indeed he can do almost anything he likes, except earn his daily bread as a scribbler . . . When scriveners' palsy first commences, the victim of it only feels its direful influence after a hard day's work. He regards it only as a sign of fatigue, and, as he starts fresh the next morning, attaches no importance to it as the first attack of a serious enemy; but in a short time he is obliged to rest earlier in the day, and hails his early dinner hour with joy, as giving him some respite from the fangs of his tormentor. He tries to overcome his difficulty by holding the pen firmer, but this really only increases the evil. Suddenly he finds his pen dash off at a tan gent, and the work that he intended to write in the proper line is, to his horror, commenced in the left-hand corner of the page. Not unfrequently [sic] the act of writing is arrested, not by such sudden diversion, but by trembling, and a shaking palsy limited to the right hand. (Solly, 1864, p. 709)*

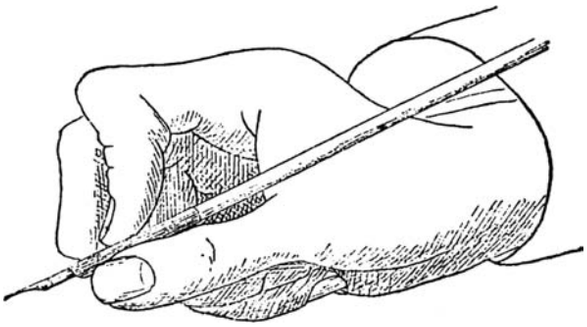

Fig. 33.6. Writer's cramp or "scrivener's palsy" was prevalent in the 19th century, before the advent of typewriters or writing instruments (e.g., ballpoint pens) that moved smoothly across the paper. The figure illustrates the "cramped method of holding pen, habitual to a patient who suffered from writer's cramp" (Gowers, 1888, p. 662).

Writer's cramp became a fairly common disabling problem in the 19th century, in part because of the large amount of writing performed, and in part because the available writing instruments required greater force to move across the page (Fig. 33.6) (Gowers, 1888). Case series of writer's cramp in the 19th century were often very large, including many dozens or even hundreds of patients (Poore, 1878). In 1864, Solly noted that "the greatest part of the middle classes of London get their bread by the use of the pen, either as the exponent of their own thoughts or the thoughts of others, or in recording the sum gained, lost, or spent in this great emporium of commerce—this vast Babylon [i.e., London]" (Solly, 1864). As noted by Sheehy and Marsden (1982, p. 462): "The frequency of the disorder in [the] late Victorian era must stand as a tribute to the success of the British Empire, the enormous office staff required to run it, and the difficulties of manipulating the quill pen".

There was a general recognition in the late-19th century that writer's cramp is analogous to other conditions that would later be recognized as forms of focal dystonia, including other occupational dystonias and torticollis (Solly, 1864; Beard and Rockwell, 1871; Lewis, 1885–1886; Burr, 1895). For example, Solly noted that, "Scriveners' palsy is not the only instance of a set of muscles being cramped and paralyzed [sic] by long-continued exertion. There is, as has been observed by Virchow, showmakers' cramp, milking cramp, the musicians' cramp, compositors' and the sempstresses cramp" (Solly, 1864, p. 709). Similarly, George Beard and Alphonso Rockwell noted in 1871 that writer's cramp "seems to differ but little from certain other spasmodic conditions, such as wry neck [torticollis] and histrionic spasm" (Beard and Rockwell, 1871).

Instruments used in the treatment of writer's cramp evolved over time, and most were largely abandoned when the development of better writing instruments and alternative means of written communications (e.g., the typewriter) decreased the frequency of and disability associated with writer's cramp. Patients initially devised a number of simple but cumbersome methods of minimizing the muscle contractions associated with writing, including enlarging the dimensions of their pens (e.g., with a piece of cork, potato, or apple). A large number of simple mechanical writing aids were subsequently devised and reported in the 19th-century medical literature. Most of these instruments limited thumb and finger flexion, and instead utilized unaffected finger extensors or more proximal muscles moving the wrist, elbow, or shoulder (Fig. 33.7).

Nevertheless, many authorities considered any benefit of such aids to be limited, temporary, and in no way curative (Lewis, 1885–1886; Robins, 1885a; Burr, 1895), and some argued that use of such instruments ultimately resulted in clinical involvement of the entire arm and even greater disability. With improvements in writing instruments, there was "no temptation to exert pressure" while writing (Putnam, 1879); these changes followed replacement of quills and dip pens upon the development of workable stylographic pens in the 1870s and fountain pens ca. 1883 and after. After the development of the typewriter in the late-19th century, the use of such mechanical aids decreased markedly (Gowers, 1888; Blackwood, 1889).

Nineteenth-century authorities on writer's cramp also frequently advocated varying degrees of rest (Gowers, 1888), and sometimes applied splints or slings to ensure that the limb would not be used: e.g., some physicians enforced rest by fastening the hand upon a splint (Buzzard, 1872), while others similarly ordered the "arm to be carried in a sling for a week or so, to remind the patient that all writing is to be shunned" (Robbins, 1885b).

MYOCLONUS

Myoclonus is a sudden, non-suppressible, shock-like muscular contraction triggered within the central nervous system. Myoclonic movements can be "positive" or "negative": positive myoclonus results in the contraction of a muscle or muscles, whereas negative myoclonus (e.g., asterixis) is instead associated with a brief loss of muscle tone (Shahani and Young, 1976; Young and Shahani, 1986). By 1903, Lundborg proposed a classification system that remains largely in use today, with primary (essential), secondary, and epilepsy-associated categories (Lundborg, 1903; Goetz et al., 2001h).

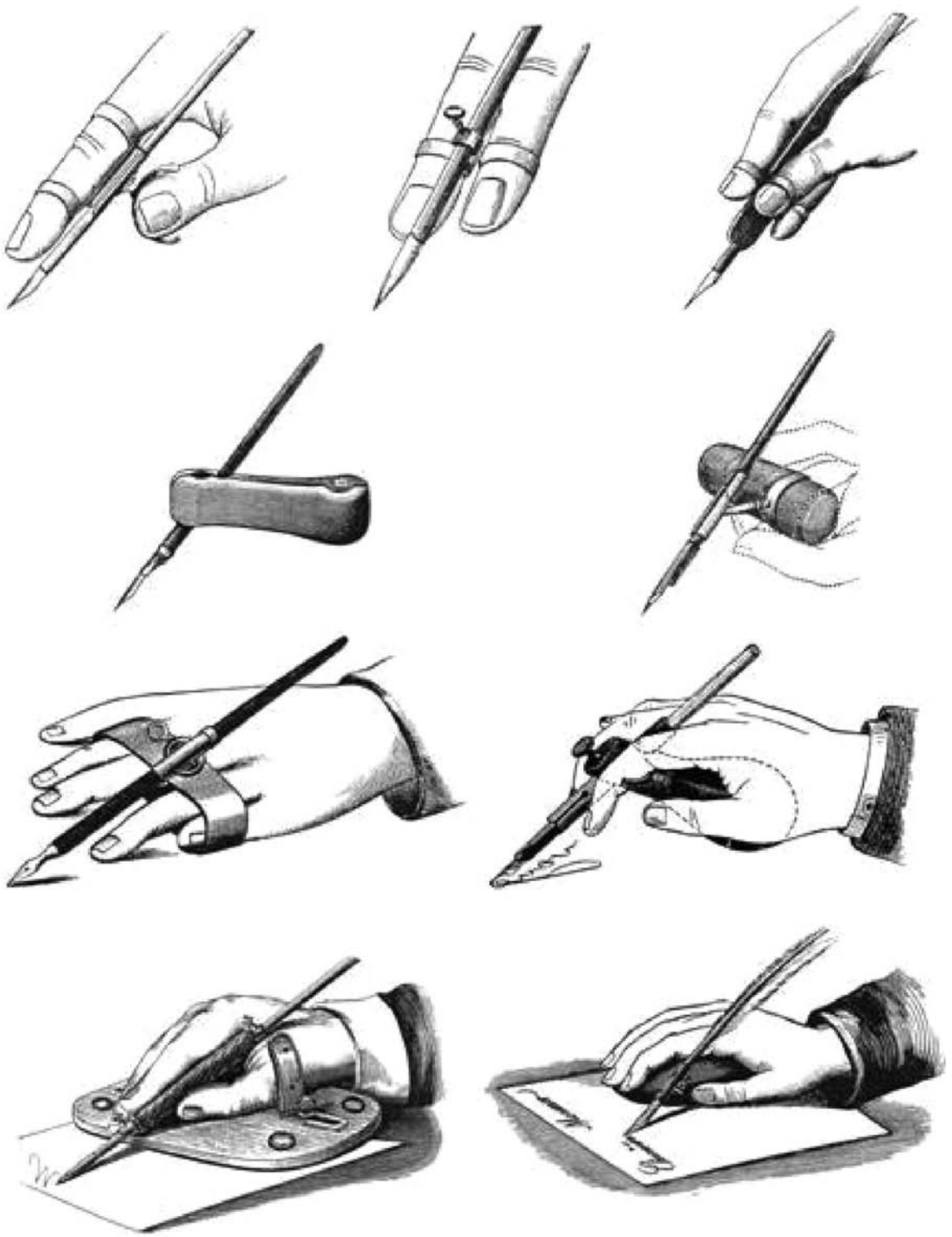

Fig. 33.7. In the 19th century, numerous writing aids were invented to facilitate writing for those with writer's cramp. Shown are a range of aids distributed by George Tiemann and Company of New York (Tiemann, 1899). All of the instruments serve to redirect the type of hand and finger muscle contractions used to grip or move the writing instrument. The top row shows various loop attachments for the fingers (to minimize the need to pinch the writing instrument), the second row shows grip devices (with a similar intent), and the bottom rows show devices that allow a sliding motion along the writing surface (in some cases resembling a modern "mouse" for a personal computer). With permission.

Essential myoclonus

In 1881, Nikolaus Friedreich (1825–1882) reported a 50-year-old man with a 5-year history of multifocal muscle jerking, occurring at a rate of 10 to 50 per minute, and affecting both sides of the body symmetrically but asynchronously. The rapid muscle jerks affected the bulk of a full muscle, without marked limb or joint movement, except in the most powerful contractions. Friedreich called the syndrome "paramyoclonus multiplex" to indicate quick movements, distinct from epilepsy, symmetrically affecting multiple sites of the body (Friedreich, 1881; Goetz et al., 2001h). Although Friedreich suspected the problem was caused by a spinal cord disorder, no pathology of the spinal cord was later identified at autopsy (Hallett, 1986).

Friedreich's term was adopted in shortened form as "myoclonus" and in modern terminology his case would be classified as essential or idiopathic myoclonus. Lindemulder (1933) later reported a family with essential myoclonus, which helped demonstrate that such generalized myoclonus could occur in the absence of neurodegenerative disorders, epilepsy, or obvious metabolic derangement.

Myoclonic epilepsy

Throughout the 19th century, myoclonic jerks in association with epilepsy were recognized by various authors, including as part of what would now be called infantile spasms (West, 1861). In 1891, Unverricht reviewed the literature on myoclonus, dismissed the majority of cases reported to that point as incorrectly designated, and also described patients with progressive multifocal myoclonus and epilepsy (Unverricht, 1891). In 1903, Lundborg described additional patients with familial progressive myoclonic epilepsy, distinct from "paramyoclonus multiplex" or essential myoclonus. In the 1990s, progressive myoclonic epilepsy of Unverricht-Lundborg was linked to mutations in the cystatin B gene on chromosome 21q.22, which codes for a small protein in the superfamily of cysteine protease inhibitors. Other forms of progressive myoclonic epilepsy were also recognized, including lysosomal storage diseases (e.g., neuronal ceroid lipofuscinosis), mitochondrial disorders (e.g., myoclonic epilepsy with ragged red fibers or MERRF), and glycogen storage diseases (e.g., Lafora's disease).

Secondary or symptomatic myoclonus

In the 1920s and 1930s, multifocal myoclonus was recognized as a feature of encephalitis lethargica (Walshe, 1920; von Economo, 1929), Creutzfeldt-Jakob disease (Creutzfeldt, 1920; Jakob, 1921), and subacute sclerosing panencephalitis (Dawson, 1934). Secondary myoclonus is now recognized in a wide variety of disorders, including infections, metabolic derangements, hypoxia, and neurodegenerative diseases (Goetz et al., 2001h).

Au36

Asterixis and metabolic tremor

Asterixis is characterized by brief, arrhythmic interruptions of sustained (tonic) voluntary muscle contraction with associated brief lapses of posture, causing bilateral asynchronous flapping movements associated with intermittent pauses of electrical activity of from 50–200 milliseconds on EMG tracings (Adams and Foley, 1949, 1953; Leavitt and Tyler, 1964; Young and Shahani, 1986).

In 1949, Raymond Adams and Joe Foley first noted an "almost rhythmical" tremor during maintenance of posture in patients with advanced hepatic encephalopathy (Adams and Foley, 1949). In 1953, Adams and Foley expanded on their clinical description, correctly recognized that the flapping tremor is due to pauses in electromyographic activity and not to intermittent increases in electrical activity as had been supposed, and proposed the term "asterixis" for the "intermittency of the sustained contraction of groups of mucles" that characterized the abnormal movements:

> *A practical clinical test by which it may be elicited is having the patient hold the arms outstretched with wrists and fingers dorsiflexed. With the extremities in this position there occurs, in addition to a fine tremor of the fingers, a sudden lapse of the assumed posture, lasting a fraction of a second, in the fingers, wrist, and sometimes the elbow and shoulder. It is irregular in frequency and variable in amplitude; usually the rate is about once every one to five seconds. When the limb is in repose it disappears and during strong muscle contraction it is temporarily suppressed . . . Inasmuch as this movement disorder is essentially an inability to maintain a fixed posture the term asterixis (a—privative, sterixis—maintenance of posture) is suggested. Electromyographic analysis of the disorder reveals that the tremor has a frequency of 6–8 per second and that with the lapse of posture there is a reduction or cessation of electrical activity in both the muscles sustaining the posture and in their antagonists . . . Although present in the majority of cases of hepatic coma, we have seen it in three cases of polycythemia with mental confusion and in three cases of uremia. Therefore, it may be regarded as a characteristic but not specific clinical sign of hepatic coma. (Adams and Foley, 1953, p. 51)*

Others soon recognized that asterixis occurred with various metabolic encephalopathies, including uremia, respiratory failure, drug intoxications, and electrolyte imbalances (Conn, 1960; Leavitt and Tyler, 1964), or unilaterally with various focal brain lesions located in the cerebral hemisphere contralateral to the asterixis (Leavitt and Tyler, 1964; Young and Shahani, 1976).

