PART I
Introduction

1

Akathisia: development of the concept

Akathisia, a stepchild of movement disorders and an orphan of psychiatry, is beginning to receive the serious attention and clarification it deserves.

Stephen Stahl (1985)

The term *akathisia* is of Greek derivation and, translated literally into English, means 'not to sit'. It was first used by Lad Haskovec (1902) (see Appendix A) to describe two patients with restlessness and an inability to sit still. Descriptions of a syndrome resembling akathisia can, however, be traced to much earlier than the beginning of the twentieth century. The first documented description has been attributed to the British physician and anatomist Thomas Willis[1] (1621–1675), better known for his careful studies of the nervous system. The first edition of his *London Practice of Physik* was published in 1685, but Critchley (1955) quoted from his second edition, printed in 1695, as follows: 'Wherefore to some, when being a Bed they betake themselves to sleep, presently in the Arms and Leggs, Leapings and Contractions of the Tendons, and so great a Restlessness and Tossings of their Members ensue, that the diseased are no more able to sleep, than if they were in a Place of the greatest Torture' (p. 101).

The earliest nineteenth-century account resembling akathisia has been attributed to Wittmaack (1861), who referred to the syndrome as *anxietas*

[1] Thomas Willis introduced the experimental approach to the study of the nervous system, thus placing the brain and the nervous system on a modern footing. Willis has a number of firsts to his credit: descriptions of the hexagonal circle of arteries at the base of the brain (which gave him eponymic fame when it became known as the 'Circle of Willis'), the eleventh cranial nerve, myasthenia gravis and puerperal fever. He won great renown as a physician, researcher and teacher and, as the Sedleian Professor of Natural History, had a number of gifted pupils, among whom were Robert Hook, the inventive physicist and microscopist; John Locke, the physician-philosopher; Richard Lower and Edmund King, who performed the first blood transfusion in a human; Thomas Millington, later physician to the king; and Christopher Wren (Feindel, 1970).

tibiarum and gave a one-page account of 'die von den alteren Aerzten so genannte Anxietas tibiarum' (p. 459). It is apparent from Wittmaack's writings that earlier accounts of anxietas tibiarum existed, but Ekbom (1960) reportedly could not definitely trace them. During this period in history, the phenomenon was construed as a symptom of hysteria and, therefore, psychogenic in origin.

A late-nineteenth-century description by George Beard (1880) of what to him was 'one of the myriad results of spinal irritation' is again close to the later descriptions of akathisia. This phenomenon was broadly included under the syndrome of 'neurasthenia': 'Fidgetiness and nervousness, inability to keep still – a sensation that amounts to pain – is sometimes unspeakably distressing. When the legs feel this way, the sufferer must get up and walk or run, even though he be debilitated and is made worse by severe exercise' (pp. 41–42).

Early in the twentieth century, Haskovec (1902) described two patients with restlessness and an inability to sit (see Appendix A for a translation of Haskovec's paper). One 40-year-old man was described as follows: 'When he was required to stay seated, he rose up and down quickly and involuntary, sitting down again and repeating his behaviour. The movements impressed one as being automatic, involuntary and compulsive, and the patient also considered them this way.' The other patient, a 54-year-old man, had the following problem: 'When he was seated, he rose up and down compulsively and violently. . . . He needed to hold on to the table to stop himself from rising up involuntarily' (p. 128). Consistent with the concepts that preceded him, Haskovec's diagnoses were 'hysteria' in the first case and 'neurasthenia' in the other. Akathisia in one patient was associated with clonic movements of the diaphragm and spasm of the larynx which 'he could partially stop when one told him to keep still, to speak slowly and to breathe calmly' (p. 197). Even though the syndrome now had a distinctive name and a detailed description, and was distinguished from the restlessness associated with anxiety, depression or psychosis, it continued to be seen as psychogenic in its aetiology. Haskovec distinguished it from chorea, which was accepted as a neurological disorder.

Akathisia continued to be regarded as a nonorganic psychiatric disorder for the next two decades. Raymond and Janet (*Nouv Iconogr. de la Salpetriere,* 1902; cited in Bing, 1923) described a case which was considered to be an expression of a so-called professional abulia. While sitting, which had become for him a symbol of his profession as a goldworker, the patient was overcome by a tormented feeling of fear which eventually forced him to jump up. Beduschi (*Rivista di Patol nerv e ment,* 1904; cited in Bing, 1923)

referred to an intense fear of sitting (kathisophobia). Oppenheim[2] (1923), in his book entitled *Lehrbuch der Nervenkrankheiten,* wrote: 'An unusual kind of subjective dysruption of sensations as the restlessness in the legs, it can become a tormenting problem that may continue for years and decades, and be passed on genetically, i.e. become familial. In Oppenheim's observations, psychological factors played a major role' (p. 1774).

