A PHYSIOLOGICAL MECHANISM OF BRADYKINESIA

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INTRODUCTION

ONE of the most striking features of the motor disability of patients with Parkinson's disease is bradykinesia. Bradykinesia has many different aspects including prolonged reaction time to initiate a movement (Draper and Johns, 1964; Barbeau and DeGroot, 1966; Brumlik and Bosches, 1966), prolonged time to arrest a false movement (Angel, Alston and Higgins, 1970), prolonged time to change a motor pattern (Joubert and Barbeau, 1969) and weakness, at least to the extent of rapid fatigue on prolonged tasks (Schwab, England and Peterson, 1959; Joubert and Barbeau, 1969). The most characteristic feature, however, is slowness of movement (Draper and Johns, 1964; Barbeau and DeGroot, 1966; Brumlik and Bosches, 1966; Joubert and Barbeau, 1969).

Normally, people are able to move their limbs with a continuous spectrum of velocities. The fastest movements are often called ballistic, even though these movements may just be at one end of the spectrum rather than qualitatively different from other slower movements. Bradykinesia must reflect itself in an abnormality of ballistic movements, and it is the purpose of this paper to define the underlying pathophysiology.

As the term 'ballistic movement' is used differently by different authors, it is necessary to specify its meaning in relation to this study. As recently summarized by Desmedt and Godaux (1978), following Richer (1895a, b) and Stetson and McDill (1923), the initial use of the term ballistic referred to those movements which are so brief that the agonist would cease firing before the end of the movement. Such movements were thought to be unmodifiable once set into action by virtue of their brevity. Other authors, such as Flowers (1975, 1976), have extended the meaning of ballistic to refer to any movement performed 'open-loop', without possibility of modification, even if taking a longer period of time.

We would prefer, as do Desmedt and Godaux (1978), to use ballistic more in the original sense, but to be defined electromyographically as fitting a characteristic pattern of activation. Wachholder and Altenburger (1926) first described the initial part of the electromyographic pattern of the most rapid movements as being

triphasic with a burst of activity in the agonist, followed by a burst in the antagonist while the agonist is silent, followed by another burst in the agonist. These bursts of activity can be referred to as Ag 1, An 1 and Ag 2, respectively. This pattern has been repeatedly confirmed in both proximal (Hallett, Shahani and Young, 1975a) and distal muscles (Hallett and Marsden, 1979a, b). In the fastest movements the burst duration of the first agonist and first antagonist components are fixed independent of the distance of the movement (Freund and Büdingen, 1978; Hallett and Marsden, 1979a). Desmedt and Godaux (1977, 1978) have shown that these movements exhibit a different pattern of motor unit behaviour than slower, 'ramp' movements. Operationally, normal subjects and patients will produce ballistic movements with this physiological pattern if they are urged to make their movements as rapidly as possible. Thus, even weak patients with pyramidal tract or alpha motor neuron lesions, if they try to move as rapidly as possible, will produce triphasic patterns even if the movements are slower than those seen in normally strong subjects (Hallett, 1979a).

Flowers has made several important quantitative observations about brady-kinetic movement in his studies of ballistic movements performed by patients with Parkinson's disease. In his first study step-tracking performance was analysed for both large and small displacements (Flowers, 1975). The short ballistic movements were accomplished with normal speed while larger ballistic movements were performed more slowly than normal. In a second study, this phenomenon was studied with a series of steps of different distance (Flowers, 1976). Normals accomplish each of the different steps in the same time period; longer movements are made with faster velocity. This is the consequence of the fact noted above that the durations of the first agonist and antagonist bursts are constant independent of distance; longer movements are made by increasing EMG activity within the set time of the burst (Hallett and Marsden, 1979a). Patients with Parkinson's disease made all the movements with constant speed, taking a longer time for longer movements.

