PARKINSON'S DISEASE IN THE ELDERLY PATIENT:

AN OBJECTIVE ASSESSMENT OF NIGHT-TIME

MOVEMENT AND DAYTIME BRADYKINESIA

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ABSTRACT

The disability caused by Parkinson's disease in old age is difficult to quantify and the response to medication may be small. Consequently, emphasis has been placed on objective methods of assessment of night-time and daytime mobility in the following work.

The size and frequency of movement during sleep were recorded using a bed movement monitor. Mean move size was reduced in those with either Parkinson's disease or a low cognitive function score. When both these factors coexisted the resultant reduction in mobility was associated with a higher prevalence of pressure sores. Furthermore, frequency of movement was inversely proportional to cognitive function score.

A double-blind, placebo-controlled, cross-over study of nocturnal dosing with Sinemet-Plus in patients with Parkinson's disease was carried out. Following active treatment, there was an improvement in sleep both as assessed subjectively and by measurement of night-time mobility. Despite the long interval between dosing and morning assessment, walking time was also faster.

In a further double-blind, placebo-controlled, cross-over study, a pedobarograph and a gait assessment trolley were used in a novel way to measure the effect of Sinemet-Plus on daytime bradykinesia. After active treatment, the nature of foot strike improved and the double support time was reduced. Serial plasma

concentrations of levodopa and 3-O-methyldopa were measured using high-performance liquid chromatography. As duration of levodopa therapy increased there was a decrease in the area under the levodopa plasma concentration/time curve and an increase in the mean 3-O-methyldopa plasma concentration. However, no relationship was found between parameters of gait and plasma concentrations of levodopa and 3-O-methyldopa, or measurements of mean arterial blood pressure.

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THE SCOPE OF THE THESIS

Levodopa used in conjunction with peripheral dopa-decarboxylase inhibitors is the current treatment of choice for patients with idiopathic Parkinson's disease. However, it is often difficult, particularly in the elderly patient, to select that dose of the drug which will optimise the improvement in the quality of life of the patient. In this thesis, the possibility of using objective tests of movement and bradykinesia to monitor response to levodopa/carbidopa therapy in this sector of the population has been studied. For this purpose, two novel methods of assessing movement, namely a bed movement monitor and a gait assessment trolley, have been used, along with other more conventional tests. An attempt has been made to relate patient mobility to dosage regimen and in a later study to concomitant plasma levels of levodopa and 3-O-methyldopa.

Several different disciplines have been involved in the work presented here and the author required specialist assistance from a number of persons. As a result, some clarification of the author's contribution to the studies is required.

Drs. R.J. and S.M. Dobbs were responsible for the provision of the medical support. This involved the diagnosis of Parkinson's disease and the rating of the severity of the disease where appropriate; the

selection of suitable patients for study; obtaining informed consent for the studies from the patients; inserting intravenous cannulae for serial blood sampling; and the clinical care of the patients before, during and after the studies.

The prototype bed monitors and the gait assessment trolley were devised by Dr. P.W. Nicholson and Mr. C. Weller respectively. Mrs. J. Hughes was the specialist operator of the pedobarograph, who also took the video recordings of the patients walking. Dr. S.G. Bowes, Miss C.J.A. O'Neill and Dr. A.A. Deshmukh set up the H.P.L.C. assay for levodopa and its metabolites. Dr. S.G. Bowes supervised the author in assaying the plasma samples from nine patients in the daytime Sinemet-Plus study and assayed the samples from the remaining patients (numbers 7, 9, 10 and 11).

With these exceptions, the author has been responsible for generating the data reported in this thesis. This involved a) testing and developing the prototype bed monitor, collection of bed movement data and development of a method for the manual analysis of the traces; b) collection and interpretation of the gait analysis data, the measurement of which was again non-automated; c) devising a "foot strike index" using the data generated by the pedobarograph; and d) H.P.L.C. analysis of the blood samples of nine patients from the daytime Sinemet-Plus study.