In 1964, Leavitt and Tyler added several important clinical observations concerning asterixis and the associated tremor:

> *The characteristic tremulousness and asterixis occurred only after a latent period of 2–30 seconds, tremulousness appearing first . . . [In] the context of increasing tremulousness, yet clearly interrupting the pattern of tremulousness, the hand, almost as a unit, but with fingers leading, lapsed forward anywhere from 2 to 5 cm only to be jerked back to its original position. The backward movement was often more violent than the lapse forward. The patients had no control over the lapse and no warning of its occurrence. Positional lapses were unassociated with any lapse in attention or consciousness . . . No patient was able to prevent himself from jerking his hand back once the lapse had occurred. The lapse occurred at similar rates in both hands, but asynchronously. Although commonly evoked with the dorsiflexed hand in pronation, asterixis* against *gravity occurred when the dorsiflexed hand was supinated. (Leavitt and Tyler, 1964, p. 361)*

Leavitt and Tyler found that the average duration of electrically silent periods associated with asterixis on electromyography was 50–70 milliseconds. Although lapses in electrical activity were *initiated* simultaneously in different muscles within the same limb, the degree of electrical silence varied between muscles and even across locations within the same muscle. The EMG correlate of a flapping movement was found to be "a triple pattern of silence, discharge, and silence," with the initial period of electrical silence occurring approximately 70 milliseconds before the movement artifact, followed by an "asymmetrical burst of electrical activity" corresponding to "a braking and withdrawal of the forward loss of position," and then terminating with a 20–30 millisecond period of electrical silence which represented a "terminal pause inhibition of the'braking-withdrawal' discharge to prevent an overshoot" (Leavitt and Tyler, 1964, p. 364).

Leavitt and Tyler's electrophysiological studies also showed that much of the tremulousness seen with asterixis was in fact due to shorter pauses or sudden brief decrements in voluntary electromyographic activity occurring asynchronously in different muscle groups of the same limb (Leavitt and Tyler, 1964). They labeled this tremulousness "metabolic tremble" or "metabolic tremor," and felt this was "a manifestation of the same phenomena that underlie asterixis" (Leavitt and Tyler, 1964).

Shahani and Young later labeled as "negative myoclonus" the postural lapses associated with reductions in EMG activity: "Because these synchronous brief *pauses*, which occur at irregular intervals in the ongoing voluntary EMG activity, produce movements that appear clinically to be myoclonic, one may characterize this as 'negative myoclonus'" (Shahani and Young, 1976, p. 780; Young and Shahani, 1986). Young and Shahani considered negative myoclonus to be "a more inclusive term encompassing asterixis and tremor in patients with metabolic encephalopathy and other circumstances in which brief periods of EMG silence produce an abnormal movement" (Young and Shahani, 1986, p. 154).

Lance–Adams syndrome (posthypoxic action myoclonus)

Acute posthypoxic myoclonus is characterized by generalized, often massive, muscle jerks, associated with generalized spike and polyspike activity on electroencephalography. In 1963, James Lance and Raymond Adams described intention or action myoclonus in patients who had post-hypoxic encephalopathy (Lance and Adams, 1963). Chronic posthypoxic myoclonus was often restricted to the limbs, increased markedly in frequency and intensity with attempts to move a limb, particularly for precise motor tasks, and was also triggered by sensory stimulation, startle, or strong emotions. In addition to the "positive" spontaneous, action, and stimulus-sensitive forms of myoclonus, affected patients also had "negative myoclonus," with postural lapses in their legs while standing or walking, causing leg buckling and falls, with associated periods of electrical silence in the leg muscles (Frucht and Fahn, 2000; Lance and Adams, 2001). "Positive myoclonus" often followed spike discharges on EEG with a latency of from 7 to 32 msec, whereas "negative myoclonus" was associated with post-spike slow waves or occurred in isolation. Additional associated neurologic findings included dysarthria, cerebellar dysfunction (i.e., dysmetria, intention tremor, and ataxia), gait disturbance, and grand mal seizures.

PATHOLOGIC STARTLE SYNDROMES

Startle is a universal and phylogenetically ancient stereotyped reflex response to sudden, intense stimulation, which can be exaggerated in a wide variety of

neuropsychiatric disorders, including various culture-bound syndromes (e.g., jumping, myriachit, and latah), hyperekplexia, startle epilepsy, benzodiazepine and alcohol withdrawal syndromes, post-traumatic stress disorder, and general anxiety disorder (Howard and Ford, 1992).

Jumping

In 1878, American neurologist George Beard (1839–1883) described the "Jumpers, or jumping Frenchmen" found among the French Canadians of northern Maine (Beard, 1878, 1880a, b). His initial report was based on conversations and correspondence (Beard, 1878), but he subsequently investigated the cases personally (Beard, 1880a, b). He noted excessive reactivity to sounds, automatic obedience, and echolalia. The term "jumping" encompassed all of the associated abnormal startle manifestations, including "lifting the shoulders, raising the hands, striking, throwing, crying, and tumbling" (Beard, 1880b, p. 174). Jumpers were physically healthy and active, and clearly distinguishable from the state of nervous exhaustion which he had previously described and labeled as "neurasthenia" (Beard, 1869). Symptoms persist throughout life, or in Beard's (1880b, p. 176) words: "once a jumper, always a jumper."

Beard felt jumping could only be practically studied by psychological means:

> *Far out of the range of the aided senses, far beyond the reach of the microscope, or perhaps the spectroscope, there may be molecular changes or disturbances which manifest themselves in these jumpings and strikings and throwings as a result and correlative. But for the present, possibly for all time, we can only study this subject psychologically . . . (Beard, 1880b, p. 175)*

The cause of jumping remains unknown. Beard noted that jumping was familial, and believed that jumping was therefore necessarily "hereditary"; however, jumping is rarely seen in women and no detailed pedigrees supporting Mendelian inheritance have been published. Clinical authorities who have examined jumpers have most commonly interpreted jumping to be a culturally standardized startle response or an operant-conditioned response (Saint-Hilaire et al., 1986).

Jumping was largely forgotten until further cases were described in the mid-1960s and afterwards (Kunkle, 1965, 1967; Rabinovitch, 1965). These later descriptions include a somewhat expanded clinical spectrum, which includes pathologic startle reaction, automatic obedience, echolalia, and rarely echopraxia and coprolalia.

Miryachit

In 1884, New York neurologist and former Surgeon General William Hammond (1828–1900) noted similarities between Beard's description of "jumping" and a recently published description of Siberian "miryachit" (meaning "to act foolishly") (Hammond, 1884). Several US Navy officers had observed an affected Siberian ship's steward while on the Ussuri River in southeastern Siberia in 1882. The steward was afflicted by echopraxia, echolalia, and excessive startle, but without reported automatic obedience or actual jumping; he was unable to resist imitating the grunts, shouts, or pounding on the bulkhead intentionally produced by the crew and passengers to provoke his behavior. Unlike Beard, who had personally examined jumpers, Hammond did not make his own personal observations of miryachit.

Hyperekplexia

Hyperekplexia or "startle disease" was described in the late 1950s and early 1960s, and is characterized by generalized hypertonia and hypokinesia in infancy, followed by an exaggerated startle response to unexpected stimuli, gait difficulties, frequent falls without loss of consciousness, nocturnal myoclonus, and increased frequency of hip dislocations and inguinal hernias (Suhren et al., 1966; Anderman et al., 1980; Kurczynski, 1983). An autosomal dominant pattern of transmission was recognized in a pedigree spanning five generations by Suhren et al. (1966). In the 1990s, mutations in the a_1 subunit of the glycine receptor were identified (Shiang et al., 1993). Subsequently, both autosomal dominant and autosomal recessive forms were recognized, with mutations affecting the presynaptic glycine transporter-2, the a_1 and β subunits of the glycine receptor, and other postsynaptic glycinergic proteins including gephyrin and RhoGEF collybistin.

TICS

Tics are involuntary, rapid, non-rhythmic, stereotyped movements that are episodically present and occur on a background of normal movements. Tics can be categorized as motor (e.g., brief movements) or vocal (e.g., abnormal sounds produced by moving air through the nose, mouth, or throat) (The Tourette Syndrome Classification Study Group, 1993). French physician Jean Itard (1775–1838) offered the first clear description of tic disorders in 1825 (Itard, 1825), a report later cited by Gilles de la Tourette (1885), who included Itard's case in his larger series of nine cases. Tics were also recognized by French physician Armand Trousseau (1801–1867), who wrote:

Non-dolorous tic consists of abrupt momentary muscular contractions more or less limited as a general rule, involving preferably the face, but affecting also neck, trunk, and limbs. Their exhibition is a matter of everyday experience. In one case it may be blinking of the eyelids, a spasmodic twitch of cheek, nose, or lip; in another, it is a toss of the head, a sudden, transient, yet ever-recurring contortion of the neck; in a third, it is a shrug of the shoulder, a convulsive movement of diaphragm or abdominal muscles, – in fine, the term embodies an infinite variety of bizarre actions that defy analysis. These tics are not infrequently associated with a highly characteristic cry or ejaculation—a sort of laryngeal or diaphragmatic chorea—which may of itself constitute the condition; or there may be a more elaborate symptom in the form of a curious impulse to repeat the same word or the same exclamation. Sometimes the patient is driven to utter aloud what he would fain conceal. (Trousseau, 1873, p. 267 quoted by Meige and Feindel, 1907, p. 27).

Au41

Tics gained wider recognition late in the 19th century, after Charcot presented cases before his classroom audience (Charcot, 1887/1987). Tics occur as a required diagnostic feature of Tourette syndrome (see below), but can also occur in a wide variety of neurologic disorders.

Gilles de la Tourette syndrome

In 1881, French neurologist Georges Gilles de la Tourette (1857–1904), house physician at the Salpêtrière under Jean-Martin Charcot (1825–1893), translated Beard's report of "jumping Frenchmen" (Gilles de la Tourette, 1881). In 1884, Gilles de la Tourette contrasted American jumping, Siberian miryachit, and a similar Malaysian condition called latah (Gilles de la Tourette, 1884; Lajonchere et al., 1996). He concluded that the three disorders were identical, and reported seeing similar cases on Charcot's service with hyperexcitability, motor tics, echolalia, and coprolalia.

Gilles de la Tourette's classic description of what Charcot later called *maladie des tics de Gilles de la Tourette* was written "with the help of Professor Charcot" and based upon a series of nine patients:

The condition which we will describe generally starts at a young age . . . Although the movements can vary in their form from one individual to another, they still maintain general characteristics which are the same in all subjects. One of these characteristics is the abruptness with which the movements appear and another is their rapidity. Suddenly, and without warning, a grimace or contortion appears once, twice or several times. Then all is quiet. But soon afterwards (for generally the intervals between movements are quite close) new jerks appear. Importantly, most of these movements are limited either to the face, an extremity, or a combination of these two . . . Emotional upset caused by internal conflict or physical discomfort will aggravate both the frequency and the intensity of the abnormal movements. These patients are particularly sensitive to external stimuli: the least surprise will exaggerate the tics, as will strong emotional encounters . . . On the other hand, tics may be diminished and in fact completely suppressed by various factors . . . The movements completely cease during sleep . . . Patients can experience spontaneous periods of remission where incoordination becomes minimal, although never disappearing completely . . . These patients' mental state is perfectly normal . . . During a period of excitement, when the patient has an incoordinated movement, he will begin to shout an inarticulated sound—usually when the movement is at its height. It is often difficult to translate this sound—"hem," "ouh," "ouah," or "ah" . . . Our patients are echolalics, and this marks one of their major symptoms . . . Echolalia should not be considered in its most restricted sense, since these people also will imitate a gesture or an act . . . Not only do these patients say obscene words, but it seems that there can be a combination of echolalia and coprolalia . . . The progression of this condition, as much as we can tell, is slow and insidious . . . Could a patient eventually overcome the problem altogether, after many episodes of remission? We cannot be absolutely certain, but from our case histories, we would conclude that the condition never completely disappears . . . Let us recall first some of the fundamental symptoms: (1) this illness is hereditary; it is characterized by motor incoordination in the form of abrupt muscular jerks that are often severe enough to make the patient jump; (2) the incoordination can be accompanied by articulated or inarticulated sounds. When articulated, the words are often repetitions of words which the patient may have just heard. Such vocal imitation (echolalia) may have a physical corollary whereby the subject imitates an act or gesture that he has just seen; (3) among the expressions which the patient may repeatedly utter during one of his convulsions, some have the special

character of being obscene (coprolalia); (4) the physical and mental health of these patients is otherwise basically normal. The condition seems incurable and life long, with onset in childhood. (Gilles de la Tourette, 1885/1982; as translated by Goetz and Klawans, 1982, pp. 4–10)

Au42

Despite clinical overlap between "jumping" and Gilles de la Tourette syndrome, these entities are now recognized as distinct. In "jumping," the key feature is an abnormal startle response, the abnormal reaction is always *provoked*, and tics are absent; whereas, in Gilles de la Tourette syndrome, the key feature is *spontaneous* motor and vocal tics, although patients with Gilles de la Tourette syndrome may also have an exaggerated startle response.

Gilles de la Tourette did not emphasize spontaneous tics as the essential feature of this syndrome, in part because of his attempt to establish a close relationship between the patients he reported and those with jumping, myriachit, and latah. Echolalia is no longer considered a major clinical feature, and a strict concordance between vocal tics and simultaneous motor tics is no longer accepted. Nevertheless, the modern definition of Gilles de la Tourette syndrome incorporates all the original diagnostic criteria proposed by Gilles de la Tourette (1885) with Charcot's input (Kuschner et al., 1999): childhood onset, motor and vocal tics, natural waxing and waning, and chronicity.

Au43

Freudian psychodynamic and psychological theories of the etiology Gilles de la Tourette syndrome were dominant in the early-20th century. In the 1960s, the discovery that neuroleptic medications, particularly haloperidol, were useful in treating tic disorders provided support for a biological origin for tic disorders, and further supported an important role for dopamine in the pathophysiology (Seignot, 1961; Shapiro et al., 1973). A pathophysiologic role for dopamine has been further suggested by later findings in the 1970s and 1980s that (1) levodopa and dopamine agonists can induce or exacerbate tic disorders; (2) tardive tic disorders can occur after long-term neuroleptic treatment (suggesting facilitation by dopamine receptor hypersensitivity); (3) cerebrospinal fluid metabolites of dopamine (i.e., homovanillic acid) are selectively reduced (suggesting decreased dopamine turnover); and clinical improvement with haloperidol is associated with an increase in cerebrospinal fluid metabolites of dopamine (Klempel, 1974; Klawans et al., 1978; Butler et al., 1979; Cohen et al., 1979; Mitchell and Matthews, 1980; Singer et al., 1982).