In a previous study of patients with Parkinson's disease the EMG patterns of a sterotyped 10-degree rapid elbow flexion movement were analysed (Hallett, Shahani and Young, 1977). The patterns in the patients with Parkinson's disease were normal with respect to durations of the individual bursts and alternation of activity in the antagonist muscles. Many patterns appeared normal in all respects, but fairly often it was observed that the movement was not completed during the time of the triphasic pattern, but required the additional time of an additional cycle of alternating bursts in the biceps and triceps (fig. 1F in Hallett, Shahani and Young, 1977). If in patients with Parkinson's disease, short ballistic movements could be accomplished in the normal one cycle of the triphasic pattern, but longer ballistic movements require additional cycles, then all of Flowers' kinematic observations can be explained. The goal of this investigation was to show whether this physiological process of additional cycles could indeed be a mechanism of bradykinesia.

METHODS

In an experimental protocol approved by the Peter Bent Brigham Hospital Human Studies Committee, normal subjects and patients with Parkinson's disease gave informed consent to participate. There were 19 patients with Parkinson's disease, 12 men and 7 women, ranging in age from 47 to 82 years. They displayed varying degrees of disability and were being treated with different regimens. The normal subjects were laboratory personnel or neurological patients without known disorders of the motor system (for example, patients with back pain). There were 11 normal subjects, 6 men and 5 women, ranging in age from 30 to 83 years. In both patients and controls rapid elbow flexion movements of the dominant arm were studied.

The subject sat in a chair facing an oscilloscope (fig. 1). The arm was strapped into a light plastic splint with one section for the forearm and one for the upper arm. The two sections of the splint were joined together by a light metallic frame which had a hinge at the level of the elbow into which was incorporated a potentiometer. By means of the potentiometer, rotation of the elbow was converted into a variable voltage. Another part of the metal frame had a handle for the subject to grip which rotated the forearm into supination. (This is important so as to maintain biceps, rather than brachioradialis, as the chief flexor of the elbow). Movements were made in the horizontal plane by abducting the shoulder to 90 degrees by suspending the splint with wires attached to a hook on the ceiling. The splinting and suspending processes were comfortable and non-fatiguing.

The oscilloscope screen facing the subject displayed the voltage from the potentiometer as the height of the single beam which was running rapidly so to appear as a line. The graticule was illuminated and the lowest line of the graticule corresponded to an elbow angle of 120 degrees. The first line up from the bottom corresponded to 110 degrees, the second line up corresponded to 100 degrees, and the fourth line up, which was the middle of the graticule, corresponded to 80 degrees.
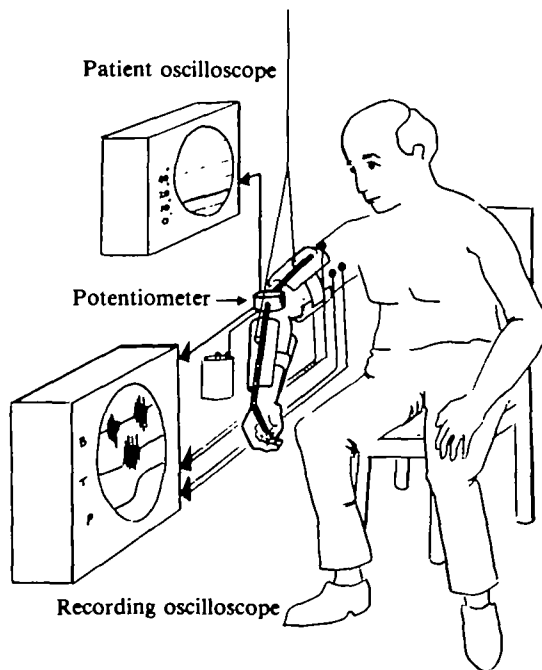

Fig. 1. A diagrammatic representation of the experimental set-up.

Subjects were asked to make rapid, accurate elbow flexion movements beginning at 120 degrees, with the line under their control superimposed upon the bottom of the graticule. Three movements of differing angular distance were studied, 10 degrees (to the first line up on the graticule), 20 degrees (to the second line up) and 40 degrees (to the fourth line up). Only well practised movements were studied and during the course of the experiment the subjects were constantly urged to move as rapidly as they could.