Once patients had been selected for study and had given their informed consent, the author was

responsible for the day to day organisation of the patient studies reported in this thesis. This involved attending out-patient clinics; booking beds, transport and meals; ensuring that treatment sheets were written up, the correct medication was on the ward for the patient and giving medication in the case of the daytime Sinemet-Plus study; liasing with patients, nursing and medical staff; ensuring that any specialist equipment would be available on the proposed day of study; etc. A considerable period of time was spent building up interpersonal relationships between the author and the patients involved. By ensuring that the patients knew the author well and were comfortable in her presence they could be as relaxed as possible during the data collection. Nevertheless, the patients taking part in these studies were elderly and many were frail and disabled. This meant that the time taken for the patients to undertake the tests and for reliable measurements to be made was much longer than it would have been for a younger age group, and certainly considerably longer than had been anticipated.

To my husband, Paul, and my family

for their support and understanding throughout

the course of this work.

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INTRODUCTION

In elderly patients with idiopathic Parkinson's disease, response to therapy may be small, especially where multiple pathologies exist. Clinical observation suggests that the control of Parkinson's disease in many elderly patients does not improve consistently following a dose of levodopa/peripheral dopa decarboxylase (PDD) inhibitor combination therapy, nor does it deteriorate obviously when the next dose is due. The absence of fluctuations in control may be due to the lack of effective treatment or to modulation of the response as a result of storage of dopamine.

Night-time is fraught with problems for this patient group. Difficulty turning in bed is a particularly distressing symptom (Stephen and Williamson, 1984; Lesser *et al*, 1979) and may lead to functional incontinence and pressure sores. In patients receiving treatment with levodopa, poverty of movement may be exacerbated due to an end of dose effect (Marsden and Parkes, 1976) or alleviated by reaccumulation of central dopamine stores during rest (Parkes, 1983). Similarly early morning performance on arising from bed may either be influenced adversely or favourably by treatment. Furthermore, insomnia is a more frequent complaint in elderly patients with Parkinson's disease than might be expected because of the effect of age alone (Kales *et al*, 1971; Askenasy and Yahr, 1983). The association between insomnia and

Parkinson's disease has been attributed on the one hand to an unwanted effect of long-term (Nausieda *et al*, 1982) or high dose (Bergonzi *et al*, 1974) levodopa treatment and on the other to inadequate dopaminergic therapy (Bergonzi *et al*, 1974 and 1975; Askenasy and Yahr, 1985). It would thus be desirable if a number of objective methods of assessing night-time and daytime mobility could be devised which would demonstrate response to therapy in a controlled manner.

LITERATURE REVIEW

CHAPTER ONE

PARKINSONISM AND PARKINSON'S DISEASE

1.1   AETIOLOGY

In 1817, Dr. James Parkinson published his classic "Essay on the Shaking Palsy" in which he gave a vivid description of the condition which came to bear his name. Although he described the symptoms of resting tremor, flexed posture and festinant gait, he did not mention the facial immobility, rigidity or the hypokinesia which would today be associated with the diagnosis of Parkinsonism (Pallis, 1971). In the nineteenth century, Parkinsonism was rarely seen in younger patients and was considered to be a reflection of a degenerative process. Since its cause was unknown, Parkinson's disease was termed an idiosyncracy or "idiopathy" (Pallis, 1971). The current incidence of idiopathic Parkinson's disease in England and Wales is about 1 in 1000 and with advancing age there is a steep rise in its prevalence (Brewis *et al*, 1966; Broe *et al*, 1976). However in the first half of this century, Parkinsonism arising as a result of the great viral epidemic encephalitis lethargica affected people of all ages. Postencephalitic Parkinsonism is today of little importance but in recent decades neuroleptic drugs (reserpine, phenothiazines and butyrophenones) have sometimes produced a similar clinical picture. Drug-induced Parkinsonism is usually reversible (Pallis, 1971).

Fahn (1977) distinguished between three classes of Parkinsonism. Whereas Primary Parkinsonism (idiopathic

Parkinson's disease) has an unknown aetiology,

Secondary Parkinsonism develops as a sequel to an

identifiable aetiological factor. The third class

comprises various heterogeneous system degenerations in

which Parkinsonism occurs in conjunction with clinical

signs of a widespread nervous system involvment. A

modification of this classification due to Teravainen

et al (1981) is shown in Figure 1.

