A clinical lecture on shaking palsy. By Thomas Buzzard, MD, FRCP. (Physician to the National Hospital for the Paralyzed and Epileptic). Brain 1882; 4: 473–492 and On-off fluctuations in Parkinson’s disease. A clinical and neuropharmacological study. By RJ Hardie, AJ Lees and GM Stern. (From the Department of Neurology, University College Hospital, London WC1). Brain 1984; 107: 487–506.

Thomas Buzzard (1831–1919) never attended medical school but was one of the last doctors to enter medicine through apprenticeship to a general practitioner. Appointed to the staff of the National Hospital for the Paralyzed and Epileptic in 1867, at the suggestion of Hughlings Jackson, Buzzard was one of that small group of physicians who helped ‘Queen Square’ acquire its international reputation (Fig. 1). He doubled-up as a medical journalist; dealt with the Soho (London) outbreak of cholera in 1854; and served with the Turkish army in the Crimean War. He resigned his hospital appointment in 1906. Sir Gordon Holmes did not consider that Thomas Buzzard contributed much to the advancement of neurology but acknowledged that he was a sound and practical physician who taught well. Buzzard wrote on The simulation of hysteria by organic disease (1891), delivered the Harveian Lectures for 1885 on Some forms of paralysis from peripheral neuritis (1886) and published on Clinical aspects of syphilitic nervous affections (1874). In 1882, Buzzard published a series of 25 lectures, mostly delivered at the National Hospital, as Clinical lectures on disease of the nervous system. The one on paralysis agitans is also the first article in Brain on Parkinson’s disease (printed without mutual attribution having a few sentences omitted or inserted but otherwise unchanged).

So graphic and admirable is James Parkinson’s original description that little remains for subsequent observers to add: ‘involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards and to pass from a walking to a running pace; the sense and intellect being injured’. Sylvius de la Boë had previously distinguished tremors contaminating voluntary movement from those occurring at rest; and—as ‘tremor coactus’—Sauvages (1763) gave a prophetic account of the tremulous parts that leap even when supported in contrast to all other tremors that subside when voluntary exertion ceases.

The points are well made by observing Mrs G who sits with the chin resting on her chest, the lower lip and associated muscles shaking, and her mouth drooling saliva. Her arms, at rest, are in a state of constant tremor at a rate of 160–170/min. With attention, the amplitude but not the frequency of the movement increases. She walks with short ‘toddling’ steps, the head carried low, the body stooped forward. Her face has no expression. Pulled by the dress when standing still, Mrs G falls backwards. Reaching for a cup, the tremor stops. Not weak, she is feeble through inability to use the hands; sensibility is normal; her bowels are costive and the bladder unstable. Although tremor persists throughout voluntary movement in some patients, its persistence when the muscles are abandoned differentiates paralysis agitans from disseminated sclerosis. Thus, the artist with paralysis agitans can paint; with intention tremor, he cannot. That said, Dr Buzzard thinks he can recall patients with disseminated sclerosis in whom tremor was present at rest and with movement, and those with paralysis agitans having tremor on movement but nothing at rest. Posture of the hands—the fingers flexed at 45° to the palm against which the thumb appears to roll some object—is characteristic. Not described by Parkinson, but apparent to all who examine as well as observe their patients, is the muscular rigidity. Of course, these features may differ in their intensity and frequency between cases. Although Charcot has drawn attention to the quality of speech in Parkinson’s disease, Dr Buzzard considers that the voice has a characteristic shrill piping note similar to that habitually used by an actor when seeking to mimic extreme old age. Buzzard has not himself noted this tone in elderly healthy individuals of his own acquaintance. Rather, he thinks it likely that an influential thespian might have encountered an aged person with Parkinson’s disease and

Fig. 1 The honorary medical staff of the national hospital, Queen Square, 1897. Thomas Buzzard is standing at the back right. From Holmes, G. The National Hospital Queen Square, 1860–1948 (1954). Edinburgh and London: E. & S. Livingstone. Plate III facing page 41.
handed down this eccentric interpretation—‘as we know is the stage custom’—to successive generations of players.