EMG with surface electrodes was recorded from biceps and triceps. EMG activity and elbow angle were recorded on moving light-sensitive paper with a TECA TE-4 electromyograph.

RESULTS

Ten of the 11 normal subjects were able to accomplish the three movements of different length with a single cycle of the triphasic pattern, Ag 1, An 1 and Ag 2 (fig. 2). EMG burst durations were relatively unchanged for movements of greater
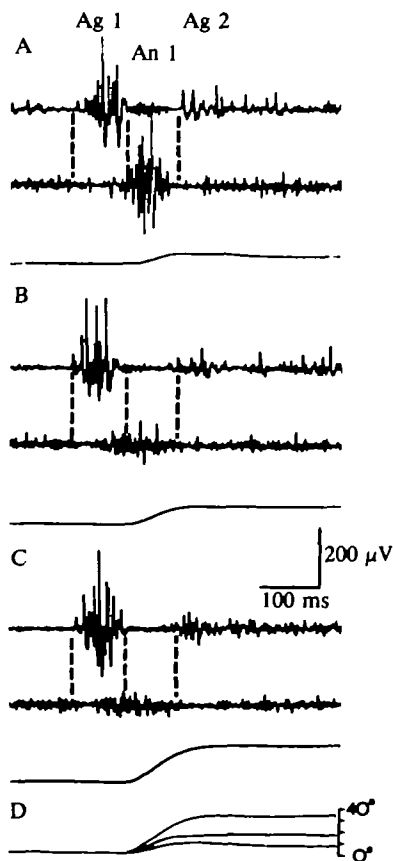
FIG. 2. Attempted ballistic movements of 10 deg (A), 20 deg (B) and 40 deg (C) by a normal 83-year-old woman. In A, B and C the traces are, from above downwards, biceps EMG, triceps EMG and position of the elbow. D shows the three position traces superimposed. The parts of the figure were aligned so that the movements all began at the same time from the beginning of the traces. The dashed vertical lines are discontinuous straight lines indicating the correspondence of the timing of EMG bursts in the different movements.

distance, but the amount of EMG activity within the bursts increased to provide the necessary additional force. All movements were accomplished in approximately the same time (the time of the triphasic pattern), and correspondingly the velocity increased for movements of greater distance. One of the normal subjects made only 'fast ramp' movements characterized by continuous agonist activity without significant antagonist participation.
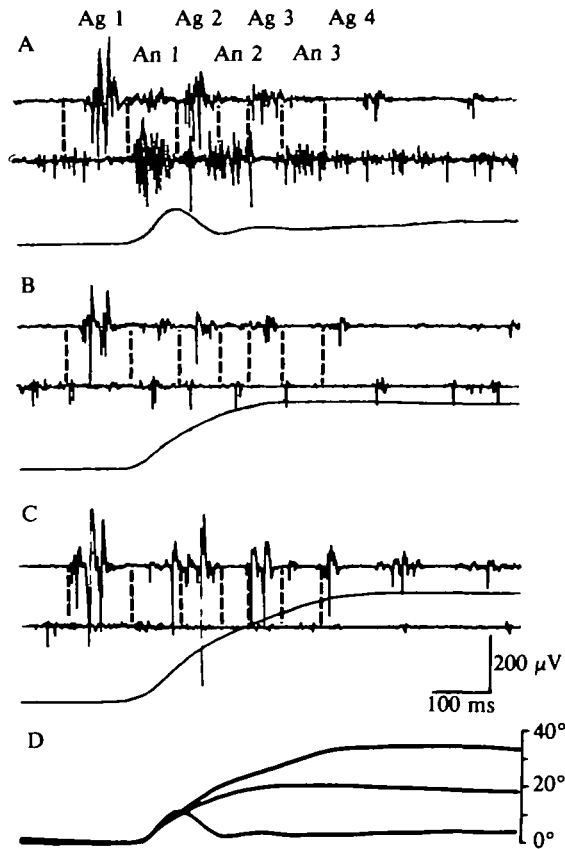