I Primary

    Idiopathic Parkinsonism (Parkinson's
    disease, paralysis agitans)

II Secondary

    A Infections
       1 Postencephalitic (encephalitis lethargica)
       2 Other encephalitides
       3 Jakob-Creutzfeldt
       4 Luetic

    B Toxins, Mn, Li, CO, CS_2, CCl_4, CN,
       organophosphates, methanol

    C Drugs
       1 Phenothiazines
       2 Butyrophenones
       3 Reserpine
       4 Tetrabenazine

    D Brain tumours

    E Trauma - physical, electric shock

    F Vascular

    G Metabolic
       1 Hypoparathyroidism and basal ganglia
          calcification
       2 Chronic hepatocerebral degeneration

III Heterogeneous system degenerations

    A Striatonigral degeneration

    B Olivopontocerebellar atrophy

    C Ophthalmoplegia - Steele Richardson Olszewski
       syndrome

    D Orthostatic hypotension - Shy Drager syndrome

    E Dementia
       1 Parkinsonism - dementia of Guam
       2 Normal pressure hydrocephalus

    F Hereditary disorders
       1 Wilson's disease
       2 Hallervorden-Spatz disease
       3 Pallidal atrophy
       4 Joseph's disease

Figure 1 Classification of Parkinsonism (from
         Teravainen *et al*, 1981)

1.2 CLINICAL FEATURES

Parkinsonism is a clinical syndrome characterised by the presence of two or more of the following signs: tremor, rigidity, hypokinesia and postural abnormality (Martilla, 1983; Quinn and Husain, 1986).

Tremor is often the earliest and most noticeable sign of Parkinsonism (Lieberman, 1974; Calne and Pallis, 1987) although it may be absent in the elderly (Hildick-Smith, 1982). It is often unilateral initially, particularly affecting the hand and forearm before the foot and leg are involved. Later it may become bilateral (Webster, 1968; Lieberman, 1974; Calne and Pallis, 1987). The most characteristic tremor is a resting tremor. This is a slow (4 to 7 cycles per second) rhythmic tremor observed when the patient is relaxed (Webster, 1968) which may usually be inhibited by voluntary movement of the affected part (Webster, 1968; Lieberman, 1974; Calne and Pallis, 1987).

Conversely, some patients may exhibit an action or postural tremor, fine and rapid (8 to 12 cycles per second) in nature, that is most apparent when the affected part is voluntarily activated to maintain a posture (Webster, 1968; Lieberman, 1974). Patients with the most prominent resting tremor tend to have little or no action tremor, and vice versa (Lance et al, 1963). The tremors of other diseases may also be present, independent of the Parkinsonism, for example

cerebellar and benign essential tremors (Webster, 1968; Lieberman, 1974).

Rigidity is an increased tone of the muscles, equal in both flexors and extensors, that can be detected at rest by electromyography (Lieberman, 1974). Clinically, it is characterised by a constant uniform increase in resistance to passive movement throughout the range of joint displacement, hence the term "lead-pipe" rigidity. Rigidity in one limb can be greatly enhanced by the active movement by the patient of the contralateral limb (Lieberman, 1974; Calne and Pallis, 1987). Brief lapses in rigidity can occur, resulting in the clinical phenomenom of "cogwheel" rigidity (Lieberman, 1974; Calne and Pallis, 1987). It may occur in the absence of resting tremor and, indeed, may have a higher frequency (6 to 12 cycles per second) than that of the resting tremor.

Hypokinesia involves both slowness (bradykinesia) and poverty of movement, at its most extreme severity there is akinesia. It includes a number of components:

a) initiation of voluntary movement may be delayed, with periods of complete immobility in some patients;

b) the speed of movement, and rate of repetition of alternating movements may be slower than normal;

c) precision of complex movements may be reduced;

d) bimanual performance may deteriorate (Teravainen and

Calne, 1980).