Sicard's[3] 1923 description of a patient is reminiscent of Haskovec's account of an inability to remain seated, but he attributed it to upper-body pain. He reviewed Haskovec's cases and came to the conclusion that one patient suffered from epidemic encephalitis and the other from tic or myoclonus. He also described a series of three patients with the symptoms of forced walking (tasikinesia), diplopia and somnolence, which he diagnosed as epidemic encephalitis lethargica. The term *tasikinesia* was thus introduced. Sicard had come to the conclusion that this was part of an organic disorder, and he distinguished it from similar symptoms seen in mania, anxiety and phobia, dementia praecox, depression and certain epileptic states. Sicard (*Revue Neurologique,* 28:672) gave this description of the syndrome:

> People thus affected are ceaselessly agitated, in perpetual need of movement, not being able to stay still, getting up from one seat to sit down in another, and walking up and down ceaselessly in the area of the apartment where they find themselves. A sort of anxiety siezes them, gripping them as soon as they are seated, and forcing them to leave the chairs they have chosen. They don't know rest in the seated position. They are calmer and more stable in the recumbent position.

Bing (1923) described akathisia in association with the parkinsonian syndrome related to epidemic encephalitis. In his reference to one of Haskovec's cases, he wrote:

> If this case had caught our attention today (instead of Spring 1897), we would surely have made a diagnosis of the myoclonic form of epidemic encephalitis . . . we shall not attempt to hypothesise too far in this area and only stress that in our current standing of knowledge, Haskovec's patient without doubt had suffered from an acute organic brain disturbance favouring the corpus striatum. (p. 168)

[2] Hermann Oppenheim (1858–1919) is remembered for his description of amyotonia congenita (now called 'Oppenheim's disease') and for providing the term *dystonia musculorum deformans* (also called 'Oppenheim–Ziehen's disease'). He was an expert diagnostician, and it was on the basis of his diagnosis that the first surgical removal of a brain tumour was performed by Koehler. His treatise went to seven German editions and was translated into many European languages (Weil, 1970).

[3] Jean Athanse Sicard (1872–1929), a Parisian neurologist, is best remembered for his introduction, with his pupil Jacques Forestier, of radio-opaque iodized oil (lipiodil). He gained eponymic fame for his description of a case of traumatic injury of the neck in which the ninth, tenth, eleventh and twelfth cranial nerves were damaged (Bucy, 1970).

He agreed with Wilson that 'the symptoms . . . fall openly under the understanding of the release phenomena . . . because it is the result of the pathological release of automatically working mesencephalic centres from the inhibiting apparatus of the higher centres' (p. 169). In a later treatise, Bing (1939) distinguished this syndrome from the restlessness of Parkinson's disease (PD), which he considered to be secondary to the discomfort of muscular rigidity.

With the descriptions of Sicard and Bing, akathisia came to be seen as sometimes being a symptom of idiopathic or postencephalitic parkinsonism. An influential statement in this direction was that of Kinnier Wilson[4] (1940), who wrote that even though Haskovec used the term *akathisia* for cases of 'hysterical or psychopathic nature', it could be applied to parkinsonian patients. He described patients with a mild form of the disorder who, while evidencing bradykinesia generally, tended to move their feet and legs. Others had a 'paradoxical' inability to sit even though immobilized by their illness. He felt that this was 'no doubt because they feel the cramping effect of fixed posture and have to move and stretch their limbs at intervals'. It is, therefore, not clear whether akathisia was recognized as a distinct symptom of parkinsonism or essentially a secondary symptom with its basis in rigidity. This issue has remained unresolved until recently.