FIG. 3. Ballistic movements of a 68-year-old man with Parkinson's disease. The organization of the figure is similar to fig. 2. Note the additional cycles of bursts; the third and fourth agonist bursts are labelled Ag 3 and Ag 4 and the second and third antagonist bursts are labelled An 2 and An 3. In D, the initial part of the position traces are similar indicating similar velocities of the different movements. In A, the subject did not sustain the attempted 10-deg position, but returned quickly to near the starting point.

Seventeen of the 19 patients had at least some movements characterized by a series of alternating bursts longer than the three bursts of the triphasic pattern (figs. 3 and 4). Prolonged bursting tended to occur more often for the longer movements, and some movements required as many as five cycles (six agonist bursts alternating with five antagonist bursts).

It was our impression that multiple cycles of the triphasic pattern tended to occur more often when there was more bradykinesia, but the phenomenon was variable. If a patient made a movement requiring multiple bursts and was urged to move faster, then the next movement would often require fewer bursts. Although patients with tremor-at-rest often had multiple bursts, it was certainly not necessary for patients to have this tremor in order to show multiple bursts. Despite the bursting the movements usually were relatively smooth.
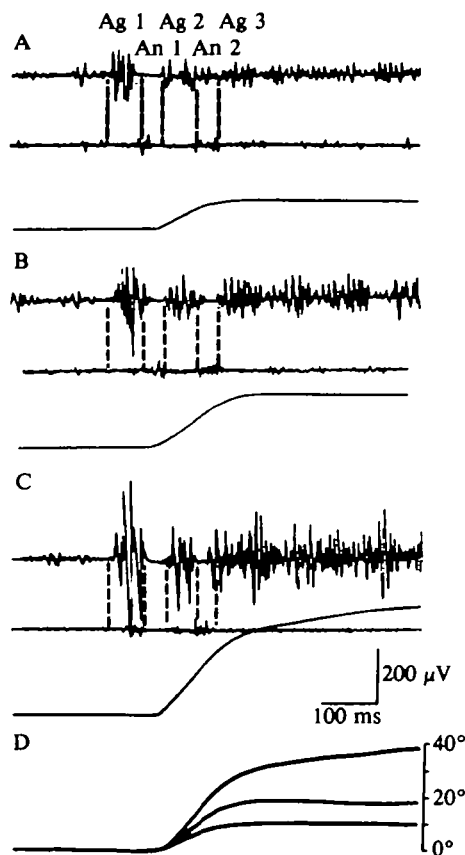

Fig. 4. Ballistic movements of a 63-year-old man with Parkinson's disease. The organization of the figure is similar to figs. 2 and 3. This person is able to increase EMG activity within the bursts to some degree, but still requires additional cycles to make longer movements.

Thirteen of the 17 patients showing a prolonged series of bursts produced at least one example of a longer movement taking more cycles of bursts than a shorter movement. In most of the examples the longer movement had about the same velocity as the shorter movement, but was continued for a longer period of

time (fig. 3). It must be that the amount of EMG activity in each burst is about the same and therefore more bursts are needed to produce the force for a longer movement.

A few patients were able to increase velocity to a certain extent with longer movements, but still required extra cycles for these longer movements (fig. 4). The amount of EMG activity in each burst could be increased so that velocity could be increased, but this was not quite sufficient to complete the movement in the usual time. These patients exhibited a combination of both the normal and abnormal mechanisms. Although theoretically possible, no patient demonstrated the mechanism of increasing the frequency of bursts to make a faster and longer movement.