There is also a general poverty of involuntary and

associated movements (Calne and Pallis, 1987).

Postural abnormalities occur as a flexed posture

and/or impaired postural reflexes (Lieberman, 1974;

Quinn and Husain, 1986). The first indication of a

flexed posture is a slight elevation of the hands due

to flexion at the elbow. As the disease advances, so

the hands will be held progressively above the

waistline, and flexion of the head on the neck, and

that of the trunk will cause the stooped or "simian"

posture of severe disease (Webster, 1968; Lieberman,

1974). Impaired postural reflexes lead to difficulty

in standing unaided, and a lack of balance, with

patients tending to fall without the usual defensive

reactions (Lieberman, 1974; Calne and Pallis, 1987).

1.3 DIAGNOSIS

At present, a definite diagnosis of idiopathic Parkinson's disease can only be made by post-mortem examination at which time the diseased brain is often found to exhibit marked depigmentation. The most constant pathological findings at a microscopic level are loss of pigmented cells of the substantia nigra together with rounded eosinophilic intra-cytoplasmic inclusions known as Lewy bodies in some of the affected neurons (Greenfield and Bosenquet, 1953; Turner, 1968; McGeer and McGeer, 1978).

In life, early cases of Parkinson's disease in younger patients can be difficult to diagnose, and may be mistaken for anxiety states, depressive reactions or mild strokes (Webster, 1968). The diagnostic difficulty is even greater in the aged (Hildick-Smith, 1982). The patient and his/her family may dismiss relevant symptoms such as slowness of the gait and flexed posture of the neck and trunk as simply due to old age, especially as the best known symptom, tremor, may not be present (Hildick-Smith, 1982; Calne and Pallis, 1987). Parkinsonism may be masked by other disabilities such as those due to a cerebral vascular accident (Calne and Pallis, 1987) or arthritis. Alternatively, the symptoms may be ascribed to other causes. For example, unilateral Parkinsonian rigidity may be mistaken for the spasticity of a stroke (Hildick-Smith, 1982; Calne and Pallis, 1987) and

autonomic symptoms of Parkinson's disease such as
seborrhoea and wide-eyed facies may lead to a suspicion
of hyperthyroidism (Hildick-Smith, 1982). Conversely,
non-specific tremor, hesitant gait after several small
strokes, and the slowness and immobility of depressed
or hypothyroid patients may all be attributed to
Parkinsonism (Hildick-Smith, 1982). Such patients will
obviously not benefit from treatment with anti-
Parkinsonian medication, since they require quite
different therapies.