Brief descriptions of the syndrome continued to be published in the early 1940s. Mussio-Fournier and Rawak (1940) published a case of 'hyperkinesis of the lower extremities caused by paresthesias appearing during rest' associated with pruritus and urticaria. This patient had a strong family history of the same disorder. Allison (1943) described 'leg jitters', which he reported to be a common problem. The paper by Ekbom (1944) was the first detailed account of the syndrome, which he denoted as 'irritable legs' and later the restless legs syndrome (RLS) (Ekbom, 1945), based on his own experience of many cases. He described the most characteristic symptom of this disorder as 'creeping or crawling sensations most frequently localised to the lower leg'. He clearly distinguished these sensations from acroparaesthesiae in that they were present not in the skin 'but deep inside, in the muscles or "bones" '. The peculiar feature of the sensations was that they appeared only when the limbs were at

[4] Samuel Alexander Kinnier Wilson (1878–1937) was one of the group of brilliant neurologists at the National Hospital, which included Gowers, Hughlings Jackson, Bastian and Horsley. He is best remembered for his 'progressive lenticular degeneration: a familial nervous disease associated with cirrhosis of the liver', which came to be known as Wilson's disease. He made a number of contributions to the study of what he called the 'extrapyramidal system', and his two-volume textbook *Neurology* (London: Arnold, 1940) was a landmark publication (Haymaker, 1970).

rest and they were relieved by movement. They were almost invariably present in the evening and at night. Some patients described pain rather than creeping sensations. The neurological examination was otherwise normal. Ekbom went on to describe further cases, as well as perform epidemiological studies, to suggest that RLS was a common disorder in otherwise healthy people, was equally common in both sexes, could start at any age and was often familial (Ekbom, 1945, 1946a,b, 1950, 1960). He reported that if mild cases were included, the disorder was present in 5% of otherwise normal individuals (Ekbom, 1960), and the prevalence might be as high as 11% in pregnant women and 24% in those with iron deficiency (serum iron less than 60 μg/dl). He recognized as other causes poliomyelitis and other infectious diseases, avitaminosis, diabetes, lengthy exposure of the legs to cold and the intake of neuroleptic drugs. He discussed the various treatment options and remarked that 'it should be remembered that promethazine makes the symptoms worse' (Ekbom, 1960). Ekbom recognized that a number of cases of RLS were dismissed as being 'psychogenic' or 'nervous' and that many patients 'are ashamed to talk about their discomforts to other persons', but he firmly believed that the disorder was organic. It is interesting, however, that he did not use the term *akathisia* or make any reference to Haskovec's papers in his reports. His inclusion of neuroleptics as a cause and an exacerbating factor for RLS suggests that a clear distinction between RLS and drug-induced akathisia had not emerged.

Even after the publication of Ekbom's 1944 and 1945 papers describing RLS, doubt existed about its distinct status. Purdon-Martin (1946) attributed the symptom of restlessness to acroparaesthesiae, and Masland (1947) to myokymia. Other papers were published which supported Ekbom's descriptions and some extended them. Nordlander (1953, 1954) reported restless legs in anaemic patients. Ask-Upmark and Meurling (1955) reported its presence as a late effect of gastrectomy. Subsequently, basing his claim on the anecdotal presence of postural dependence of symptoms, Ask-Upmark (1959) attributed the disorder to vascular congestion of the spinal cord. French interest in this syndrome was significant, as demonstrated by the Bonduelle and Jolivet (1953) paper and the Tolivet thesis (cited in Ekbom, 1960). In the French literature, it was referred to as *impatience musculaire.*

By the 1960s, RLS was firmly established as a neurological disorder, albeit of unknown aetiology. Grinker and Sahs (1966, p. 336) devoted a short paragraph to it, and Brain and Walton (1969, pp. 881–882) described it under the 'miscellaneous disorders of muscle', while suggesting that chlorpromazine was of great help in some patients.

Restless legs and the neuroleptic era

The first discussion of drug-induced akathisia is credited to Sigwald et al (1947), who reported that a patient with PD had developed restlessness when treated with the phenothiazine drug promethazine. After antipsychotic drugs became generally available, a number of reports of akathisia appeared in the literature, with descriptions of patients being restless, being unable to sit, marching like soldiers, etc. The similarity with the akathisia syndrome of the preneuroleptic era was recognized from the beginning, and reference was often made to the Haskovec papers. The term *akathisia* was not used consistently, however, to describe the drug effects. Barsa and Kline (1956), in referring to the effects of reserpine in psychosis, spoke of 'turbulent reactions' involving psychic excitation and motor stimulation. Sarwer-Foner and Ogle (1956) described 'paradoxical reactions'. Freyhan (1958) was one of the early authors to refer consistently to the 'akathisia syndrome' and provide a lucid description: 'If akathisia is mild, patients complain of a feeling of inner unrest, of pulling or drawing sensations in the extremities but chiefly in the legs. Once akathisia is fully developed, patients pace back and forth and can neither sit down to read or play or sleep. In severe cases, patients appear continuously agitated' (p. 198).