Gilles de la Tourette syndrome has been recognized as familial since Gilles de la Tourette's original report (Gilles de la Tourette, 1885). However, no clear pattern of inheritance and no specific gene defect have been documented, although an autosomal dominant pattern with incomplete penetrance and variable expression is most widely accepted. Modern genetic studies of Gilles de la Tourette syndrome have been frustrating because of difficulties in defining phenotypes, and determining whether subjects with obsessive-compulsive symptoms or elements of attention deficit disorder should be considered as affected cases (Goetz et al., 2001e).

CONCLUSION

At the beginning of the 21st century, clinicians and neuroscientists can look with some satisfaction at the progress made in the field of movement disorders, particularly in the half century since Barbeau's historical review in 1958 (Barbeau, 1958) – for example, improved understanding of how the basal ganglia modulate cortical motor function, improved understanding of the pathophysiology of several diseases (e.g., parkinsonism, Wilson's disease, and Huntington's disease), development of effective therapies (e.g., for Parkinson's disease and Wilson's disease), and effective prevention (e.g., for rheumatic fever and its effects, including Sydenham's chorea), development of useful animal models (e.g., the MPTP model of Parkinson's disease, and transgenic mouse, fly, worm, and cellular models of Huntington's disease), and identification of genes for several disorders (e.g., Huntington's disease, Wilson's disease, some familial forms of torsion dystonia, essential tremor, and Parkinson's disease). Still, much more work remains to be done to understand these disorders and treat them effectively. The rapid pace of increasing knowledge in this area, and the recent development of powerful new technologies (e.g., in the fields of neuroimaging, genetics, molecular biology, among others), suggest strongly that further significant progress can be anticipated.

References

Adams RD, Foley JM (1949). The neurological changes in the more common types of severe liver disease. Trans Am Neurol Assoc 74: 217–219.

Adams RD, Foley JM (1953). The neurological disorders associated with liver disease. Res Publ Assoc Res Nerv Ment Dis 32: 198–237.

Adams RD, van Bogaert (1964). Striato-nigral degeneration. J Neuropathol Exp Neurol 23: 584–608.

Albin RL, Aldridge JW, Young AB et al. (1989a). Feline subthalamic nucleus neurons contain glutamate-like but not GABA-like or glycine-like immunoreactivity. Brain Res 491: 185–188.

Albin RL, Young AB, Penney JB (1989b). The functional anatomy of basal ganglia disorders. Trends Neurosci 12: 366–375.

Albin RL, Young AB, Penney JB et al. (1990). Abnormalities of striatal projection neurons and N-methyl-D-aspartate receptors in presymptomatic Huntington's disease. N Engl J Med 322: 1293–1298.

Albin RI, Reiner A, Anderson KD et al. (1992). Preferential loss of striato-external pallidal projection neurons in presymptomatic Huntington's disease. Ann Neurol 31: 425–430.

Alexander GE, DeLong MR (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci 9: 357–381.

Alzheimer (1911). Über die anatomische Grundlage der Huntingtonischen Chorea und der choreatischen Bewegungen überhaupt. Z Gesamte Neurol Psychiatr 3: 566–567.

American College of Medical Genetics/American Society of Human Genetics Huntington Disease Genetic Testing Working Group (1998). ACMG/ASHG statement: Laboratory guidelines for Huntington disease genetic testing. Am J Hum Genet 62: 1243–1247.

Anden NE, Carlsson A, Dahlstroem A et al. (1964). Demonstration and mapping out of nigro-neostriatal dopamine neurons. Life Sci 3: 523–530.

Anden NE, Dahlstrom, Fuxe K et al. (1965). Further evidence for the presence of nigro-strital dopamine neurons in the rat. Am J Anat 116: 329–333.

Andermann F, Keene DL, Andermann E et al. (1980). Startle disease or hyperekplexia: further delineation of the syndrome. Brain 103: 985–997.

Andrew SE, Goldberg YP, Kremer B et al. (1993). The relationship between trinucleotide (CAG) repeat length and clinical features of Huntington's disease. Nat Genet 4: 398–403.

Arima K, Ueda K, Sunohara N et al. (1998). NACP/alpha-synuclein immunoreactivity in fibrillary components of neuronal and oligodendroglial cytoplasmic inclusions in the pontine nuclei in multiple system atrophy. Acta Neuropathol (Berl) 96: 439–444.

Ayd JL Jr (1961). A survey of drug-induced extrapyramidal reactions. JAMA 75: 1054–1060.

Aziz TZ, Peggs D, Sambrook MA et al. (1991). Lesions of the subthalamic nucleus for the alleviation of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism in the primate. Mov Disord 6: 288–292.

Barbeau A (1958). The understanding of involuntary movements: an historical approach. J Nerv Ment Dis 127: 469–489.

Barbeau A (1965). Degenerescence plurisystematisee du nevraxe. Syndrome de Steele–Richardson–Olszewski. Un Med Can 94: 715–718.

Barbeau A (1970). Parental ascent in the juvenile form of Huntington's chorea. Lancet 2: 927.

Barbeau A, Sourkes TL, Murphy GF (1962). Les catécholamines dans la maladie de Parkinson. In: J de Ajuriaguerra (Ed.), Monoamines et Système Nerveux Central. Georg, Genève and Masson, Paris, pp. 247–262.

Barraquer-Bordas L, Giménez-Roldán S (1988). Idiopathic torsion dystonia as described by Barraquer-Roviralta. Adv Neurol 50: 665–666.

Barraquer Roviralta L (1897). Contribución al estudio de la atetosis. Gac Med Catalana 20: 385–391.

Beal MF, Kowall NW, Ellison DW et al. (1986). Replication of the neurochemical characteristics of Huntington's disease by quinolinic acid. Nature 32: 168–171.

Beard GM (1869). Neurasthenia, or nervous exhaustion. Boston Med Surg J 80: 217–221.

Beard G (1878). Dr. Beard's verbal communication. J Nerv Ment Dis 5: 525–526.

Beard GM (1880a). Experiments with the "jumpers" or "jumping Frenchmen" of Maine. J Nerv Ment Dis 7: 487–490.

Beard GM (1880b). Experiments with the "jumpers" of Maine. Popul Sci Monthly 18: 170–178.

Beard GM, Rockwell AD (1871). A Practical Treatise on the Medical and Surgical Uses of Electricity Including Localized and General Electrolization. William Wood, Philadelphia, PA, p. 452.

Bearn AG (1957). Wilson's disease. An inborn error of metabolism with multiple manifestations. Am J Med 22: 747–757.

Bearn AG (1960). A genetical analysis of 30 families with Wilson's disease (hepatolenticular degeneration). Ann Hum Genet 24: 33–43.

Bearn AG, Kunkel HG (1952). Biochemical abnormalities in Wilson's disease. J Clin Invest 31: 616.

Bell C (1830). The Nervous System of the Human Body. Longmans, London, p. 221.

Benabid AL, Pollak P, Louveau A et al. (1987). Combined (thalmotomy and stimulation) stereotactic surgery of the VIM thalamic nucleus for bilateral Parkinson's disease. Appl Neurophysiol 50: 344–346.

Benabid AL, Pollak P, Gervason C et al. (1991). Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus. Lancet 337: 403–406.

Benabid AL, Pollak P, Gross C et al. (1994). Acute and long-term effects of subthalamic nucleus stimulation in Parkinson's disease. Stereotact Funct Neurosurg 62: 76–84.

Benazzouz A, Gross C, Feger J et al. (1993). Reversal of rigidity and improvement in motor performance by subthalamic high-frequency stimulation in MPTP-treated monkeys. Eur J Neurosci 5: 382–389.

Berciano J, Combarros O, Polo JM et al. (1999). An early description of striatonigral degeneration. J Neurol 246: 462–466.

Bergman H, Wichmann T, DeLong MR (1990). Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. Science 249: 1436–1438.

Bergman H, Wichmann T, Karmon B et al. (1994). The primate subthalamic nucleus. II. Neuronal activity in the MPTP model of Parkinsonism. J Neurophysiol 72: 507–520.

Bertler A, Rosengren E (1959). Occurrence and distribution of catechol amines in brain. Acta Physiol Scand 47: 350–361.

Birkmayer W, Hornykiewicz O (1961). Der L-3,4-Dioxyphenylalanin (=DOPA)-Effekt bei der Parkinson-Akinese. Wien Klin Wochenschr 73: 787–788. [English translation in Parkinsonism Rel Dis 1998; 4: 59–60.]

Blackwood WRD (1889). Mechanical writing in the prevention and cure of writers' cramp and allied disorders. Au48 Medical Register 5: 365–366.

Blocq P, Marinescu G (1893). Sur un cas de tremblement parkinsonien hemiplegique symptomatique d'une tuneur du peduncle cerebral. C R Hebd Seances et Memoires Au49 Soc Bio 5: 105–111.

Boutielle EM (1810). Traite de la Choree, ou Danse de St. Guy. Vincard, Paris.

Bramwell B (1916). Familial cirrhosis of the liver: Four cases of acute fatal cirrhosis in the same family, the patients being respectively nine, ten, fourteen and fourteen years of age: suggested relationship to Wilson's progressive degeneration of the lenticular nucleus. Edinburgh Med J 17: 90–99.

Brandt J, Bylsma FW, Gross R et al. (1996). Trinucleotide repeat length and clinical progression in Huntington's disease. Neurology 46: 527–531.

Brewer GJ, Hill GM, Prasad AS et al. (1983). Oral zinc therapy for Wilson's disease. Ann Intern Med 99: 314–320.

Brewer GJ, Dick RD, Johnson V et al. (1998). Treatment of Wilson's disease with zinc: XV. Long-term follow-up studies. J Lab Clin Med 132: 264–278.

Bright R (1831). Reports of Medical Cases Selected with a View of Illustrating the Symptoms and Cure of Disease by Reference to Morbid Anatomy. Longman, London.

Brin MF, Fahn S, Moskowitz C et al. (1987). Localized injections of botulinum toxin for the treatment of focal dystonia and hemifacial spasm. Mov Disord 2: 237–254.

Brissaud E (1895). Leçons sur les Maladies du Systeme Nerveux. Masson, Paris.

Broadbent WH (1869). On the pathology of chorea. Br Med J 86: 345–347, 369–371.

Browning W (1908a). Rev. Charles Oscar Waters, M.D. Neurographs 1: 137–144.

Browning W (1908b). Irving Whitall Lyon, M.D. Neurographs 1: 147–149.

Brusa A, Stoehr R, Pramstaller PP (2004). Progressive supranuclear palsy: New disease or variant of postencephalitic parkinsonism. Mov Disord 19: 247–252.

Bull PC, Thomas GR, Rommens JM et al. (1993). The Wilson disease gene is a putative copper transporting P-type ATPase similar to the Menkes gene. Nat Genet 5: 327–337.

Burke RE, Fahn S, Marsden CD (1986). Torsion dystonia: a double-blind, prospective trial of high-dosage trihexphenidyl. Neurology 36: 160–164.

Burns RS, Chiueh CC, Markey SP et al. (1983). A primate model of parkinsonism: selective destruction of dopaminergic neurons in the pars compacta of the substantia nigra by N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Au50 Proc Natl Acad Sci USA 80: 4564–4550.

Burr CW (1895). Local spasms. Occupation spasms. In: FX Dercum (Ed.), A Text-book on Nervous Diseases by American Authors. Lea Brothers and Co., Philadelphia, PA, pp. 275–279.

Butler IJ, Koslow SH, Seifert WE Jr et al. (1979). Biogenic amine metabolism in Tourette syndrome. Ann Neurol 6: 37–39.

Buzzard T (1872). Two cases of impaired writing power treated successfully by electricity. Practitioner 9: 65–74.

Calne DB, Reid JL, Vakil SD et al. (1971). Idiopathic parkinsonism treated with extracerebral decarboxylase inhibitor in combination with levodopa. Br Med J 3: 729–732.

Calne DB, Teychenne PF, Claveria LE et al. (1974). Bromocriptine in parkinsonism. Br Med J 4: 442–444.

Campion D, Martin C, Heilig R et al. (1995). The NACP/synuclein gene: chromosomal assignment and screening for alterations in Alzheimer disease. Genomics 26: 254–257.

Canfield RM, Putnam JJ (1884). A case of acute hemiplegic chorea; with autopsy and remarks. Boston Med Surg J 111: 220–223. Au51

Carlsson A (1959). The occurrence, distribution and physiological role of catecholamines in the nervous system. Pharmacol Rev 11: 490–493.

Carlsson A (2003). A half-century of neurotransmitter research: Impact on neurology and psychiatry. In: H Jörnvall (Ed.), Nobel Lectures, Physiology or Medicine 1996–2000. World Scientific, Singapore, pp. 303–322.

Carlsson A, Lindqvist M, Magnusson T (1957). 3,4-Dihydroxyphenylalanine and 5-hydroxytryptophan as reserpine antagonists. Nature 180: 1200.

Carpenter MB (1950). Athetosis and the basal ganglia: Review of the literature and study of forty-two cases. Arch Neurol Psychiatry 63: 875–901.

Carpenter MB (1955). Ballism associated with partial destruction of the subthalamic nucleus of Luys. Neurology 5: 479–489.

Carpenter MB, Carpenter CS (1951). Analysis of somatotopic relations of the corpus Luysi in man and monkey: Relation between the site of dyskinesia in distribution of lesions within the subthalamic nucleus. J Comp Neurol 95: 349–370.

Carpenter MB, Whittier JR, Mettler FA (1950). Analysis of choreoid hyperkinesias in the rhesus monkey. Surgical and pharmacological analysis of hyperkinesias resulting from lesions in the subthalamic nucleus of Luys. J Comp Neurol 92: 293–331.

Charcot JM (1877a). Introductory. In: G Sigerson (Trans.), Lectures on Diseases of the Nervous System: Delivered at La Salpêtrière. Vol. 1. New Sydenham Society, London, pp. 1–19.

Charcot JM (1877b). On paralysis agitans. In: G Sigerson (Trans.), Lectures on Diseases of the Nervous System: Delivered at La Salpêtrière. Vol. 1. New Sydenham Society, London, pp. 129–156.

Charcot JM (1881). On athetosis. In: G Sigerson (Trans.), Lectures on Diseases of the Nervous System: Delivered at La Salpêtrière. Vol. 2. New Sydenham Society, London, pp. 390–394.

Charcot JM (1887). Tremblements et mouvements chroréiformes. Chorée rhythmée. In: Leçons sur les maladies Au52 du système nerveux faites a la Salpêtrière. A. Delahaye et E. Lecrosnie, Paris, pp. 209–225.

Charcot J-M (1887/1987). Gilles de la Tourette syndrome: a child with convulsive tic and coprolalia: December 13, 1887. In: CG Goetz (Trans.), Charcot: The Clinician: The Tuesday Lessons: Excerpts from Nine Case Presentations on General Neurology Delivered at the Salpêtrière Hospital in 1887–88. Raven Press, New York, pp. 56–70.