Even when a diagnosis of Parkinsonism has been
made, the differential diagnosis of idiopathic
Parkinson's disease depends upon the recognition of
unusual clinical features that may indicate alternative
causes of the syndrome (Martilla, 1983; Quinn and
Husain, 1986). A clinical "algorithm" (Figure 2)
developed by Quinn and Husain (1986) gives a scheme for
the differential diagnosis of idiopathic Parkinson's
disease in which such unusual clinical features are
used as exclusion criteria. These authors claim that
clinical improvement of 50 per cent or more on adequate
dopamine replacement therapy is the most useful single
distinguishing sign. However, this may be somewhat
optimistic when dealing with elderly patients who may
have multiple pathologies.
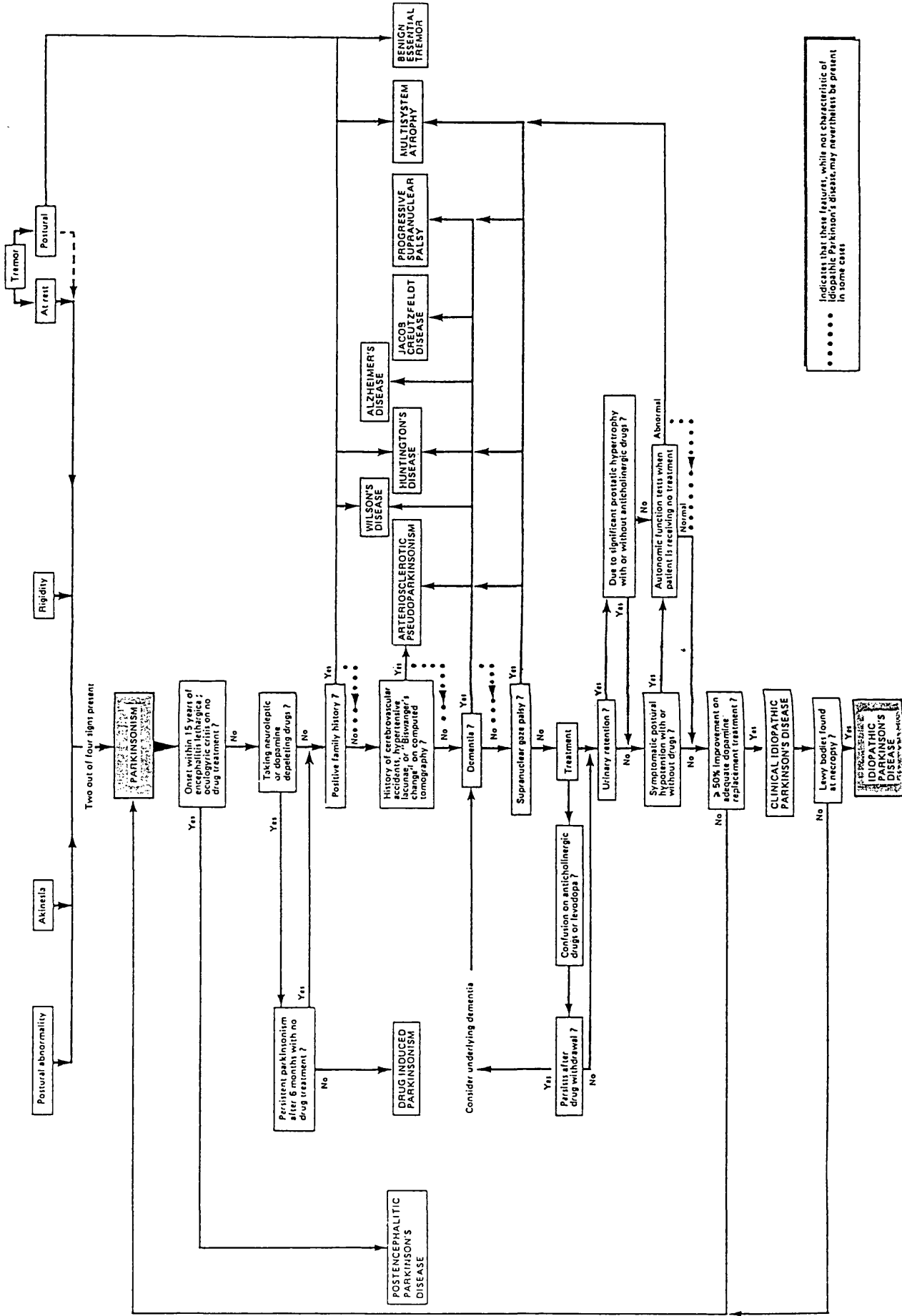
Figure 2   Clinical "algorithm" for the differential diagnosis of idiopathic Parkinson's disease (from Quinn and Husain, 1986)

1.4 TREATMENT

In the nineteenth century Charcot introduced the
belladonna alkaloids (atropine and hyoscine) for the
treatment of Parkinsonism (Ordenstein, 1867) and in the
following century atropine or similar drugs which block
the "muscarinic" actions of acetylcholine formed the
basis of conventional therapy. Anticholinergic drugs
in current use include benzhexol, benztropine,
orphenadrine and procyclidine, and are all muscarinic
antagonists. Although their anti-Parkinsonian activity
is much less than that of levodopa or dopamine
agonists, they continue to find a place in the
treatment of Parkinson's disease. Studies have shown
that a third to a half of patients taking
anticholinergics in conjunction with levodopa
deteriorate when the former drugs are withdrawn (Hughes
et al, 1971; Birket-Smith, 1975). These drugs are also
useful when side effects prevent the use of optimal
doses of levodopa.