From its earliest descriptions, the 'paradoxical' nature of akathisia was apparent to clinicians and investigators alike; ie, drugs that were generally recognized to produce a calming effect on psychotically disturbed individuals themselves produced 'nervousness' and restlessness. The early European authors referred to it as an extrapyramidal phenomenon; its association with drug-induced parkinsonism was recognized; it was noted to be dose-related and occurring soon after the introduction of phenothiazines and related drugs; and it was known to be reversible (Deniker, 1960; Denham and Carrick, 1961). Some investigators, however, construed such symptoms as psychological responses to the physiological effects of drugs. The *American Illustrated Medical Dictionary* (Dorland, 1951) described akathisia as a 'psychosis marked by morbid fear of sitting down and resulting inability to sit still'. Lang's *German–English Medical Dictionary* (Meyers, 1951) described it as stemming from a 'neurotic inability to remain seated'. Sarwer-Foner and Ogle (1956) argued that the 'holding down' effect of the phenothiazines created feelings of increased passivity, fears of impaired bodily function and changes in bodily image, thereby resulting in enhanced anxiety and even an exacerbation of psychosis. According to them, some patients saw the administration of the drug as an assault or seduction, or otherwise resisted the abandonment of the symptoms because of the secondary gain. Sarwer-Foner (1960b) elabo-

rated on these paradoxical behavioural reactions (listing nine categories of patients who were particularly vulnerable to drug side-effects) but accepted that a proportion of restlessness was caused by akathisia, which was a 'neurologically determined' reaction. The nature of the arguments proposed by Sarwer-Foner is suggested by the following quotation:

> Drugs with powerful pharmacological effects are interpreted by some of these patients as decreasing their ability to control their own bodies. Some patients with such problems interpret the side effects as markedly threatening. These side effects suggest bodily impairment, and bring closer to the surface their fears of retribution for 'sins' and guilt in terms of bodily disease, as though it is expressed in a living tableau before their very eyes. (p. 314)

Akathisia therefore was described as either psychogenic or organic in origin, with different authors favouring different explanations. Hodge (1959) clearly described akathisia as part of the 'parkinsonian syndrome', which generally referred to the akinetic-hypertonic reaction, whereas Winkelman (1961) emphasized the similarity in the restlessness seen as a consequence of neuroleptic medication, PD or a psychoneurosis. In spite of the few interesting papers examining the psychological and psychodynamic meaning of the akathisic reaction, consensus was emerging in the early 1960s that akathisia was an extrapyramidal side-effect of neuroleptic medication. It was demonstrated that akathisia could occur in psychiatrically normal individuals when treated with neuroleptic drugs (Hollister et al, 1960). It was also suggested that akathisia could be distinguished from anxiety (Hodge, 1959; Freedman and De Jong, 1961) and that patients who developed akathisia could not be distinguished from those who did not on the basis of preexisting psychiatric or personality factors (Freedman and De Jong, 1961). The four major classes of drugs used in the 1950s and 1960s to treat psychosis (rauwolfia alkaloids, phenothiazines, thioxanthenes and butyrophenones) shared the propensity to induce akathisia as well as other neurological side-effects.

Akathisia and the efficacy of antipsychotic drugs

The prominence of extrapyramidal symptoms of antipsychotic drugs prompted a number of early investigators to consider the presence of such symptoms to be essential for achieving therapeutic effects. Two seemingly opposing concepts emerged: one group favoured the need to increase drug dosage to produce parkinsonian effects, while the other favoured the use of low dosages to avoid them and recommended the use of medication to eliminate or reduce the parkinsonian effects. The Paris school – Delay, Deniker, Green and Madaret – essentially belonged to the first group. Delay favoured

the use of the term *neuroleptics* (literally, 'that which takes the neuron') to describe these drugs, and Delay and Deniker (1961) noted that the psychic excitation and dystonic reactions of the drugs (the 'excitomotor syndrome') were essential for therapeutic purposes. The synthesis of butyrophenones by Janssen in 1956 and the subsequent demonstration of their clinical profiles reaffirmed the conviction. The Leige school – Divry, Bobon, Collard, Nols, Pinchard, and Damaret – supported this viewpoint. In their report of the clinical trial of triperidol, Divry et al (1960) concluded that the manifestation of major or acute (mainly dystonia) or minor or subacute (impatience musculaire, akathisia, tasikinesia) 'neurodysleptic' excitatory reactions was of special value in the treatment of withdrawn or amotivated schizophrenics. Morosini (1967) from Italy supported this view. These investigators therefore considered the dramatic neurodysleptic manifestations to be a necessary phase in the path to improvement and were not alarmed if anxiety and panic accompanied these reactions.