One of the 19 patients performed normally, not showing any examples of extra cycles. This patient was clinically assessed (before the experiment) to have only mild bradykinesia, but other patients with similar assessment did show the abnormality. The nineteenth patient showed only brief (20–40 ms) EMG bursts synchronous in the biceps and triceps which occurred at irregular intervals. Such activity might be called myoclonic and has been noted previously in patients with Parkinson's disease (Growdon, Young and Shahani, 1975).

DISCUSSION

The study of ballistic movements is a convenient window into human motor physiology. The triphasic pattern of 'agonist burst–antagonist burst–agonist burst' has been known since the early days of electromyography and has been noted repeatedly over the years for rapid movements of different joints. The normal physiology of the constancy of EMG burst lengths for movements of differing distances has been discovered only recently and has been documented for hand and forearm muscles (Freund and Büdingen, 1978; Hallett and Marsden, 1979a) and for animal limb movement (Ghez and Vicario, 1978). This principle of burst length constancy is here extended to elbow flexion for movements from 10 to 40 degrees. Burst durations are prolonged for patients with cerebellar lesions (Hallett, Shahani and Young, 1975b), patients with pyramidal tract lesions and lower motor neuron lesions (Hallett, 1979a), but as verified here again, burst durations remain normal in Parkinson's disease (Hallett, Shahani and Young, 1977).

It appears that the abnormal phenomenon of multiple cycles of bursts seen in some movements in patients with Parkinson's disease does explain Flowers' observations of abnormal ballistic movements. Short ballistic movements are accomplished in normal time because only the normal one cycle is required. Longer movements take longer time because more cycles are required and each cycle requires a relatively fixed amount of time. Movements of different distance are accomplished with constant velocity because the initial cycles of bursts have about the same amount of EMG activity. Thus, longer movements are made by

continuing the bursting for a longer period of time. Normally the amount of EMG activity in a burst is increased for longer movements; it appears that the amount of activity is limited in Parkinson's disease and the mechanism of additional cycles is used to accomplish these longer movements.

This apparent deficit in ability to increase the amount of EMG activity in a burst gives an insight into the essence of bradykinesia and thereby into the normal role of the basal ganglia in movement. Despite the large body of data about the physiology and neurology of the basal ganglia, the normal role of these structures remains remarkably obscure. Kornhuber (1971, 1974) has proposed a theory which has attracted much attention. In his view the basal ganglia and cerebellum participate in setting up the central commands for voluntary movement. This seems true and is in accord with the currently understood anatomical connections of the motor system as summarized by Kemp and Powell (1971) and Allen and Tsukahara (1974). Kornhuber has further suggested that the cerebellum helps plan ballistic movements and the basal ganglia help plan ramp movements. The evidence for this view comes mostly from studies of deranged eye movements seen as a consequence of lesions of the cerebellum and basal ganglia. There was also apparent support for this view from studies in primates by DeLong and Strick (1974) who showed that neurons in the putamen and pallidum fired more often in relation to ramp than ballistic movements.

It is quite clear that ballistic limb movements in patients with Parkinson's disease are abnormal; the data in this paper confirm and clarify the nature of the abnormality. Moreover, the recent work of DeLong and Georgopoulos (1979) shows that neurons in the basal ganglia do not fire preferentially to slower movements. The basal ganglia must contribute to the planning of ballistic movements. The notion that the basal ganglia plan only ramp movements seems wrong.

An alternative view to that of Kornhuber which has not been as popular, but which has been held by a number of workers over many years, is that the basal ganglia 'facilitate' movement. Several early thinkers suggested that the basal ganglia supplied a motor energy (*see* De Ajuriaguerra, 1975). Schwab, who made numerous clinical observations about weakness in Parkinson's disease, showed quantitatively that repetitive movements fatigued more rapidly in patients than in normals (Schwab *et al.*, 1959; England and Schwab, 1961). Additionally, he showed that patients had difficulty in trying to perform two simultaneous voluntary motor acts (Schwab, Chafetz and Walker, 1954). Schwab summarized these facts and other clinical observations with the concept that there was a difficulty in Parkinson's disease in elaborating a motor plan (Schwab and Zieper, 1965). Joubert and Barbeau (1969), on the basis of a series of tests including repetitive tasks, reaction time measures and ability to simulate gestures, came to the conclusion that there was an inability in Parkinson's disease to elaborate a motor pattern.