In 1960, Ehringer and Hornykiewicz reported that
the concentration of the central neurotransmitter
substance dopamine was severely depleted in patients
with idiopathic or postencephalitic Parkinsonism. The
therapeutic implications of this finding were persued
independently by Birkmayer and Hornykiewicz (1961) and
Barbeau et al (1962), and rather than reducing
cholinergic activity as in the traditional therapy, an

attempt was made to replenish brain dopamine by administration of the immediate precursor "dopa". Birkmayer and Hornykiewicz gave levodopa doses of 50mg, 100mg and 150mg intravenously to their patients and noted an improvement in hypokinesia. Barbeau used oral levodopa doses of 100mg to 200mg and reported an improvement in rigidity and tremor, no comment being made on hypokinesia. However, due to the small doses of levodopa that were used and side effects such as nausea, clinical improvement was limited and the initial optimistic reports were superseded by others showing that little benefit could be expected from this treatment. It was not until 1967 that Cotzias *et al* found that much larger doses could be tolerated if these doses were gradually built up. They reported impressive clinical improvement when Parkinsonian patients received high doses (1.6 to 12g per day orally) of racemic dl-dopa. Subsequent studies using mean daily doses of levodopa ranging from 2g to 8g (Barbeau, 1969; Calne *et al*, 1969; Cotzias *et al*, 1969; Godwin-Austen *et al*, 1969; Klawans and Garvin, 1969; Yahr *et al*, 1969; Mawdsley, 1970; Mones *et al*, 1970; Peaston and Bianchine, 1970; Stellar *et al*, 1970) confirmed these results and provided evidence that levodopa was less toxic than the racemic mixture. Unfortunately, the high doses necessary to achieve clinical benefit often led to side effects of such severity that treatment had to be discontinued.

Adverse reports of the effects of high dose
levodopa therapy in aged and debilitated patients
(Jenkins and Groh, 1970; Sacks *et al*, 1970 and 1972)
often resulted in the elderly being given treatment
with anticholinergic drugs in preference to levodopa.
Subsequent clinical trials found a lower dosage of
levodopa (ranging from a mean daily dose of 1.0g to
2.4g) to be more appropriate in patients of 70 years or
more (Broe and Caird, 1973; Sutcliffe, 1973; Vignalou
and Beck, 1973; Grad *et al*, 1974). The need for
reduced dosage in this age group may reflect age
related alterations in the handling of the drug.

The side effects experienced with levodopa therapy
are chiefly due to the peripheral decarboxylation of
levodopa to dopamine and Bartholini *et al* (1967)
suggested that levodopa should be administered with an
extracerebral decarboxylase inhibitor. Subsequently
two such inhibitory compounds, carbidopa (Porter *et al*,
1962) and benserazide (Bartholini *et al*, 1967) were
synthesized, neither of which cross the blood-brain
barrier at therapeutic doses. Carbidopa and
benserazide are available in combination with levodopa
as Sinemet or Sinemet-Plus (Merck Sharp and Dohme Ltd.,
Hoddesdon, Hertfordshire) and Madopar (Roche Products
Ltd., Welwyn Garden City, Hertfordshire) respectively.
Sinemet contains levodopa and carbidopa in the ratio of
10:1 by weight(levodopa 100mg plus carbidopa 10mg,
levodopa 250mg plus carbidopa 25mg), and Sinemet-Plus
contains the two in the ratio of 4:1 (levodopa 100mg

plus carbidopa 25mg). Madopar contains levodopa and benserazide in the ratio of 4:1 (levodopa 50mg plus benserazide 12.5mg, levodopa 100mg plus benserazide 25mg, levodopa 200mg plus benserazide 50mg). Sinemet and Madopar have been shown to have an equal therapeutic effect in equivalent doses with respect to levodopa content (Korten et al, 1975; Greenacre et al, 1976; Pakkenberg et al, 1976; Diamond et al, 1978; Lieberman et al, 1978; Rinne and Molsa, 1979), although more side effects (particularly nausea and vomiting) have been reported following Sinemet than following Madopar (Pakkenberg et al, 1976; Rinne and Molsa, 1979). Increasing the ratio of carbidopa to a fixed dose of levodopa has been reported to reduce side effects in both Parkinsonian patients (Hoehn, 1980) and healthy subjects (Kaakkola et al, 1985), and to be more beneficial therapeutically than Sinemet (Tourtellotte et al, 1980; Sotaniemi et al, 1983).