Charcot JM (1889). Tremors and choreiform movements – Rhythmical chorea. In: T Savill (Trans.), Clinical Lectures on Diseases of the Nervous System: Delivered at the Infirmary of La Salpêtrière. Vol. 3. New Sydenham Society, London, pp. 183–197.

Charcot JM, Vulpian A (1861). De la paralysie agitante. Gaz Au53 Hebdomadaire Med Chirurg 8: 765–767, 816–820, and 1861; 9: 54–59.

Chen X, de Silva HA, Pettenati MJ et al. (1995). The human NACP/alpha-synuclein gene: Chromosome assignment to 4q21.3-q22 and TaqI RFLP analysis. Genomics 26: 425–427.

Chien CP, DiMascio DI, DiMascio A (1967). Drug-induced extra-pyramidal symptoms and their relations to clinical efficacy. Am J Psychiatry 123: 1490–1498.

Ciechanover A (2005). Intracellular protein degradation: From a vague idea thru the lysosome and the ubiquitin-proteasome system and onto human diseases and drug targeting. In: T Frängsmyr (Ed.), Les Prix Nobel. The Nobel Prizes 2004. Nobel Foundation, Stockholm, pp. 151–175.

Coburn AF (1931). The Factor of Infection in the Rheumatic State. Williams and Wilkins, Baltimore, MD.

Coburn AF, Moore LV (1939). The prophylactic use of sulfonamide in streptococcal respiratory infections, with special reference to rheumatic fever. J Clin Invest 18: 147–155.

Cohen DJ, Shaywitz BA, Young JG et al. (1979). Central biogenic amine metabolism in children with syndrome of chronic multiple tics of Gilles de la Tourette: Norepinephrine, serotonin, and dopamine. J Am Acad Child Psychiatry 18: 320–341.

Conn HO (1960). Asterixis in non-hepatic disorders. Am J Med 29: 647–664.

Corbin KB (1949). Trihexyphenyl: Evaluation of a new agent in the treatment of Parkinson's disease. JAMA 141: 373–381.

Correns CG (1900). Mendel's Regel über das Verhalten der Nachkommenschaft der Rassenbastarde. Berichte der Au54 Deutschen Botanischen Gesellschaft 18: 158–168.

Corrodi H, Fuxe J, Hökfelt T et al. (1973). Effect of ergot drugs on central catecholamine neurons: Evidence for a stimulation of central dopamine neurons. J Pharm Pharmacol 25: 409–412.

Cotzias GC, Van Woert MH, Schiffer LM (1967). Aromatic acids and modification of parkinsonism. N Engl J Med 276: 374–379.

Cotzias GC, Papavasiliou PS, Gellene R (1969). Modification of parkinsonism – chronic treatment with L-DOPA. N Engl J Med 280: 337–345.

Cotzias GC, Papavasiliou PS, Fehling C et al. (1970). Similarities between neurologic effects of L-dopa and of apomorphine. N Engl J Med 282: 31–33.

Cotzias GC, Papavasiliou PS, Tolosa ES et al. (1976). Treatment of Parkinson disease with apomorphines: possible role of growth hormone. N Engl J Med 294: 567–572.

Coyle JT, Schwarcz R (1976). Lesion of striatal neurons with kainic acid provides a model for Huntington's chorea. Nature 263: 244–246.

Creutzfeldt HG (1920). Uber eine eigenartige herdomige Erkrankung des Zentralnervensystems. Z Gesamte Neurol Psychiatr 57: 1–18. Au55

Critchley M (1949). Observations on essential (heredofamilial tremor). Brain 72: 113–139.

Crossman AR (1989). Neural mechanism in disorders of movement. Comp Biochem Physiol A 93: 141–149.

Cumings JN (1948). The copper and iron content of brain and liver in the normal and in hepatolenticular degeneration. Brain 71: 410–415.

Cumings JN (1951). The effects of BAL in hepatolenticular degeneration. Brain 74: 10–22.

Dale RC, Church AJ, Sutees RA et al. (2004). Encephalitis lethargica syndrome: 20 new cases and evidence of basal ganglia autoimmunity. Brain 127: 21–33.

Dana CL (1887). Hereditary tremor: A hitherto undescribed form of motor neurosis. Am J Med Sci 94: 386–393.

Davies SW, Turmaine M, Cozens BA et al. (1997). Formation of neuronal intranuclear inclusions underlies the neurological dysfunction in mice transgenic for the HD mutation. Cell 90: 537–548.

Davis CH Jr, Kunkle EC (1951). Benign essential (heredofamilial) tremor. Arch Intern Med 87: 808–816.

Davis GC, Williams AC, Markey SP et al. (1979). Chronic parkinsonism secondary to intravenous injections of meperidine analogues. Psychiatry Res 1: 249–254.

Dawbarn D, De Quidt ME, Emson PC (1985). Survival of basal ganglia neuropeptide Y-somatostatin neurons in Huntington's disease. Brain Res 340: 251–260.

Dawson JR (1934). Cellular inclusions in cerebral lesions of epidemic encephalitis (Second report). Arch Neurol Psychiatry 31: 685–700.

de la Böe F (Sylvius) (1663). Disputationes medicarum. Van den Bergh, Amstelodami.

De Vries H (1900). Sur la loi de disjonction des hybrids. C R Acad Sci 130: 845–847. Au56

Degwitz R, Frowein R, Kulenkampff C et al. (1960). Über die Wirkungen des L-DOPA beim Menschen und deren Beeinflussung durch Reserpin, Chlorpromazin, Iproniazid und Vitamin B6. Wien Klin Wochenschr 38: 120–123.

Dejerine JJ, Thomas A (1900). L'atrophie olivo-ponto-cérébelleuse. Nouvelle Iconographie de la Salpêtrière, Paris 13: 330–370.

Dejerine JJ, Thomas A (1900/1977). Olivopontocerebellar atrophy. In: DA Rottenberg, FH Hochberg (Eds.), Neurological Classics in Modern Translation. Hafner Press, New York, pp. 219–251.

Delay J, Deniker P, Harl JM (1952). Utilisation en therapeutique psychiatrique d'une phénothiazine d'action centale elective. Ann Med Psychol (Paris) 110: 112–117.

DeLong MR (1990). Primate models of movement disorders of basal ganglia origin. Trends Neurosci 13: 281–285.

Dening TR, Berrios GE (1990). Eponymous confusion over Bruno Fleischer. Lancet 335: 291.

Denny Brown D, Porter H (1951). The effects of BAL (2,3-dimercaptopropanol) on hepatolenticular degeneration (Wilson's disease). N Engl J Med 245: 917–925.

Dewey RB Jr, Jancovic K (1989). Hemiballism-hemichorea. Clinical and pharmacologic findings in 21 patients. Arch Neurol 46: 862–867.

Dickman MS (2001). von Economo encephalitis. Arch Neurol 58: 1696–1698.

DiFiglia M, Sapp E, Chase KO et al. (1997). Aggregation of huntingtin in neuronal intranuclear inclusions and dystrophic neurites in brain. Science 277: 1990–1993.

Dooling EC, Adams RD (1975). The pathological anatomy of posthemiplegic athetosis. Brain 98: 29–48.

Dorshay LJ, Constable K (1949). Active therapy for parkinsonism. JAMA 140: 1317.

Dupont E, Hansen HJ, Dalby MA (1973). Treatment of benign essential tremor with propranolol. A controlled clinical trial. Acta Neurol Scand 49: 75–84.

Duyao M, Ambrose C, Myers R et al. (1993). Trinucleotide repeat length instability and age of onset in Huntington's disease. Nat Genet 4: 387–392.

Ehringer H, Hornykiewicz O (1960). Verteilung von noradrenalin und domapin (3-hydroxytyramin) im gehirn des menschen. Wien Klin Wochenschr 38: 1236–1239.

Eldridge R (1970). The torsion dystonias: literature review and genetic and clinical studies. Neurology 20: 1–78.

Elston JS, Russell RW (1985). Effect of treatment with botulinum toxin on neurogenic blepharospasm. Br Med J (Clin Res Ed) 290: 1857–1859.

Ernst AM (1965). Relation between action of dopamine and apomorphine and the O-methylated derivatices upon the CNS. Psychopharmacology (Berl) 7: 391–399.

Eshner AA (1897). A graphic study of tremor. J Exp Med 2: 301–312.

Fahn S (1983). High-dosage anticholinergic therapy in dystonia. Adv Neurol 37: 177–188.

Fahn S (1988). Concept and classification of dystonia. Adv Neurol 50: 1–8.

Farrer LA, Cupples LA, Kiely DK et al. (1992). Inverse relationship between age at onset of Hungtinton disease and pateranal age suggests involvement of genetic imprinting. Am J Hum Genet 50: 528–535.

Faurbye A, Rasch RJ, Bender Petersen P et al. (1964). Neurological symptoms in phyarcotherapy of psychosis. Acta Psychiatr Scand 40: 10–27.

Fehling C (1966). Treatment of Parkinson's syndrome with L-DOPA: A double blind study. Acta Neurol Scand 42: 367–372.

Ferrante RJ, Kowall NW, Beal MF et al. (1985). Selective sparing of a class of striatal neurons in Huntington's disease. Science 230: 561–563.

Ferrante RJ, Kowall NW, Beal MF et al. (1987). Morphologic and histochemical characteristics of a spared subset of striatal neurons in Huntington's disease. J Neuropathol Exp Neurol 46: 12–27.

Ferrier D (1876). The Functions of the Brain. Smith, Elder and Company, London.

Findley LJ, Cleeves L, Calzettti S (1985). Primidone in essential tremor of the hands and head a double-blind controlled clinical study. J Neurol Neurosurg Psychiatry 481: 911–915.

Flatau E, Sterling W (1911). Progressiver Torsionspasmus bie Kindern. Z Gesamte Neurol Psychiatr 7: 586–612.

Fleischer B (1903). Zwei weitere Fälle von grünlicher Verfärbung der Kornea. Klin Monatsbl Augenheilkd 41: 335–352.

Foley P (2000). The L-DOPA story revisited. Further surprises to be expected? The contribution of Isamu Sano to the investigation of Parkinson's disease. J Neural Transm Suppl 60: 1–20.

Foley P (2003). Beans, roots and leaves: a brief history of the pharmacological therapy of parkinsonism. Wurzbg Medizinhist Mitt 22: 215–234.

Forel A (1877). Untersuchungen über die Haubenregion und ihre oberen Verknupfungen im Gehirne des Menschen und einiger Saügethiere, mit Beiträgen zu den Methoden des Gehirnuntersuchungen. Arch Psychiatry 7: 182, 393–495.

Forno LS, Langston JW, DeLanney LE et al. (1986). Locus ceruleus lesions and eosinophilic inclusions in MPTP-treated monkeys. Ann Neurol 20: 449–455.

Freidreich N (1863). Über degenerative Atrophie der spinalen Hinterstränge. Virchows Arch Pathol Anat Physiol Klin Med 26: 391–419, 433–459; 27: 1–26.

Freidreich N (1881). Neuropathologische Beobachtung beim Paramyoklonus Multiplex. Virchows Arch Pathol Anat Physiol Klin Med 86: 421–434.

Freyhan FA (1957). Psychomotility and parkinsonism in treatment with neuroleptic drugs. Arch Neurol Psychiatry 78: 465–472.

Fritsch G, Hitzig E (1870/1960). On the electrical excitability of the cerebrum. In: G von Bonin (Ed.), Some Papers on the Cerebral Cortex. Charles C Thomas, Springfield, IL, pp. 73–96.

Frucht S, Fahn S (2000). The clinical spectrum of posthypoxic myoclonus. Mov Disord 15: 2–7.

Frydman M, Bonne-Tamir B, Farrer LA et al. (1985). Assignment of the gene for Wilson disease to chromosome 13: Linkage to the esterase D locus. Proc Natl Acad Sci USA 82: 1819–1821.

Furtado S, Suchowersky O, Rewcastle NB et al. (1996). Relationship between trinucleotide repeats and neuropathological changes in Huntington's disease. Ann Neurol 39: 132–136.

Galilei G (1610/1978). Letter dated January 7, 1610. In: S Drake (Ed.), Galileo at Work: His Scientific Biography. University of Chicago Press, Chicago, IL, p. 147.

Giasson BI, Duda JE, Murray IVJ et al. (2000). Oxidative damage linked to neurodegeneration by selective alpha-synuclein nitration in synucleinopathy lesions. Science 290: 985–989.

Gibb WRG, Luthert PJ, Marsden CD (1989). Corticobasal degeneration. Brain 112: 1171–1192.

Gildenberg PL (1998). The history of surgery for movement disorders. Neurosurg Clin N Am 9: 283–293.

Gilles de la Tourette G (1881). Les 'sauters' du Maine (États-Unis): Par G. Beard. Arch Neurol (Paris) 2: 146–150.

Gilles de la Tourette G (1884). Jumping, Latah, Myriachit. Arch Neurol (Paris) 8: 68–74.

Gilles de la Tourette G (1885). Étude sur une affection nerveuse caracteris'e par de l'incoordination motrice accompagn'e de echolalie et de copralalie. Arch Neurol (Paris) 9: 19–42, 158–200.

Gilliam TC, Tanzi RE, Haines JL et al. (1987). Localization of the Huntington's disease gene to a small segment of chromosome 4 flanked by D4S10 and the telomere. Cell 50: 565–571.

Gilman AG (1997). G proteins and regulation of adenylyl cyclase. In: N Ringertz (Ed.), Nobel Lectures, Physiology or Medicine 1991–1995. World Scientific, Singapore, pp. 182–212.

Glazebrook AJ (1945). Wilson's disease. Edinburgh Med J 52: 83–87.

Goetz CG (1986). Charcot on Parkinson's disease. Mov Disord 1: 27–32.

Goetz CG, Klawans HL (1982). Gilles de la Tourette on Tourette syndrome. Adv Neurol 35: 1–16.

Goetz CG, Bonduelle M, Gelfand T (1995). Charcot: Constructing Neurology. Oxford University Press, New York, pp. 113–120.

Goetz CG, Chmura TA, Lanska DJ (2001a). The basal ganglia: Part 1 of the MDS-sponsored History of Movement Disorders Exhibit, Barcelona, Spain, June 2000. Mov Disord 16: 152–155.

Goetz CG, Chmura TA, Lanska DJ (2001b). The history of Parkinson's disease: Part 2 of the MDS-sponsored History of Movement Disorders Exhibit, Barcelona, Spain, June 2000. Mov Disord 16: 156–161.

Goetz CG, Chmura TA, Lanska DJ (2001c). History of chorea: Part 3 of the MDS-sponsored History of Movement Disorders Exhibit, Barcelona, Spain, June 2000. Mov Disord 16: 331–338.

Goetz CG, Chmura TA, Lanska DJ (2001d). History of dystonia: Part 4 of the MDS-sponsored History of Movement Disorders Exhibit, Barcelona, Spain, June 2000. Mov Disord 16: 339–345.