Buchwald, Hull, Levine and Villablanca (1975) propose that the basal ganglia

make 'response sets' and 'cognitive sets' which prepare the motor system to respond to stimuli. A response set is the facilitation of the initiation and execution of a series of movements composing a complex action. Evidence for this comes in part from the facts that electrical stimulation or ablation of one caudate nucleus leads to no simple sensory or motor deficit, but to a general inhibitory and slowing effect on the contralateral limbs. A cognitive set is the facilitation of appropriate behaviours in a particular situation. Evidence for this comes in part from the fact that electrical stimulation of the basal ganglia interferes with learning and other cognitive skills such as delayed response. Hassler's (1978) view of the function of the basal ganglia is also based in part on the results of electrical stimulation studies. Stimulation of the putamen in the cat produces mostly inhibitory effects and with some parameters of stimulation will also produce some locomotor activity and facilitation of spontaneous turning. Pallidal stimulation produces excitatory effects characterized mostly by turning to the contralateral side. Hassler concludes '. . . the function of the putamen is at the same time to focus the attention, the emotional participation and the excitability on one single event by simultaneously suppressing and fading out all other happenings and motivational objects', while 'the pallidal function is . . . directing of attention to the contralateral side'.

Denny-Brown has held the view for some time from clinical observations and animal studies that the chief symptom of basal ganglia dysfunction is akinesia (Denny-Brown, 1962, 1968). Recent behavioural analysis of monkeys with restricted lesions in parts of the basal ganglia (Denny-Brown and Yanagisawa, 1976) shows a deficiency in '. . . the preparation of the mechanism preparatory to a motor performance oriented to the environment', especially visual stimulation. These authors note physiological studies which show that caudate stimulation produces widespread inhibition and restricted excitation in thalamic and cortical neurons (Buser, 1966; Frigyesi, 1972). They conclude that '. . . the basal ganglia have all the aspects of a 'clearing house' that accumulates samples of ongoing projected activity and, on a competitive basis, can facilitate any one and suppress all others'.

A possible mechanism for the facilitation of movement is to energize specific muscles for that particular movement (Hallett, 1979b). The notion of energizing includes *selection*, since a muscle is selected only if it is energized, and *inhibition* of inappropriate muscles. Any movement can be fully characterized by how muscles are energized and the time order in which the energized muscles are activated. It is conceivable that these two descriptors may be two separate functions. One function, which might be referred to as 'the timing', sets up programs of properly timed and sequenced muscle activity including specification of relative amplitudes in order to produce an orchestrated pattern of flexions and extensions at several joints. The second function, 'the energizing', selects the specific set of muscles to be used for a particular performance and sets the absolute amplitude for the general level of muscle activity. The energizing process might be viewed as channelling the

timing program to the specific set of muscles. That the basal ganglia might aid in this second function is anatomically and physiologically plausible since the basal ganglia take non-somatotopic input (for example, visual input) and produce somatotopic output. DeLong and Georgopoulos (1979) have shown that cells in monkey basal ganglia are related more to the fact of a particular muscle being involved in a movement than with any parameter of the movement such as amplitude or velocity.

Handwriting is a good example to illustrate how these two motor functions can be separated. The style of a person's handwriting, which can be viewed as a timing program, is the same whether channelled to finger muscles using a pencil on paper or channelled to arm muscles using chalk on a blackboard. Another example would be the ability to use (or 'energize') the non-dominant arm to perform a skilled complex motor task even if in all prior experience with this task the dominant arm had been utilized.