James H, a patient aged 64 of Dr (Charles Edward) Beevor (1854–1908), progresses from difficulty using a knife and fork and dressing, with ‘thick’ speech, to being bed-bound within a year of presentation. He shows mental hebetude, or extreme slowness of response and expression; movements are equally slow and he cannot raise himself in bed, lying for hours in the same position; he is wasted but has no tremor. ‘There is a very curious circumstance to be noted…in response to my request, he raises his hand or his foot to some distance above the couch, and there he lets it remain for several seconds until…he is told to drop it; and if I lift one of his limbs, and place it in any position, so it remains in a cataleptic fashion’. As for the diagnosis, ‘I have been led to conclude that the patient represents an anomalous form of paralysis agitans partly by the necessity of excluding other explanations.’ Which disorders has he considered? It is not lead poisoning nor progressive muscular atrophy, bilateral sclerosis or Charcot’s amytrophic lateral sclerosis. The course is progressive so widespread softening (vascular disease), in which a more or less sudden loss of power occurs and the paralysis increases ‘by leaps’, is unlikely. The lack of headache and symptoms or signs (using the ophthalmoscope) of raised intracranial pressure make cerebral tumour improbable. Furthermore, Dr Buzzard considers that the preserved sphincter function and absence of bed-sores (although James H was nursed from arrival on a water bed) exclude many of these disorders. His gait cannot be observed but, in favour of paralysis agitans is his fixed look and extreme immobility, the rigidity and retardation in execution of movements, and the characteristic hand posture.

Professor Charcot and Dr William Gowers have commented on cases in which rigidity progresses despite negligible tremor. But, having considered all the evidence, Dr Buzzard diagnoses paralysis agitans and ‘looking back to past experience… I think I have seen several such cases in work-houses and hospitals, where they have been classed with cases of softening of the brain.’ He has also observed the converse. Mrs M has experienced a very slow clinical evolution with profound tremor but no rigidity. And when attempting to walk, William W—an engine-driver—remains for a time unable to start, his feet beating the ground rapidly as he marks time before setting off at a fair pace—the patient likening his condition to ‘the wheels of a locomotive failing to bite the rails when they are slippery with frost and making, in consequence, ineffective revolutions’. Benjamin L, aged 22 years, has developed all the features of paralysis agitans in less than a year from presentation but the patient blames himself for this parlous state on the basis of having lived freely—indulging in alcohol, thrice daily onanism as a teenager and, subsequently, ‘the greatest excess in sexual intercourse’. Much the same louché lifestyle is blamed for the development, aged 38 years, of paralysis agitans in William V. Elizabeth B develops transient wild violent movements of the acutely weakened left sided limbs that recover within 3 weeks, after which she has some residual intention tremor but no abnormality of hand posture. Reasonably, Dr Buzzard prefers the diagnosis of apoplexy to paralysis agitans.

In the absence of any pathological studies, consideration of the nature of paralysis agitans hinges on clinical analysis of the two features that Dr Buzzard considers to be pathognomic. The posture of the hands reflects differential muscular activity of the interossei as in tetany; and the piping voice ‘may be dependent upon a functional imperfection of the soft palate, perhaps due to a vibratile condition of its muscular structure’. And there he leaves it.

Prior to 1967, the clinical course of Parkinson’s disease was considered to be chronic and predictable other than occasional fluctuations due to an altered emotional state. That has changed with the introduction of levodopa-containing medicines; but although many symptoms now improve, the therapeutic effect diminishes after a few years and some patients show ‘prominent variations from hour to hour in their symptoms and signs’ that are not seen as part of the natural history in untreated individuals. At a descriptive level, these fluctuations are hyperkinetic, dystonic and hypokinetic; and they seem to occur at the presumed peak or end-of-dose, with diphasic cycling related to medication, diurnal timing, or only in the early morning. It seems obvious to Richard Hardie, Andrew Lees and Gerald Stern that these must surely depend on fluctuating drug availability, and that hypothesis is supported by the response to continuous infusion of levodopa reported in the literature. But direct correlations with plasma levodopa concentrations are lacking, not least because many confounding factors related to drug interactions and catabolism may have dissociated random measurements of drug concentration from the dynamics of clinical fluctuations. The features that have to be understood are not gradual waning of the therapeutic effect towards the end of each interval between doses, but sudden flipping from an ‘on’ to an ‘off’ state and vice versa; and the apparent random timing of these clinical complications with respect to ingestion. It follows that perhaps a better explanation will be found by examining the neuropharmacology of substances that interact with levodopa or their metabolites—circadian rhythms of endogenous catecholamines, the formation of tetrahydroisoquinolones and 3-ortho-methyl-dopa, alkaloid condensation products of dopamine, derenervation hypersensitivity and (conversely) sudden desensitisation of striatal dopamine receptors analogous to depolarization block at the neuromuscular junction. Each has been proposed as an explanation for the ‘on-off syndrome’.