Goetz CG, Chmura TA, Lanska DJ (2001e). History of tic disorders and Gilles de la Tourette syndrome: Part 5 of the MDS-sponsored History of Movement Disorders Exhibit, Barcelona, Spain, June 2000. Mov Disord 16: 346–349.

Goetz CG, Chmura TA, Lanska DJ (2001f). Seminal figures in the history of movement disorders: Sydenham, Parkinson, and Charcot: Part 6 of the MDS-sponsored History of Movement Disorders Exhibit, Barcelona, Spain, June 2000. Mov Disord 16: 537–540.

Goetz CG, Chmura TA, Lanska DJ (2001g). Parkinson-plus syndromes: Part 7 of the MDS-sponsored History of Movement Disorders Exhibit, Barcelona, Spain, June 2000. Mov Disord 16: 541–544.

Goetz CG, Chmura TA, Lanska DJ (2001h). History of myoclonus: Part 8 of the MDS-sponsored History of Movement Disorders Exhibit, Barcelona, Spain, June 2000. Mov Disord 16: 545–547.

Goetz CG, Chmura TA, Lanska DJ (2001i). Seminal figures in the history of movement disorders: Gilles de la Tourette, Oppenheim, the Vogts, von Economo, Wilson, and Marsden: Part 12 of the MDS-sponsored History of Movement Disorders Exhibit, Barcelona, Spain, June 2000. Mov Disord 16: 940–946.

Goff DC, Arana GW, Greenblatt DJ et al. (1991). The effect of benztropine on haloperidol-induced dystonia, clinical efficacy and pharmacokinetics: A prospective, double-blind trial. J Clin Psychopharmacol 11: 106–112.

Golbe LI, Di Iorio G, Banavita V et al. (1990). A large kindred with autosomal dominant Parkinson's disease. Ann Neurol 27: 276–282.

Goldman MS, Ahlskog JE, Kelly PJ (1992). The symptomatic and functional outcome of stereotactic thalamotomy for medically intractable essential tremor. J Neurosurg 76: 924–928.

Goldstein M, Anagoste B, Owen S et al. (1966). The effects of ventromedial segmental lesions on the biosynthesis of catecholamines in the striatum. Life Sci 5: 2171–2176.

Gowers WR (1876). On "athetosis" and post-hemiplegic disorders of movement. Medical-Chirurgical Trans 59: Au60
271–326.

Gowers WR (1888). A Manual of Diseases of the Nervous System. J and A Churchill, London.

Gowers WR (1906). On tetanoid chorea and its association with cirrhosis of the liver. Rev Neurol Psychiatry Au61
4:249–258.

Graham JG, Oppenheimer DR (1969). Orthostatic hypotension, and nicotine sensitivity in a case of multiple system atrophy. J Neurol Neurosurg Psychiatry 32: 28–34.

Greenfield JG, Bosanquet FD (1953). The brain-stem lesions in parkinsonism. J Neurol Neurosurg Psychiatry 16: 213–226.

Greenfield JG, Wolfsohn JM (1922). The pathology of Sydenham's chorea. Lancet 2: 603–606.

Groth CG, Dubois RS, Corman J et al. (1973). Hepatic transplantation in Wilson disease. Birth Defects Orig Artic Ser 9: 106–108.

Grundmann K (2005). Primary torsion dystonia. Arch Neurol 62: 682–685.

Guridi J, Obeso JA (2001). The subthalamic nucleus, hemiballismus and Parkinson's disease: Reappraisal of a neurosurgical dogma. Brain 124: 5–19.

Gusella JF, Wexler NS, Conneally PM et al. (1983). A polymorphic DNA marker genetically linked to Huntington's disease. Nature 306: 234–238.

Gusella J, Tanzi RE, Bader PI et al. (1985). Deletion of Huntington's disease linked G8 (D4S10) locus in Wolf-Hirschhorn syndrome. Nature 318: 75–78.

Hall HC (1921). La degenerescence Hepatolenticulare. Maladie de Wilson-pseudosclerose. Masson, Paris.

Hall RA, Jackson RB, Swain JM (1956). Neurotoxic reactions resulting from chlorpromazine administration. JAMA 161: 214–218.

Hallett M (1986). Early history of myoclonus. Adv Neurol 43: 7–10.

Hamani C, Saint-Cyr JA, Fraser J et al. (2003). The subthalamic nucleus in the context of movement disorders. Brain 127: 4–20.

Haméleers R, Temel Y, Visser-Vandewalle V (2006). History of the corpus Luysii: 1865–1995. Arch Neurol 63: 1340–1342.

Hammond GM (1890). Pathological findings in the original case of athetosis. J Nerv Ment Dis 17: 555.

Au62 Hammond WA (1871). Athetosis. In: A Treatise on Diseases of the Nervous System. D. Appleton and Co., New York, pp. 654–662.

Hammond WA (1884). Miryachit: a newly described disease
Au63 of the nervous system, and its analogues. N Y Med J 39: 191–192.

Au64 Hammond WA, Hammond GM (1893). Athetosis. In: A Treatise on Diseases of the Nervous System. D. Appleton and Co., New York, pp. 315–325.

Hamon J, Paraire J, Velluz J (1952). Remarques sur l'action du 4560 RP sur l'agitation maniaque. Ann Med Psychol (Paris) 110: 331–335.

Haškovec L (1901). L'Akathisie. Rev Neurol 9: 1107–1109.

Hassler R (1938). Zur Pathologie der Paralysis agitans und des post-encephalitischen Parkinsonismus. J Psychol
Au65 Neurol 18: 387–455.

Hassler R, Riechert T (1954). Indikationen und lokalisationsmethode der gezielten hirnoperationen. Nervenartz 25: 441–447.

Haurowitz F (1930). Ueber eine Anomalie des Kupferstoffwechsels. Hoppe-Seylers Z Physiol Chem 190: 72–74.

Hayashi S, Wakabayashi K, Ishikawa A et al. (2000). An autopsy case of autosomal-recessive juvenile parkinsonism with a homozygous exon 4 deletion in the parkin gene. Mov Disord 15: 884–888.

Heikkila RL, Manzio L, Cabbat FS et al. (1984). Protection against the dopaminergic neurotoxicity of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine by monoamine oxidase inhibitors. Nature 311: 467–469.

Hershko A (2005). The ubiquitin system for protein degradation and some of its roles in the control of the cell division cycle. In: T Frängsmyr (Ed.), Les Prix Nobel. The Nobel Prizes 2004. Nobel Foundation, Stockholm, pp. 187–200.

Herz E (1944a). Dystonia, I: Historical review, analysis of dystonic symptoms and psychologic mechanisms involved. Arch Neurol Psychiatry 51: 305–318.

Herz E (1944b). Dystonia, II: Clinical classification. Arch Neurol Psychiatry 51: 319–355.

Herz E (1944c). Dystonia, III: Pathology and conclusions. Arch Neurol Psychiatry 52: 20–26.

Holdorff B (2002). Friedrich Heinrich Lewy (1885–1950) and his work. J Hist Neurosci 11: 19–28.

Holmberg CG, Laurell CB (1947). Investigations in serum copper. I. Nature of serum copper and its relation to the iron-binding protein in human serum. Acta Chem Scand 1: 944–950.

Holmberg CG, Laurell CB (1948). Investigations in serum copper. II. Isolation of the copper containing protein, and a description of some of its properties. Acta Chem Scand 2: 550–556.

Hoogenraad TU, Koevoet R, De Ruyter Korver EGWM (1979). Oral zinc sulfate as long-term treatment in Wilson's disease (hepatolenticular degeneration). Eur Neurol 18: 205–211.

Hoogenraad TU, Van Hattum J, Van den Hamer CJA (1987). Management of Wilson's disease with zinc sulfate: Experience in a series of 27 patients. J Neurol Sci 77: 137–146.

Hoogeveen AT, Willemsen R, Meyer N et al. (1993). Characterization and localization of the Huntington disease gene product. Hum Molec Genet 2: 2069–2073.

Hornykiewicz O (2001). How L-DOPA was discovered as a drug for Parkinson's disease 40 years ago. Wien Klin Wochenschr 113: 855–862.

Howard R, Ford R (1992). From the jumping Frenchmen of Maine to post-traumatic stress disorder: The startle response in neuropsychiatry. Psychol Med 22: 695–707.

Huntington G (1872). On chorea. Med Surg Rep 26: Au66
317–321.

Huntington's Disease Collaborative Research Group (1993). A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. Cell 72: 971–983.

Husby G, van de Rijn I, Zabriskie JB et al. (1976). Antibodies reacting with cytoplasm of subthalamic and caudate nuclei neurons in chorea and acute rheumatic fever. J Exp Med 144: 1094–1110.

Ishikawa A, Miyatake T (1995). A family with hereditary juvenile dystonia-parkinsonism. Mov Disord 10: 482–488.

Itard JMG (1825). Mémoire sur quelques functions involuntaires des appareils de la locomotion, de l'apprehension et de la voix. Arch Gen Med 8: 385–407. Au67

Jackson JH (1868/1932/1996). Observations on the physiology and pathology of hemi-chorea. In: J Taylor, G Holmes, FMR Walshe (Eds.), John Hughlings Jackson: Selected Writings. Vol. 2. Arts and Boeve, Nijmegen, pp. 238–245.

Jackson JH (1876/1932/1996). On epilepsies and on the after-effects of epileptic discharges (Todd and Robertson's hypothesis). In: J Taylor, G Holmes, FMR Walshe (Eds.), John Hughlings Jackson: Selected Writings. Vol. 1. Arts and Boeve, Nijmegen, pp. 135–161.

Jacob A (1921). Uber eigenartige Erkrankungen des Zentralnervensystems mit bemerkenswerten anatomischen Befunden (spastische Pseudosklerose, Encephalomyelopathie mit disseminierten Degenerationsherden). Z Gesamte Neurol Psychiatr 64: 147–228. Au68

Jager BV, King T (1955). Hereditary tremor. Arch Intern Med 95: 788–793.

Jakes R, Spillantini MG, Goedert M (1994). Identification of two distinct synucleins from human brain. FEBS Lett 345: 27–32.

Jancovic J, Cardoso F, Grossman RG et al. (1995). Outcomes after stereotactic thalamotomy for parkinsonian, essential, and other types of tremor. Neurosurgery 37: 680–686.

Johnson WG, Hodge SE, Duvoisin R (1990). Twin studies and the genetics of Parkinson's disease—a reappraisal. Mov Disord 5: 187–194.

Jummani RH, Okun MS (2001). Sydenham chorea. Arch Neurol 58: 311–313.

Kann M, Jacobs H, Mohrmann K et al. (2002). Role of parkin mutations in 111 community-based patients with early-onset parkinsonism. Ann Neurol 51: 621–625.

Kayser B (1902). Über einen Fall von angeborener grünlicher Verfärbung der Cornea. Klin Monstbl Augenheilkd 40: 22–25.

Kekabian JW, Calne DB (1979). Multiple receptor mechanism for dopamine. Nature 227: 93–96.

Keppel Hesselink JM (1996). Evolution of concepts and definitions of Parkinson's disease since 1817. J Hist Neurosci 5: 200–207.

Kitada T, Asakawa S, Hattori N et al. (1998). Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. Nature 392: 605–608.

Klawans HL, Moses H III, Nausieda PA et al. (1976). Treatment and prognosis of hemiballismus. N Engl J Med 295: 1348–1350.

Klawans HL, Falk DK, Nausieda PA et al. (1978). Gilles de la Tourette syndrome after long-term chlorpromazine therapy. Neurology 28: 1064–1068.

Klempel K (1974). Gilles de la Tourette's symptoms induced by L-dopa. S Afr Med J 48: 1379.

Koehler PJ, Keyser A (1997). Tremor in Latin texts of Dutch physicians: 16th–18th centuries. Mov Disord 12: 798–806.

Kopp JH (1836). Denkwürdkeitenin der ärztlichen Praxis. Hermann, Frankfurt.

Krack P (1999). Relics of dancing mania: the dancing procession of Echternach. Neurology 53: 2169–2172.

Krack P, Batir A, Van Blercom N et al. (2003). Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 349: 1925–1934.

Kristensen MO (1985). Origressive supranuclear palsy – 20 years later. Acta Neurol Scand 71: 177–189.

Kruse W (1960). Persistent muscular restlessness after phenothiazine treatment: Report of three cases. Am J Psychiatry 117: 152–153.

Kunkle EC (1965). The "jumpers" of Maine: Past history and present status. J Maine Med Assoc 56: 191–193.

Kunkle EC (1967). The "jumpers" of Maine: A reappraisal. Arch Intern Med 119: 355–358.

Kurczynski TW (1983). Hyperekplexia. Arch Neurol 40: 246–248.

Kushner HL, Luzzatti C, Finger S (1999). A perplexing document in the early history of Gilles de la Tourette syndrome: Melotti's rendition of a "Lecture by Charcot" (Including a complete translation from the Italian with commentary). J Hist Neurosci 8: 5–20.

Lahti RA, Roberts RC, Tamminga CA (1995). D2-family receptor distribution in human postmortem tissue: An autoradiographic study. Neuroreport 6: 2502–2512.

Laitinen LV, Bergenheim AT, Hariz MI (1992a). Leksell's perteroventral pallidotomy in the treatment of Parkinson's disease. J Neurosurg 76: 53–61.

Laitinen LV, Bergenheim AT, Hariz MI (1992b). Ventroposterolateral pallidotomy can abolish all parkinsonian symptoms. Stereotact Funct Neurosurg 58: 14–21.

Lajonchere C, Nortz M, Finger S (1996). Gilles de la Tourette and the discovery of Tourette syndrome: Includes a translation of his 1884 article. Arch Neurol 53: 567–574.

Lance JW, Adams RD (1963). The syndrome of intension or action myoclonus as a sequel to hypoxic encephalopathy. Brain 86: 111–136.

Lance JW, Adams RD (2001). Negative myoclonus in posthypoxic patients: Historical note. Mov Disord 16: 162–163.

Lang AE, Sheehy MP, Marsden CD (1982). Anticholinergics in adult-onset focal dystonia. Can J Neurol Sci 9: 313–3319.

Langston JW, Ballard P, Tetrud JW et al. (1983). Chronic parkinsonism in humans due to a product of meperidine-analog synthesis. Science 219: 979–980.

Langston JW, Irwin I, Lanston EB et al. (1984). Pargyline prevents MPTP-induced parkinsonism in primates. Science 225: 1480–1482.

Langston JW, Palfreman J (1995). The Case of the Frozen Addicts. Pantheon Books, New York.

Lanska DJ (2000a). George Huntington (1850–1916) and hereditary chorea. J Hist Neurosci 9: 76–89.

Lanska DJ (2000b). 19th-century American contributions to the recording of tremors. Mov Disord 15: 720–729.