The position taken by a number of Anglo-American investigators was somewhat different. Freyhan (1959) initially indicated that 'compounds which failed to elicit extrapyramidal symptoms showed the least favorable therapeutic results'. On detailed examination of his data, he modified his position, stating that drugs with higher potency (ie, with greater capacity to produce extrapyramidal side-effects) were more efficacious in mania but not in schizophrenia (Freyhan, 1961). Furthermore, the introduction of antiparkinsonian agents, while ameliorating the parkinsonism, did not antagonize the antipsychotic effect (Freyhan, 1961). Goldman, like Freyhan, changed his position after a review of 4,030 case records and concluded that 'good antipsychotic activity is available without the production of parkinsonism in most patients' (Goldman, 1958, 1961). The introduction of thioridazine, which was as efficacious as chlorpromazine but produced far fewer extrapyramidal side-effects (EPSE), supported this contention. A number of other studies followed that examined the relationship between clinical efficacy and the tendency to produce EPSE: Kam and Kasper (1959), Hollister et al (1960), Cole and Clyde (1961), Simpson et al (1964) and Bishop et al (1965), among others. These studies supported the position that 'gross EPSE bear no relation to drug response. Hence, the practice of deliberately increasing dosage to produce EPSE is unwarranted' (Bishop et al, 1965). It is unfortunate that these authors did not describe subtypes of EPSE, and it is not possible to say what their positions were with regard to akathisia.

The positions taken by Haase (1961) and Brune et al (1962) were somewhat intermediate. Haase found that clinical efficacy was apparent only when fine-motor abnormalities (eg, handwriting) were apparent, but when 'coarse'

EPSE (severe akinesia, rigidity, akathisia and dystonia) occurred, the patients did not respond. He therefore advocated the use of 'fine handwriting measures', although his data did not directly suggest that. Brune et al (1962) supported Haase's contention. This position was still different from that of Divry et al, who advocated the development of neurodysleptic symptoms such as akathisia and dystonia. It must be emphasized that the conclusions were based on different observations. For example, in the Brune et al (1962) study, the early development of anxiety or panic was seen as a negative development, but Divry et al (1960) did not place emphasis on the early developments and waited for the final outcome.

A synthesis of these contrasting positions was attempted with the suggestion that even though EPSE per se may not be necessary for the effectiveness of a drug, certain side-effects may be helpful in certain kinds of patients. The excited and assaultive patient might be helped by drugs that produce akinesia, and the inert, withdrawn patient by drugs that caused neurodysleptic excitation (Ayd, 1965). Clinicians recognized, however, that this did not work in practice and some patients reacted adversely to these effects (Chien and DiMascio, 1967). The adverse reactions continued to be considered to be psychological responses to the side-effects, much in the vein of Sarwer-Foner's (1960a,b) suggestions discussed earlier. It was not until the mid-1970s, with the influential writings of Van Putten and colleagues (Van Putten, 1974, 1975; Van Putten et al, 1974), that it started being appreciated that akathisia could have a prominent mental component that could resemble an exacerbation of schizophrenia.

In subsequent years, a number of studies have examined the relationships between neuroleptic drug doses, their plasma levels and their efficacy and propensity to produce side-effects (eg, Baldessarini et al, 1988; Rifkin et al, 1991). Most investigators now accept that it is not necessary to produce EPSE to obtain beneficial effects from neuroleptic drugs. The literature also suggests that there is a significant positive relationship between neuroleptic blood levels and EPSE, including akathisia, but the relationship is not necessarily linear (Van Putten et al, 1991). The major studies that have contributed to the development of the concepts of akathisia and restless legs syndrome are listed in Table 1.1.

The multifaceted nature of drug-induced akathisia

As akathisia became better recognized in the clinic and accepted as a common side-effect, it was apparent that its manifestations could be varied. We have already discussed some of the literature referring to the 'paradoxical' reac-