The administration of levodopa with peripheral dopa decarboxylase inhibitors had three major consequences. The dose of levodopa could be reduced by 60 to 80 per cent without the plasma concentration falling (Mars, 1973; Fahn, 1974). The incidence of side effects, notably emesis and cardiac arrhythmias declined dramatically (Mars, 1973). The alleviation of emesis allowed the dose of levodopa to be built up to maximum tolerated levels over days rather than months (Marsden et al, 1973).

Amantadine is an antiviral agent that was serendipitously found to have anti-Parkinsonian actions (Schwab *et al*, 1969). It is effective against all Parkinsonian symptoms in about 50 per cent of patients but is not as efficacious as levodopa (Dallos *et al*, 1972). It is probable that the principal mechanism of action of amantadine is to augment the presynaptic synthesis and release of dopamine (Stromberg and Svensson, 1971). However, it also reduces dopamine reuptake (von Voigtlander and Moore, 1971) and may have anticholinergic properties (Nastuk *et al*, 1976). Amantadine is generally used in the early stages of the disease when its mild action may be most beneficial, and also in more severe disease when its effects may be additive with those of levodopa (Feischi *et al*, 1970; Webster and Sawyer, 1984).

In humans, the B form of the enzyme monoamine oxidase is responsible for the degradation of dopamine in the striatum and the platelets (Glover *et al*, 1977). It can be preferentially inhibited by low doses of selegiline (l-deprenyl), although higher doses of this agent will also inhibit the A form of the enzyme (Knoll, 1978 and 1986). Although it has no anti-Parkinsonian activity of its own (Csanda *et al*, 1978), l-deprenyl has been reported to have a dose-sparing effect on levodopa (Birkmayer *et al*, 1975) and to ameliorate end of dose fluctuations in half to two thirds of patients (Lees *et al*, 1977; Rinne *et al*,

1978; Schachter *et al*, 1980). However, the use of the drug is often restricted to the early stages of the end of dose effect, its beneficial action being short lived in most cases. The drug is ineffective in patients with advanced disease who are experiencing severe "on-off" effects. In addition to inhibiting intraneural dopamine catabolism, selegiline may possibly block dopamine reuptake (Knoll, 1978). It may also possess dopamine releasing properties as it is partly metabolised to amphetamine and methylamphetamine (Schachter *et al*, 1980) both of which release presynaptic dopamine stores (Ungerstedt, 1971).

In contrast to levodopa, direct-acting dopamine agonists such as bromocriptine, lisuride and pergolide do not have to be converted in the brain in order to have an effect. Bromocriptine is the most widely used direct dopamine agonist. It has been shown to improve the end of dose effects in many patients and may benefit patients with unpredictable response swings when it is administered in conjunction with levodopa. However it is rarely effective in patients who fail to show any clinical response to levodopa (Parkes *et al*, 1976; Caraceni *et al*, 1977; Calne *et al*, 1978; Fahn *et al*, 1979; Lieberman *et al*, 1979). Studies in which patients had not received any other treatment for their Parkinson's disease prior to bromocriptine administration have shown only modest benefits from such monotherapy (Lees and Stern, 1981; Rascol *et al*,

1982) although dyskinesias and reponse fluctuations are rare. Animal studies have demonstrated that the postsynaptic dopaminergic action of bromocriptine is dependent on the presence of presynaptic dopamine stores, and that a metabolite of the drug may play a part in its striatal actions (Reavill *et al*, 1980). The actions of lisuride and pergolide, on the other hand, are independent of presynaptic dopamine synthesis and stores (Horowski and Wachtel, 1976; Duvoisin and Heikkila, 1981). Lisuride has been shown to improve clinical ratings (Gopinathan *et al*, 1981) and "on-off" effects (Lieberman *et al*, 1981) in patients receiving levodopa therapy. Pergolide has been found to have a beneficial effect on end of dose effects and, to a lesser extent, "on-off" fluctuations (Lang *et al*, 1982; Lieberman *et al*, 1982; Tanner *et al*, 1982).