Lanska DJ (2001). Characteristics and lasting contributions of 19th-century American neurologists. J Hist Neurosci 10: 202–216.

Lanska DJ (2002). Classic articles by 19th-century American neurologists: A critical review. J Hist Neurosci 11: 156–173.

Lanska DJ, Goetz CG, Chmura TA (2001a). Development of instruments for abnormal movements: Dynamometers, the dynamograph, and tremor recorders: Part 9 of the MDS-sponsored History of Movement Disorders Exhibit, Barcelona, Spain, June 2000. Mov Disord 16: 736–741.

Lanska DJ, Goetz CG, Chmura TA (2001b). Seminal figures in the history of movement disorders: Huntington, Osler, and Hammond: Part 11 of the MDS-sponsored History of Movement Disorders Exhibit, Barcelona, Spain, June 2000. Mov Disord 16: 749–753.

Lantos PL (1998). The definition of multiple system atrophy: A review of recent developments. J Neuropathol Exp Neurol 57: 1099–1111.

Larsson T, Sjögren T (1960). Essential tremor: A clinical and genetic population study. Acta Psychiatr Scand 26: 1–176.

Leavitt S, Tyler HR (1964). Studies in asterixis. Part I. Arch Neurol 10: 360–368.

Leeflang EP, Tavare S, Marjoram P et al. (1999). Analysis of germline mutation spectra at the Hungtinton's disease locus supports a mitotic mutation mechanism. Hum Mol Genet 8: 173–183.

Lehmann HE, Hanrahan AE (1954). CPZ: New inhibiting agent for psychomotor excitement and manic states. Arch Neurol Psychiatry 71: 227–237.

Lewis MJ (1885/6). The neural disorders of writers and artisans. In: W Pepper, L Starr (Eds.), A System of Practical Medicine, Vol. 5. Lea and Brothers, Philadelphia, PA, 504–543.

Lewy FH (1913). Zur pathologischen Anatomie der Parlysis agitans. Dtsch Z Nervenkrankheit 50: 50–55.

Limousin P, Pollak P, Benazzouz A et al. (1995). Effect of parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. Lancet 345: 91–95.

Limousin P, Krack P, Pollak P et al. (1998). Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 339: 1105–1111.

Limousin O, Speelman JD, Gielen F et al. (1999). Multicentre European study of thalamic stimulation in parkinsonian and essential tremor. J Neurol Neurosurg Psychiatry 66: 289–296.

Lindemulder FG (1933). Familial myoclonis occurring in three successive generations. J Nerv Ment Dis 77: 489.

Lloyd KG, Davidson L, Hornykiewicz O (1975). The neurochemistry of Parkinson's disease: Effect of L-dopa therapy. J Pharmacol Exp Ther 195: 453–464.

Louis ED (1997). The shaking palsy, the first forty-five years: a journey through the British literature. Mov Disord 12: 1068–1072.

Louis ED (2001). Etiology of essential tremor: should we be searching for environmental causes. Mov Disord 16: 822–829.

Lucking CB, Durr A, Bonifati V et al. (2000). Association between early-onset Parkinson's disease and mutations in the parkni gene. N Engl J Med 342: 1560–1567.

Lundborg H (1903). Die progressive Myoklonus-Epilepsie. Almqvist and Wiksell, Uppsalla.

Luys JB (1865). Recherches sur la Système Nerveux Cerebrospinal: Sa Structure, Ses Fonctions, et Ses Maladies. Baillière, Paris.

Lyon IW (1863). Chronic hereditary chorea. Med News 55: 39–41.

Ma S, Davis TL, Blair MA et al. (2006). Familial essential tremor with apparent autosomal dominant inheritance: Should we also consider other inheritance modes. Mov Disord 21: 1368–1374.

McCall S, Henry JM, Reid AH et al. (2001). Influenza RNA not detected in archival brain tissues from acute encephalitis lethargica cases or in postencephalitic Parkinson cases. J Neuropathol Exp Neurol 60: 696–704.

McGeer EG, McGeer PL (1976). Duplication of biochemical changes of Huntington's chorea by intrastriatal injections of glutamic acid and kainic acids. Nature 263: 517–519.

McGeer PL, Zeldowitz LR (1964). Administration of dihydroxyphenylalanine to parkinsonian patients. Can Med Assoc J 90: 463–466.

Markey SP, Johannessen JN, Chiueh CC et al. (1984). Intraneuronal generation of a pyrimidium ion metabolite may cause drug-induced parkinsonism. Nature 311: 464–467.

Marsden CD, Obeso JA, Zarranz JJ et al. (1985). The anatomical basis of symptomatic hemidystonia. Brain 108: 463–483.

Martin JP (1927). Hemichorea resulting from a local lesion of the brain: the syndrome of the body of Luys. Brain 50: 637–651.

Martin JP (1957). Hemichorea (hemiballismus) without lesions in the corpus Luysii. Brain 80: 1–12.

Matsumine H, Saito M, Shimoda-Matsubayashi S et al. (1997). Localization of a gene for an autosomal recessive form of juvenile Parkinsonism to chromosome 6q25.2-27. Am J Hum Genet 60: 588–596.

Mauriello JA Jr (1985). Blepharospasm, Meige syndrome, and hemifacial spasm: treatment with botulinum toxin. Neurology 35: 1499–1500.

Meige H, Feindel E (1907). In: SAK Wilson (Trans.), Tics and Their Treatment. Sidney Appleton, London, p. 27.

Mendel G (1865). Versuche über Pflanzenhybriden. Verh des Naturforschenden Vereines in Brünn 4: 3–47.

Merritt AD, Conneally PM, Rahman NF et al. (1969). Juvenile Huntington's chorea. In: A Barbeau, TR Brunette (Eds.), Progress in Neurogenetics. Excerpta Medica Foundation, Amsterdam, pp. 645–650.

Meyers R (1940). Surgical procedure for postencephalitic tremor, with notes on the physiology of premotor fibers. Arch Neurol Psychiatry 44: 455–459.

Mink JW (2003). The basal ganglia and involuntary movements: Impaired inhibition of competing motor patterns. Arch Neurol 60: 1365–1368.

Mitchell E, Matthews KL (1980). Gilles de la Tourette's disease associated with pemoline. Am J Psychiatry 137: 1617–1619.

Mitchell IJ, Cross AJ, Sambrook MA et al. (1985). Sites of the neurotoxic action of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in the monkey include the ventral tegmental area and the locus coeruleus. Neurosci Lett 61: 195–200.

Mitchell KJ (1903). Report of a case of familial tremor of the head. J Nerv Ment Dis 30: 158–159.

Mitchell SW (1874). Post-paralytic chorea. Am J Med Sci 68: 342–352.

Molina-Negro P, Hardy J (1975). Semiology of tremors. Can J Neurol Sci 2: 23–29.

Montague KA (1957). Catechol compounds in rat tissues and in brains of different animals. Nature 180: 245–246.

Myers RH, Madden JJ, Teague JL et al. (1982). Factors related to onset age of Huntington disease. Am J Hum Genet 34: 481–488.

Narbona J, Obeso JA, Tunon T et al. (1984). Hemidystonia secondary to localized basal ganglia tumour. J Neurol Neurosurg Psychiatry 47: 704–709.

Nausieda PA, Grossman BJ, Koller WC et al. (1980). Sydenham chorea: an update. Neurology 30: 331–334.

Nutt JG, Hammerstad JP, deGarmo P et al. (1984). Cranial dystonia: double-blind crossover study of anticholinergics. Neurology 34: 215–217.

Obeso JA, Rodriquez-Oroz MC, Rodriguez M et al. (2000). Pathophysiology of levodopa-induced dyskinesias in

Parkinson's disease: problems with the current model. Ann Neurol 47: S22–S32.

O'Brien MD, Upton AR, Toseland PA (1981). Benign familial tremor treated with primidone. Br Med J 282: 178–180.

Olney JW, de Gubareff T (1978). Glutamic neurotoxicity and Huntington's chorea. Nature 271: 557–559.

Olszewski J, Steele J, Richardson JC (1964). Pathological report on six cases of heterogeneous system degeneration. J Neuropathol Exp Neurol 23: 187–188.

Oppenheim H (1911). Über eine eigenartige Krampfkrankheit des kindlichen und jegendlichen Alters (Dysbasia lordotica progressiva, Dystonia musculorum deformans). Au72 Neurologisches Zentralblatt 30: 1090–1107.

Ørbeck AL (1959). An early description of Huntington's chorea. Med Hist 3: 165–168.

Osler W (1887). On the general etiology and symptoms of chorea: based on the records of 410 cases at the Infirmary Au73 for Nervous Diseases, Philadelphia. Med News 51: 437–441, 465–470.

Osler W (1894). On Chorea and Choreiform Affections. HK Lewis, London.

Osler W (1908). Historical notes on hereditary chorea. Neurographs 1: 113–116.

Ozelius L, Kramer PL, Moskowitz CB et al. (1989). Human gene for torsion dystonia located on chromosome 9q32-q34. Neuron 2: 1427–1434.

Ozelius LJ, Hewett J, Kramer P et al. (1997a). Fine localization of the torsion dystonia gene (DYT1) on human chromosome 9q34: YAC map and linkage disequilibrium. Genome Res 7: 483–494.

Ozelius LJ, Hewett JW, Page CE et al. (1997b). The early-onset torsion dystonia gene (DYT1) encodes an ATP-binding protein. Nat Genet 17: 40–48.

Pahwa R, Lyons KL, Wilkinson SB et al. (1999). Bilateral thalamic stimulation for the treatment of essential tremor. Neurology 53: 1447–1450.

Papp MI, Lantos PL (1992). Accumulation of tubular structures in oligodengroglial and neuronal cells as the basic alteration in multiple system atrophy. J Neurol Sci 107: 172–182.

Papp MI, Kahn JE, Lantos PL (1989). Glial cytoplasmic inclusions in the CNS of patients with multiple system atrophy (striatonigral degeneration, olivopontocerebellar atrophy and Shy-Drager syndrome). J Neurol Sci 94: 79–100.

Parent A (2002). Jules Bernard Luys and the subthalamic nucleus. Mov Disord 17: 181–185.

Parkinson J (1817). An Essay on the Shaking Palsy. Whittingham and Rowland, London.

Penny JB Jr, Vonsattel JP, MacDonald ME et al. (1997). CAG repeat number governs the development rate of pathology in Huntington's disease. Ann Neurol 41: 689–692.

Perutz MF, Johnson T, Suzuki M et al. (1994). Glutamine repeats as polar zippers: Their possible role in inherited neurodegenerative diseases. Proc Natl Acad Sci USA 91: 5355–5358.

Petrukhin K, Fischer SG, Pirastu M et al. (1993). Mapping, cloning and genetic characterization of the region containing the Wilson disease gene. Nat Genet 5: 338–343.

Pettigrew LC, Jacovic J (1985). Hemidystonia: a report of 22 patients and a review of the literature. J Neurol Neurosurg Psychiatry 48: 650–657.

Piccolomini F (1630). Illustrium Virorum Elogia. Tomasini IP, Florence.

Poirer LJ, Sourkes TL (1965). Influence of the substantia nigra on the catecholamine content of the striatum. Brain 88: 181–192.

Polymeropoulos MH, Higgins JJ, Golbe LI et al. (1996). Mapping of a gene for Parkinson's disease to chromosome 4q21-q23. Science 274: 1197–1199.

Polymeropoulos MH, Lavedan C, Leroy E et al. (1997). Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. Science 276: 2045–2047.

Poore GV (1878). An analysis of 75 cases of writer's cramp and impaired writing power. Trans R Med Chir Soc 61: Au74 111–145.

Posey WC (1904). Paralysis of upward movement of the eyes. Ann Ophthalmol 13: 523–529.

Poynton F, Paine A (1913). Researches on Rheumatism. Churchill Livingstone, London.

Pramstaller PP, Schlossmacher MG, Jaques TS et al. (2005). Lewy body Parkinson's disease in a large pedigree with 77 parkin mutation carriers. Ann Neurol 58: 411–422.

Putnam JJ (1879). A new adjuvant in the treatment of writer's palsy. Boston Med Surg J 101: 320. Au75

Rabeiz JJ, Kolodny EH, Richardson EP (1967). Corticodentatonigral degeneration with neuronal achromasia: A progressive disorder of late adult life. Trans Am Neurol Assoc 92: 23–26.

Rabeiz JJ, Kolodny EH, Richardson EP Jr (1968). Corticodentatonigral degeneration with neuronal achromasia. Arch Neurol 18: 20–33.

Rabinovith R (1965). An exaggerated startle reflex resembling a kicking horse. Can Med Assoc J 93: 130.

Rammelkamp CH, Denny FW, Wannamaker LW (1952). Studies on the epidemiology of rheumatic fever in the armed services. In: L Thomas (Ed.), Rheumatic Fever. University of Minnesota Press, Minneapolis, MN, pp. 72–89.

Ranen NG, Stine OC, Abbott MH et al. (1995). Anticipation and instability of IT-15(CAG)n repeats in parent-offspring pairs with Huntington's disease. Am J Hum Genet 57: 593–602.

Reid AH, McCall S, Henry JM et al. (2001). Experimenting on the past: the enigma of Von Economo's encephalitis lethargica. J Neuropathol Exp Neurol 60: 663–670.

Reik W (1988). Genomic imprinting: a possible mechanism for the parental origin effect in Huntington's chorea. J Med Genet 25: 805–808.

Reiner A, Albin RL, Anderson KD et al. (1988). Differential loss of striatal projection neurons in Huntington disease. Proc Natl Acad Sci USA 85: 5733–5737.

Richardson JC, Steele J, Olszewsji J (1963). Supranuclear ophthalmoplegia, pseudobulbar palsy, nuchal dystonia and dementia: A clinical report on eight cases of 'heterogeneous system degeneration. Trans Am Neurol Assoc 88: 25–29.

Ridley RM, Frith CD, Crow TJ et al. (1988). Anticipation in Huntington's disease is inherited through the male line but may originate in the female. J Med Genet 25: 589–595.

Ridley RM, Frith CD, Farrer LA et al. (1991). Patterns of inheritance of the symptoms of Huntington's disease suggestive of an effect of genomic imprinting. J Med Genet 28: 224–231.

Riley DE, Lang AE, Lewis A et al. (1990). Cortical-basal ganglionic degeneration. Neurology 40: 1203–1212.

Ristic A, Marinkovic J, Dragaševic N et al. (2002). Long-term prognosis of vascular hemiballismus. Stroke 33: 2109–2111.

Robins RP (1885a). The treatment of writers' cramp. Proc Phil Co Med Soc 7: 271–277.

Robins RP (1885b). "Writers' cramp" and its treatment, with the notes of several cases. Am J Med Sci 89: 452–462.