Clearly working in a former age with respect to healthcare economics, the authors set out to study 20 patients—12 with random and 8 with somewhat predictable patterns of fluctuation—by careful direct observation during up to 4 weeks hospital admission, and with meticulous
recording of activities in self-scoring diaries of the relationship between dosing and motor fluctuation; followed by double-blind crossover comparison of oral levodopa with a dopadecarboxylase inhibitor (benserazide or carbidopa) and continuous intravenous infusion in ambulant patients; and finally by observing the response to dopamine agonists lisuride or apomorphine (with domperidone) given parenterally within 10–15 min of the onset of sudden akinesia during which changes of up to 3 stages on the Hoehn and Yahr disability rating scale might occur.

Adjusting for differences in the timing of oral treatment, the authors suggest a mean duration of response to each dose that is shorter in those with random than semi-predictable fluctuations. Unexpected failure to respond to one of the daily doses—often after a large lunchtime meal—early morning akinesia or dystonic foot posturing, choreiform contamination of ‘on’ periods, uncontrollable yawning and stretching, diphasic dyskinesia occurring at the start and end of each period of treatment or just before going ‘on’, and various end-of-dose dystonic cramps are all observed. Emotion, stress and motivation influence these phenomena and most patients confirm that ‘off’ periods are accompanied by altered mood. The transformations are usually complete within a few minutes but the dyskinetic movements last much longer.

Within a few minutes of waking, Case 1 experiences abduction at the right shoulder; the elbow and wrist are both hyperflexed, the fingers extended and splayed, the legs flexed and the toes curled; the head is rotated towards the elevated arm or with retrocollis; the face is contorted by pouting, grimacing, twitching, jaw-clenching and blinking; speech is absent and her mood is furious; there is marked autonomic over-drive. After some hours, she responds to intravenous levodopa and, exhausted and akinetic, confirms that ‘it’s all quiet now’. Ninety percent of all other patients also respond to intravenous levodopa showing a reduction in duration and number of daily ‘off’ periods, and this improvement is better than on oral medication (Fig. 2): ‘statistical analysis does not adequately convey the true impact of the infusions’. Lisuride has a brief and unpredictable effect—working during <50% of exposures and for no more than 5 min.
with a stuttering dynamic that includes dyskinesia with nimble finger movements but a frozen gait; with apomorphine, despite nausea and headache, the benefits are invariable and consistently last more than 1 h.

What conclusions can be drawn? Although the relationship between the on–off syndrome and plasma levels of levodopa are not reconciled, and their own observations are incomplete, ‘[motor fluctuations] did not exist before the introduction of the drug, without which parkinsonian patients were in a permanent akinetic off condition’ (Fig. 3). Clinical observations on the interplay are confounded by the tendency for those with unpredictable ‘off’ periods to take medication at shorter intervals so that overlap of consecutive doses and a hang-over effect may obscure the picture. Furthermore, levodopa is normally absorbed in a pattern that may result in a double peak of drug availability. During preliminary dose-response evaluations, clinical benefit is observed in every patient during continuous levodopa infusions that were lower than those eventually used in this research. Thus, the pharmacological response is ‘all or none’ even though thresholds for its induction and maintenance may differ. Others have suggested that the introduction of oral medication with levodopa involves different induction and maintenance doses. Given that, when they occur, the clinical responses to oral or intravenous levodopa and to parenteral lisuride and apomorphine are identical—apart from gait freezing with lisuride (which has noradrenaline receptor-blocking properties in addition to dopamine agonism)—indicates that a single physiological mechanism is targeted even if pharmacological properties of the various drugs do differ. Everything suggests that the post-synaptic striatal structures are intact and sensitive during akinetic periods. There is no reason to invoke tachyphylaxis as the explanation, but since the introduction of combined levodopa and dopadecarboxylase inhibitors has not altered the incidence of response fluctuations (in fact they may emerge sooner), swings in brain rather than steady state plasma levodopa concentrations are probably responsible. Motor fluctuations occur because the brain progressively fails ‘to act as a transformer, smoothing out amplitude swings of plasma precursor concentrations into a sustained biological response’ despite erratic gut absorption and delivery to the target organ. It follows that ‘the development of a satisfactory sustained release formulation of levodopa may be of considerable value in the management of response fluctuations seen in Parkinson’s disease’.

One hundred and twenty-six years after Thomas Buzzard lectured on Parkinson’s disease and sensed but could clarify differences in age of presentation, progression and features that separate the various neurodegenerative disorders having parkinsonism as a core feature, and 24 years after the team at University College Hospital, London, catalogued so clearly the downside of the dividend from the introduction of levodopa, papers in the present issue again draw attention to the tricky issue of how best to model, understand and treat the ‘on–off syndrome’.

Alastair Compston
Cambridge