Virtually all the pathophysiology of disorders of the basal ganglia can be described in terms of a derangement of energizing muscles. Bradykinesia results from insufficient muscle energy; the data in this paper show that patients with Parkinson's disease cannot generate the appropriate amount of EMG activity within the set time-frame of ballistic movement burst. As shown by the example of micrographia, a defect in energizing muscle need not be accompanied by a defect in muscle timing. Lack of energy is failure to select, and thus akinesia is the extreme of bradykinesia, the failure to activate the muscle at all. Since the basal ganglia are somatotopically organized, it would be possible that one part of the body is affected while another part is less affected or even normal. This would lead to the situation, for example, where a person is able to use one limb for a skilled act, but not the other limb. Only when all the basal ganglia are damaged is the bradykinesia generalized. Even then the timing program is not gone and can be utilized in situations such as paradoxical kinesia when a sudden surge of emotional energy is able to overcome the bradykinesia.

Other symptoms of basal ganglia malfunction may be viewed as inappropriate muscle activation or failure of appropriate inhibition. In athetosis there is excessive activation of inappropriate muscles including even the antagonist muscles (Denny-Brown, 1968). The term 'overflow' might be used to describe excessive muscle activation at an appropriate time; overflow is then the physiological opposite of bradykinesia (this terminology was suggested in Hallett, Chadwick and Marsden, 1977). Involutary movements such as chorea and dystonia might be viewed as released fragments of normal phasic or tonic movements at inappropriate times.

The regulation of muscle timing may be a function, at least in part, of the cerebellum. This has in fact been the chief theory of cerebellar contribution to movement from the time of Holmes (1939) and recent physiological observations in man confirm this (Hallett *et al.*, 1975b; Hallett and Marsden, 1979b). Ballistic movements are more critically timed than ramp movements which may lead to the observation that ballistic movements are more deranged with cerebellar lesions.

Bradykinesia is the physiological consequence of a variety of lesions of the basal ganglia. Loss of the dopamine-containing neurons in the substantia nigra which leads to Parkinson's disease does result in bradykinesia as the central disorder. Bradykinesia is the symptom best related to the reduction in striatal dopamine (Bernheimer, Birkmayer, Hornykiewicz, Jellinger and Seitelberger, 1973). In animal models lesions limited to the substantia nigra produce only bradykinesia (Poirier, Filion, Langelier and Larochelle, 1975). Production of tremor and rigidity require additional lesions.

It should be noted that bradykinesia is a labile deficit varying in time depending in part on the changing amount of emotional investment in the movement. Paradoxical kinesia is the best example of this lability, but the phenomenon was apparent in this study in regard to the variable number of cycles of bursts for the same required movement in successive trials.

It is difficult to avoid commenting on the similarity of the EMG appearance of multiple bursts generated in attempting to make a movement to the bursts in tremor-at-rest seen also in patients with Parkinson's disease. Indeed, in patients with a prominent tremor-at-rest, it is difficult to say where the tremor ends and the movement begins. Previously the suggestion was made that tremor-at-rest might be considered the repetitive running of the ballistic movement pattern (Hallett, Shahani and Young, 1977). The observations here show how repetitive running of this pattern can be a compensatory mechanism for the major deficit of brady-kinesia in Parkinson's disease. It is not clear at the present time, however, how the tremor-at-rest itself can be compensatory unless it enables the shaking limb to initiate movement more rapidly.

SUMMARY

Patients with Parkinson's disease were asked to make ballistic elbow flexion movements of 10, 20 and 40 degrees. Normal subjects made all these movements in the same amount of time with a single 'triphasic' EMG pattern of successive bursts in biceps, triceps and biceps. Almost all the patients made some movements requiring additional cycles of alternating biceps and triceps activity. Most of the patients exhibited at least one example of a longer movement taking more cycles than a shorter movement. It is argued that this behaviour explains previous kinematic analyses of movement in patients with Parkinson's disease and represents a physiological mechanism of bradykinesia. In part on the basis of the data presented here, it is suggested that a normal role of the basal ganglia in movement is to energize the appropriate muscles required to make the movement.

ACKNOWLEDGEMENTS

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