Rodbell M (1997). Signal transduction: Evolution of an idea. In: N Ringertz (Ed.), Nobel Lectures, Physiology or Medicine 1991–1995. World Scientific, Singapore, pp. 220–236.

Roger H (1866). Recherches cliniques sur la chorea, sur le rhumatisme et sur les maladies du Coeur chez les enfants. Arch Gen Med 2: 641–665.

Rose I (2005). Ubiquitin at fox chase. In: T Frängsmyr (Ed.), Les Prix Nobel. The Nobel Prizes 2004. Nobel Foundation, Stockholm, pp. 218–225.

Rothfus WE, Hirsch WL, Malatack JJ et al. (1988). Improvement of cerebral CT abnormalities following liver transplantation in a patient with Wilson disease. J Comput Assist Tomogr 12: 138–140.

Rubinsztein DC, Leggo J, Coles R et al. (1996). Phenotypic characterization of individuals with 30-40 CAG repeats in the Huntington disease (HD) gene reveals HD cases with 36 repeats and apparently normal elderly individuals with 36–39 repeats. Am J Hum Genet 59: 16–22.

Rumpel A (1913). Ueber das Wesen und die Bedeutung der Leberveränderungen und der Pigmentierungen bei den damit verbunderen Fällen von Pseudosklerose, zugleich ein Beitrag zur Lehre der Pseudosklerose (Westphal-Strumpell). Dtsch Z Nervenheilkd 49: 54–73.

Saint-Hilaire M-H, Saint-Hilaire J-M, Granger L (1986). - Jumping Frenchmen of Maine. Neurology 36: 1269–1271.

Sano I, Gamo T, Kakimoto Y et al. (1959). Distribution of catechol compounds in human brain. Biochim Biophys Acta 32: 586–587.

Scheinberg IH, Gitlin D (1952). Deficiency of ceruloplasmin in patients with hepatolenticular degeneration (Wilson's disease). Science 116: 484–485.

Scheinberg IH, Sternlieb I (1960). Long-term management of hepatolenticular degeneration (Wilson's disease). Am J Med 29: 316–333.

Scherer HJ (1933a). Beiträge zur pathologischen Anatomie des Kleinhirns. III. Mitteilung: Genuine Kleinhirnatrophien. Z Gesamte Neurol Psychiatr 145: 335–405.

Scherer HJ (1933b). Extrapyramidale Störungen bei der olivopontocerebellaren Atrophie. Ein Beitrag zum Problem des lokalen vorzeitigen Alterns. Z Gesamte Neurol Psychiatr 145: 406–419.

Schiller F (1967). The vicissitudes of the basal ganglia (further landmarks in cerebral nomenclature). Bull Hist Med 41: 515–538.

Schiller F (1986). Parkinsonian rigidity: the first hundred-and-one years 1817–1918. Hist Philos Life Sci 8: 221–236.

Schiller F (2000). Fritz Lewy and his bodies. J Hist Neurosci 9: 148–151.

Schonecker M (1957). Ein eigentumliches Syndrom im oralen Bereich bei Magaphen Applikation. Nervenarzt 28: 35–36.

Schouwink G (1961). De hepatocerebrale degeneratie, met een onderzoek naar de zonkstrofwisseling. MD thesis (with a summary in English, French, and German), University of Amsterdam, Amsterdam.

Schuurman PR, Bosch DA, Bossuyt PMM et al. (2000). A comparison of continuous thalamic stimulation and thalamotomy for suppression of severe tremor. N Engl J Med 342: 461–468.

Schwab RS, Amador LV, Levine JY (1951). Apomorphine in Parkinson's disease. Trans Am Neurol Assoc 76: 273–279.

Schwalbe MW (1908). Eine eigentümliche tonische Krampfform mit hysterischen Symptomen: Medicin und Chirurgie. Universitäts-Buch-druckerei G. Schade, Berlin.

Sée G (1850). De la chorea. Mem Acad Med (Paris) 15: 374.

Seignot MJN (1961). A case of the syndrome of tics of Gilles de la Tourette controlled by R 1625. Ann Med Psychol 28: 92–97.

Shahani BT, Young RR (1976). Physiological and pharmacological aids in the differential diagnosis of tremor. J Neurol Neurosurg Psychiatry 39: 772–783.

Shahzadi S, Tasker RR, Lozano A (1995). Thalamotomy for essential and cerebellar tremor. Stereotact Funct Neurosurg 565: 11–17.

Shapiro AK, Shapira E, Wayne H (1973). Treatment of Tourette's syndrome: with haloperidol, review of 34 cases. Arch Gen Psychiatry 28: 92–97.

Sharp FR, Rando TA, Greenberg SA et al. (1994). Pseudochoreoathetosis: Movements associated with loss of proprioception. Arch Neurol 41: 1103–1109.

Sheehy MP, Marsden CD (1982). Writer's cramp – a focal dystonia. Brain 105: 461–480.

Shiang R, Ryan SG, Zhu Y-Z et al. (1993). Mutations in the a_1 subunit of the inhibitory glycine receptor cause the dominant neurologic disorder, hyperekplexia. Nat Genet 5: 351–358.

Shimura H, Hattori N, Kubo S et al. (2000). Familaial Parkinson disease gene product, parkin, is a ubiquitin-protein ligase. Nat Genet 25: 302–305.

Shimura H, Schlossmacher MG, Hattori N et al. (2001). Ubiquitination of a new form of alpha-synuclein by parkin from human brain: Implications for Parkinson's disease. Science 293: 263–269.

Shy GM, Drager GA (1960). A neurologic syndrome associated with orthostatic hypotension. Arch Neurol 2: 511–527.

Sider D, McVaugh M (1979). Galen on tremor, palpitation, spasm, and rigor: Valeni De tremore, palpitatione, convulsione, et rigore. Trans Stud Coll Physicians Phila 1: 183–210.

Siderowf AD, Galetta SL, Hurtig HI et al. (1998). Posey and Spiller and progressive supranuclear palsy: An incorrect attribution. Mov Disord 13: 170–174.

Siegfried J (1994). Chronic electrical stimulation of the VL-VPL complex and of the pallidum in the treatment of extrapyramidal and cerebellar disorders. Personal experience since 1985. Stereotact Funct Neurosurg 62: 71–75.

Siegfried J, Lippitz B (1994). Bilateral chronic electrostimulation of ventroposterolateral pallidum: A new therapeutic approach for alleviating all parkinsonian symptoms. Neurosurgery 35: 1126–1129.

Siemerling E, Oloff H (1922). Pseudosclerose (Westphal-Strumpell) mit cornealring (Kayser-Fleischer) under doppelseitger scheinkatarakt, die nur bei seitlicherbeleuchtung sichtbar ist und die, der nach verletzung durch kupfersplitterentstehenden katarakt ahnlich ist. Klin Wochenschr 1: 1087–1089.

Singer HS, Butler IK, Tune LE et al. (1982). Dopaminergic dysfunction in Tourette syndrome. Ann Neurol 12: 361–366.

Sinkler W (1895). Choreiform affections. In: FX Dercum (Ed.), A Text-book on Nervous Diseases by American Authors. Lea Brothers and Co., Philadelphia, PA, pp. 227–269.

Slavin KV, Baumann TK, Burchiel KJ (2004). Treatment of hemiballismus with stereotacticc pallidotomy. Case report and review of the literature. Neurosurg Focus 17: E7.

Smith Y, Parent A (1988). Neurons of the subthalamic nucleus in primates display glutamate but not GABA immunoreactivity. Brain Res 453: 353–356.

Snell RG, MacMillan JC, Cheadle JP et al. (1993). Relationship between trinucleotide repeat expansion and phenotypic variation in Huntington's disease. Nat Genet 4: 393–397.

Sokol RJ, Francis PD, Gold SH et al. (1985). Orthotopic liver transplantation for acute fulminant Wilson disease. J Pediatr 107: 549–552.

Solly S (1864). Clinical lectures on scriveners' palsy, or the paralysis of writers: Lecture I. Lancet ii: 709–711.

Solly S (1865a). Clinical lectures on scriveners' palsy, or the paralysis of writers: Lecture II. Lancet i: 84–86.

Solly S (1865b). Clinical lectures on scriveners' palsy, or the paralysis of writers: Lecture III. Lancet i: 113–115.

Special Writing Group of the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young of the American Heart Association (1992). Guidelines for the diagnosis of rheumatic fever: Jones criteria, 1992 update. JAMA 268: 2069–2073 (Correction 1993; 269: 476).

Speelman JD, Bosch DA (1998). Resurgence of functional neurosurgery for Parkinson's disease: a historical perspective. Mov Disord 13: 582–588.

Spiegel EA, Wycis HT, Marks M et al. (1947). Stereotaxic apparatus for operations on the human brain. Science 106: 349–350.

Spillantini MG, Schmidt ML, Lee VM-Y et al. (1997). Alpha-synuclein in Lewy bodies. Nature 388: 839–840.

Spillantini MG, Crowther RA, Jakes R et al. (1998). Filamentous alpha-synuclein inclusions link multiple system atrophy with Parkinson's disease and dementia with Lewy bodies. Neurosci Lett 251: 205–208.

Spiller WG (1905). The importance in clinical diagnosis of paralysis of associative movement of the eyeballs (Blick-Lahmung) especially of upward and downward associated movements. J Nerv Ment Dis 32: 417–488, 497–530.

Squitieri F, Gellera C, Cannella M et al. (2003). Homozygosity for CAG mutation in Huntington disease is associated with a more severe clinical course. Brain 126: 946–955.

Steck H (1954). Le syndrome extrapyramidal et diencephalique au cours des traitments au largactil et au serpasil. Ann Med Psychol (Paris) 112: 737–743.

Steele JC (1972). Progressive supranuclear palsy. Brain 95: 693–704.

Steele JC (1994). Historical notes. J Neural Transm Suppl 42: 3–14.

Steele JC, Richardson JC, Olszewski J (1964). Progressive supranuclear palsy. Arch Neurol 10: 333–359.

Stine OC, Pleasant N, Franz ML et al. (1993). Correlation between the onset age of Huntingtons disease and length of the trinucleotide repeat in IT-15. Hum Molec Genet 2: 1547–1549.

Stollerman GH (1997). Changing streptococci and prospects for the global eradication of rheumatic fever. Perspect Biol Med 40: 165–189.

Strümpel A (1898). Über die Westphal'sche Pseudosklerose und über diffuse Hirnsklerose insbesondere bei Kindern. Dtsch Z Nervenkrankheit 12: 115–149. Au81

Suarez JI, Metman LV, Reich SG et al. (1997). Pallidotomy for hemiballismus: Efficacy and characteristics of neuronal activity. Ann Neurol 42: 807–811.

Suhren O, Bruyn GW, Tuynman JA (1966). Hyperexplexia: A hereditary startle syndrome. J Neurol Sci 3: 577–605.

Sweeney PJ, Lloyd MF, Daroff RB (1997). What's in a name? Dr. Lewey and the Lewy body. Neurology 49: 629–630.

Sydenham T (1686). Schedula monitoria de novae febris ingressu. G Kettilby, London.

Sydenham T (1848/1979). On St. Vitus's dance. In: RG Latham (Trans.), The Entire Works of Thomas Sydenham. Vol. 2. Sydenham Society, London, pp. 257–259. [Reprinted in 1979 by The Classics in Medicine Society, Birminham, AL.]

Tanzi RE, Petrukhin K, Chernov I et al. (1993). The Wilson disease gene is a copper transporting ATPase with homology to the Menkes disease gene. Nat Genet 5: 344–350.

Taranta A, Stollerman GH (1956). The relationship of Sydenham's chorea to infection with Group A streptococci. Am J Med 20: 170–175.

Telenius H, Kremer HPH, Theilmann J et al. (1993). Molecular analysis of juvenile Huntington's disease: the major influence on $(CAG)_n$ repeats length is the sex of affected parents. Hum Mol Genet 2: 1535–1540.

Telenius H, Kremer B, Goldberg YP et al. (1994). Somatic and gonadal mosaicism of the Huntington disease gene CAG repeat in brain and sperm. Nat Genet 6: 409–414.

Telenius H, Almqvist E, Kremer B et al. (1995). Somatic mosaicism in sperm is associated with intergenerational $(CAG)_n$ changes in Huntington disease. Hum Mol Genet 4: 189–195.

The Tourette Syndrome Classification Study Group (1993). Definitions and classification of tic disorders. Arch Neurol 50: 1013–1016.

Tiemann G (1899). American Armamentarium Chirurgicum. George Tiemann and Co., New York, pp. 712–713. [Reprint edition, published by Jeremy Norman and Co. Inc., Novato, CA, 1989.]

Todd EW (1932). Antigenic streptococcal hemolysin. J Exp Med 55: 267–280.

Tomonaga M (1977). Ultrastructure of neurofibrillary tangles in progressive supranuclear palsy. Acta Neuropathol (Berl) 37: 1771–1781.

Trétiakoff C (1919). Contribution a l'etude de l'anatomie pathologique du Locus Niger de Soemmerring avec quelques deductions relatives à la pathogénie des troubles du tonus musculaire et de la maladie de Parkinson. Thèse, Faculté de Médecine. Université de Paris, Paris.

Trétiakoff C (1921). Contribution a l'etude de l'anatomie du locus niger. Rev Neurol (Paris) 28: 592–600.

Trottier Y, Biancalana V, Mandel J-L (1994). Instability of CAG repeats in Huntington's disease: Relation to parental transmission and age of onset. J Med Genet 31: 377–382.

Truong DD, Fahn S (1988). An early description of dystonia: translation of Schwalbe's thesis and information on his life. Adv Neurol 50: 651–654.

Tschermak von Seysenegg E (1900). Über künstliche Kreuzung bei Pisum sativum. Z Landwirthschaftliche Versuchswesen in Oesterreich 3: 465–555. Au82

Tsui JK, Eisen A, Mak E et al. (1985). A pilot study on the use of botulinum toxin in spasmodic torticollis. Can J Neurol Sci 12: 314–316.

Tsui JK, Eisen A, Stoessl AJ et al. (1986). Double-blind study of botulinum toxin in spasmodic torticollis. Lancet 2: 245–247.

Tsui JK, Fross RD, Calne S et al. (1987). Local treatment of spasmodic torticollis with botulinum toxin. Can J Neurol Sci 14: 533–535.

Tu PH, Galvin JE, Baba M et al. (1998). Glial cytoplasmic inclusions in white matter oligodendrocytes of multiple system atrophy brains contain insoluble alpha-synuclein. Ann Neurol 44: 415–422.

Ueda K, Fukushima H, Masliah E et al. (1993). Molecular cloning of cDNA encoding an unrecognized component of amyloid in Alzheimer disease. Proc Natl Acad Sci USA 90: 11282–11286.

Uhrbrand L, Faurbye A (1960). Reversible and irreversible dyskinesia after treatment with perphenazine, chlorpromazine, reserpine, and electroconvulsive therapy. Psychopharmacologia 1: 408–418.

Unverricht H (1891). Die Myoklonie. Franz Deutike, Leipzig.

Uzman LL, Iber FL, Chalmers TC et al. (1956). The mechanism of copper deposition in the liver in hepatolenticular degeneration (Wilson's disease). Am J Med Sci 231: 511–518.

Van Putten T (1975). The many faces of akathisia. Compr Psychiatry 16: 43–47.

Vesalius (1542). De Humani Corporis Fabrica. J Oporini, Basel.

Vidailhet M, Vercueil L, Houeto JL et al. (2005). Bilateral deep-brain stimulation of the globus pallidus in primary generalized dystonia. N Engl J Med 352: 459–467.

Vilensky JA, Robertson WM, Gilman S (2002). Denny-Brown, Wilson's disease, and BAL (British antilewisite [2,3-dimercaptopropanol]). Neurology 59: 914–916.

Vogt A (1929). Kupfer und silber aufgespeichert in auge, leber, milz und nieren als symptom der pseudosclerose. Klin Monatsbl Augenheilkd 83: 417–419.

Vogt O, Vogt C (1920). Sur Lehre der Erkrankungen des striaren Systeme. J Psychol Neurol (Leipzig) Suppl 25: 627–846. Au83

von Economo C (1917). Encephalitis Lethargica. Wien Klin Wochenschr 30: 581–583.

von Economo C (1929). Die Encephalitis lethargica, ihre Nachkrankheiten und irhre Behandlung. Urban und Schwartzenberg, Berlin.

von Economo C (1931). In: O Newman (Trans.), Encephalitis Lethargica: Its Sequelae and Treatment. Oxford University Press, London, England. Au84

Vonsattel JP, Myers RH, Stevens TJ et al. (1985). Neuropathological classification of Huntington's disease. J Neuropathol Exp Neurol 44: 559–577.

Wakabayashi K, Yoshimoto M, Tsuji S et al. (1998). Alpha-synuclein immunoractivity in glial cytoplasmic inclusions in multiple system atrophy. Neurosci Lett 249: 180–182.

Walshe FMR (1920). On the symptom complexes of lethargic encephalitis with special reference to the involuntary muscular contractions. Brain 43: 197–219.

Walshe JM (1956). Penicillamine, a new oral therapy for Wilson's disease. Am J Med 21: 487–495.

Walshe JM (1960). The treatment of Wilson's disease with penicillamine. Lancet 1: 188–192.

Walshe JM (1962). Wilson's disease. The presenting symptoms. Arch Dis Child 37: 253–256.

Walshe JM (1968). Toxic reactions to penicillamine in patients with Wilson's disease. Postgrad Med J (Suppl): 6–8. Au85

Walshe JM (1982). Treatment of Wilson's disease with trientine (triethylene tetramine) dichloride. Lancet 1: 643–647.

Walshe JM (2003). The story of penicillamine: a difficult birth. Mov Disord 18: 853–859.

Walshe JM (2006). History of Wilson's disease: 1912 to 2000. Mov Disord 21: 142–147.

Wasmuth JJ, Hewitt J, Smith B et al. (1988). A highly polymorphic locus very tightly linked to the Huntington's disease gene. Nature 332: 734–736.

Waters CO (1842). In: R Dunglison (Ed.), The Practice of Medicine, or A Treatise on Special Pathology and Therapeutics. Vol. 2. Lea and Blanchard, Philadelphia, PA, p. 312.

West WJ (1861). On a peculiar form of infantile convulsions. Lancet i: 724–725.

Westphal C (1883). Über eine dem Bilde der cerebrospinalen grauen Degeneration ähnliche Erkrankung des centralen Nervensystems ohne anatomischen Befund, nebst einigen Bemerkungen über paradoxe Contraktion. Arch Psychiatr Nervenkr 14: 87–134.

Wexler NS, Young AB, Tanzi RE et al. (1987). Homozygotes for Huntington's disease. Nature 326: 194–197.

Whittier JR (1947). Ballism and subthalamic nucleus (nucleus hypothalamicus; corpus Luysi). Review of the literature and study of thirty cases. Arch Neurol Psychiatry 58: 672–692.

Whittier JR, Mettler FA (1949a). Studies on the subthalamus of the rhesus monkey. I. Anatomy and fiber connections of the subthalamic nucleus of Luys. J Comp Neurol 90: 281–314.

Whittier JR, Mettler FA (1949b). Studies on the subthalamus of the rhesus monkey. II. Hyperkinesia and other physiologic effects of subthalamic lesions, with special reference to the subthalamic nucleus of Luys. J Comp Neurol 90: 319–372.

Wichmann T, DeLong MR (1998). Models of basal ganglia function and pathophysiology of movement disorders. Neurosurg Clin N Am 9: 223–236.

Willis T (1685). The London Practice of Physick: Or the Whole Practical Part of Physick Contained in the Works of Dr. Willis. Faithfully Made English, and Printed Together for the Publick Good. Thomas Basset, London, p. 413.

Wilson SAK (1911). Progressive lenticular degeneration: A familial nervous disease associated with cirrhosis of the liver, Thesis, University of Edinburgh, Edinburgh.

Wilson SAK (1912a). Progressive lenticular degeneration: A familial nervous disease associated with cirrhosis of the liver. Brain 34: 295–509. [Excerpts of this paper were reprinted in Arch Neurol 1971; 25: 180–186.]

Wilson SAK (1912b). Progressive lenticular degeneration: A familial nervous disease associated with cirrhosis of the liver. Lancet 1: 1115–1119.

Wilson SAK (1912c). Degeneration lenticulaire progressive: Maladie familiale associee a la cirrhose du foie. Rev Neurol (Paris) 23: 229–233.

Wilson SAK (1914). Progressive Degeneration des Linsenkerns. In: M Lewandowsky (Ed.), Handbuch der Neurologie. Vol. 5. Springer, Berlin, pp. 950–990.

Wilson SAK (1925). Disorders of motility and muscle tone with special reference to the corpus striatum (Croonian Lectures). Lancet 2: 215–291.

Winkler GF, Young RR (1974). Efficacy of chronic propranolol thereapy in action tremors of the familial, senile or essential varieties. N Engl J Med 290: 984–988.

Winslow RS, Stillner V, Coons DJ et al. (1986). Prevention of acute dystonic reactions in patients beginning high-potency neuroleptics. Am J Psychiatry 143: 706–710.

Yahr MD, Duvoisin RC, Schear MJ et al. (1969). Treatment of parkinsonism with levodopa. Arch Neurol 21: 343–354.

Yang W, Dunlap JR, Andrews RB et al. (2002). Aggregated polyglutamine peptides delivered to nuclei are toxic to mammalian cells. Hum Molec Genet 11: 2905–2917.

Yoon S-R, Dubeau L, de Young M et al. (2003). Huntington disease expansion mutations in humans can occur before meiosis is completed. Proc Natl Acad Sci USA 100: 8834–8838.

Young RR, Shahani BT (1986). Asterixis: one type of negative myoclonus. Adv Neurol 43: 137–156.

Young RR, Shahani BT, Kjellberg RJ (1976). Unilateral asterixis produced by a discrete CNS lesion. Trans Am Neurol Assoc 101: 306–307.

Zabel BU, Naylor SL, Sakaguchi AY et al. (1986). Mapping of the DNA locus D4S10 and the linked Huntington's disease gene to 4p16-p15. Cytogenet Cell Genet 42: 187–190.

Zeman W (1970). Pathology of the torsion dystonias (dystonia musculorum deformans). Neurology 20: 79–88.

Zeman W, Dyken P (1967). Dystonia musculorum deformans: Clinical, genetic and pathoanatomical studies. Psychiatr Neurol Neurochir 70: 77–121.

Zeman W, Kaelbling R, Pasamanick B (1959). Idiopathic dystonia musculorum deformans. I. The hereditary pattern. Am J Hum Genet 11: 188–202.

Zeman W, Kaelbling R, Pasamanick B (1960). Idiopathic dystonia musculorum deformans. II. The formes frustes. Neurology 10: 1068–1075.

Zesiewicz TA, Elbe R, Louis ED et al. (2005). Practice parameter: Therapies for essential tremor: Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 64: 2008–2020.

Ziehen T (1911). Ein Fall von tonischer Torsionsneurose. Neurol Centrabl 30: 109–110. Au86

Zoghbi HY, Orr HT (2000). Glutamine repeats and neurodegeneration. Annu Rev Neurosci 23: 217–247.

Zuhlke C, Riess O, Bockel B et al. (1993). Mitotic stability and meiotic variability of the $(CAG)_n$ repeat in the Huntington disease gene. Hum Molec Genet 2: 2063–2067.

Comp. by: NJayamalathiProof0000876237 Date:20/11/08 Time:10:12:41 Stage:First Proof
File Path://spiina1001z/Womat/Production/PRODENV/0000000001/0000011393/0000000016/
0000876237.3D Proof by: QC by: ProjectAcronym:BS:FINGER Volume:02133

Author Query Form

Book Series: History of Neurology vol 95
Chapter 33

Dear Author,

During the preparation of your manuscript for typesetting some questions have arisen. These are listed below. Please check your typeset proof carefully and mark any corrections in the margin of the proof or compile them as a separate list. This form should then be returned with your marked proof/list of corrections to Elsevier Science.

Disk use

In some instances we may be unable to process the electronic file of your article and/or artwork. In that case we have, for efficiency reasons, proceeded by using the hard copy of your manuscript. If this is the case the reasons are indicated below:

Disk damaged Incompatible file format LaTeX file for non-LaTeX journal
Virus infected Discrepancies between electronic file and (peer-reviewed, therefore definitive) hard copy.
Other: .....

We have proceeded as follows:

Manuscript scanned Manuscript keyed in Artwork scanned
Files only partly used (parts processed differently:.....)

Bibliography

If discrepancies were noted between the literature list and the text references, the following may apply:

The references listed below were noted in the text but appear to be missing from your literature list. Please complete the list or remove the references from the text.

Uncited references: This section comprises references which occur in the reference list but not in the body of the text. Please position each reference in the text or, alternatively, delete it. Any reference not dealt with will be retained in this section.

Query Refs.	Details Required	Author's response
AU1	Not in ref list; pls. supply	
AU2	Eshner in refs.	
AU3	Eshner in refs.	
AU4	Not et al. in refs.	
AU5	1995 in refs.	
AU6	Morbidity and morbidity – should one of these be something else?	
AU7	Benazzouz in refs.	
AU8	Montague in refs.	
AU9	Rosengren in refs.	
AU10	1957 in refs.	
AU11	1960 in refs.	
AU12	1961 in refs.	
AU13	1961 in refs.	
AU14	McGeer in refs.	
AU15	Not in ref list; pls. supply	
AU16	Not in ref list; pls. supply	
AU17	2004 in refs.	
AU18	Palfreman in refs.	
AU19	Text missing here?	
AU20	Tomonaga in refs.	

AU21	Rabeiz in refs.	
AU22	Rabeiz in refs.	
AU23	Formatting lost here – please reinstate word.	
AU24	Boutielle in refs.	
AU25	1992 in refs.	
AU26	1842 in refs.	
AU27	1982 in refs.	
AU28	Coyle and Schwarcz in refs.	
AU29	1949a or 1949b?	
AU30	1989a or 1989b?	
AU31	Not in ref list; pls. supply	
AU32	Marsden in refs.	
AU33	Not in ref list; pls. supply	
AU34	Not in ref list; pls. supply	
AU35	Not in ref list; pls. supply	
AU36	Jacob in refs.	
AU37	Young and Shahani (1986) or Young et al. (1976) in refs.	
AU38	Emphasis in original or added?	
AU39	Rabinovith in refs.	
AU40	Andermann in refs.	
AU41	Not in ref list; pls. supply	
AU42	Not in ref list; pls. supply	
AU43	Kushner in refs.	
AU44	Journal title not listed in Index Medicus is abbrevation OK?	
AU45	Journal title not listed in Index Medicus is abbreviation OK?	
AU46	Journal title not listed in Index Medicus is abbreviation OK?	
AU47	Journal title not listed in Index Medicus is abbreviation OK?	
AU48	Journal title not listed in Index Medicus is abbreviation OK?	
AU49	Journal title not listed in Index Medicus is abbreviation OK?	
AU50	Check page span	
AU51	Journal title not listed in Index Medicus is abbreviation OK?	
AU52	Pls. supply editor name(s) & initial(s)	
AU53	Journal title not listed in Index Medicus is abbreviation OK?	
AU54	Journal title not listed in Index Medicus is abbreviation OK?	
AU55	Journal title not listed in Index Medicus is abbreviation OK?	
AU56	Journal title not listed in Index Medicus is abbreviation OK?	
AU57	Journal title not listed in Index Medicus is abbreviation OK?	
AU58	Journal title not listed in Index Medicus is abbreviation OK?	
AU59	Journal title not listed in Index Medicus is abbreviation OK?	
AU60	Journal title not listed in Index Medicus is abbreviation OK?	
AU61	Journal title not listed in Index Medicus is abbreviation OK?	

AU62	Pls. supply editor name(s) & initial(s)	
AU63	Journal title not listed in Index Medicus is abbreviation OK?	
AU64	Pls. supply editor name(s) & initial(s)	
AU65	Journal title not listed in Index Medicus is abbreviation OK?	
AU66	Journal title not listed in Index Medicus is abbreviation OK?	
AU67	Journal title not listed in Index Medicus is abbreviation OK?	
AU68	Journal title not listed in Index Medicus is abbreviation OK?	
AU69	Journal title not listed in Index Medicus is abbreviation OK?	
AU70	Journal title not listed in Index Medicus is abbreviation OK?	
AU71	Journal title not listed in Index Medicus is abbreviation OK?	
AU72	Journal title not listed in Index Medicus is abbreviation OK?	
AU73	Journal title not listed in Index Medicus is abbreviation OK?	
AU74	Journal title not listed in Index Medicus is abbreviation OK?	
AU75	Journal title not listed in Index Medicus is abbreviation OK?	
AU76	Journal title not listed in Index Medicus is abbreviation OK?	
AU77	Journal title not listed in Index Medicus is abbreviation OK?	
AU78	Journal title not listed in Index Medicus is abbreviation OK?	
AU79	Journal title not listed in Index Medicus is abbreviation OK?	
AU80	Journal title not listed in Index Medicus is abbreviation OK?	
AU81	Journal title not listed in Index Medicus is abbreviation OK?	
AU82	Journal title not listed in Index Medicus is abbreviation OK?	
AU83	Journal title not listed in Index Medicus is abbreviation OK?	
AU84	Chapter title? Page span	
AU85	Pls. supply vol no.	
AU86	Journal title not listed in Index Medicus is abbreviation OK? Is this meant to be Neurologisches Zentralblatt?	
AU87	Eshner in refs.	