Despite the development of new drugs for the treatment of Parkinson's disease levodopa remains the drug of choice in most cases, including the elderly and aged. It is most commonly administered with a peripheral dopa decarboxylase inhibitor, and using such combination therapy it is rarely necessary to administer a total daily dose of more than 750mg of levodopa to the elderly patient (Broe, 1987). However, although the levodopa/dopa decarboxylase combination represents a major advance in anti-Parkinsonian therapy, even under optimal treatment conditions the progression of the disease is slowed rather than

halted. Moreover, the management of the patient is
complicated by the development of abrupt fluctuations
in mobility which may occur at the end of the interdose
period ("wearing off" reactions) or unpredictably ("on-
off" reactions).

1.5 MONITORING THE PROGRESSION OF PARKINSON'S DISEASE

The progression of a patient's disease state or response to therapy in the everyday clinical situation can only be followed if suitable quantitative bases for measurement are devised. These assessments can be subjective or objective in nature and typically involve the grading of clinical signs and symptoms in terms of numerical data. It would be desirable to be able to monitor both gross changes occurring over a number of months or even years, and smaller changes taking place over the course of a day. Tests of differing sensitivities are thus needed. Moreover, Parkinson's disease is not manifested by a single measureable abnormality and the individual signs and symptoms may vary in degree between patients with the same global rating of their disease state, and also within the same patient during any one day. Unfortunately, there is little information regarding the inter-relationships between changes in the various signs and symptoms.

The advantages and disadvantages of subjective and objective tests must be considered carefully. Some subjective tests have been found to be sensitive to changes throughout the day (for example: Muenter and Tyce, 1971; Rossor *et al*, 1980; Hardie *et al*, 1984), as well as changes over longer periods of time (for example: Parkes *et al*, 1971; Calne *et al*, 1974; Weiner *et al*, 1980; Koller, 1982). However it is likely that

objective tests would be more sensitive to the very small but clinically important changes in performance that occur in elderly patients. Many authors use both subjective and objective tests to assess Parkinsonian disability, a strategy recommended by Marsden and Schachter (1981).

1.6 DAYTIME ASSESSMENT OF PARKINSON'S DISEASE

Subjective assessment

Subjective assessments are generally based either on rating scales of signs and symptoms of Parkinson's disease, or activities of daily living which assess functional disability, or both. For example, the Webster Scale (Webster, 1968; Appendix 1) rates the signs and symptoms of Parkinson's disease, whilst the North-Western University Disability Scale (Canter de la Torre and Mier, 1961; Appendix 2) rates the functional disability relevant to the activities of daily living. The Hoehn and Yahr Staging System (Hoehn and Yahr, 1967; Appendix 3) is a broad functional staging system that is often used to define the severity of Parkinson's disease (for example: Tolosa *et al*, 1975; Rossor *et al*, 1980; Sotaniemi *et al*, 1983). Each major centre conducting research into Parkinson's disease tends to develop its own rating scale. Such scales include the New York University Parkinson's Disease rating Scale (Alba *et al*, 1968), the Columbia University Rating Scale (Duvoisin, 1970), the UCLA Disability Scale (Diamond *et al*, 1978) and the King's College Hospital Rating Scale (Quinn *et al*, 1984). Other authors may use these scales or adapt them to suit their own interest. Thus a great variety of rating scales are referred to in the literature. Their complexity varies from those which rate three parameters only (tremor, rigidity and akinesia) (for

example: Shoulson *et al*, 1975) to those in which
symptoms are rated under 20 headings and physical signs
under 37 (Godwin-Austen *et al*, 1969). All basically
involve the assignation of a numerical value to a
number of parameters, which when added together produce
a total score of disability. Some scales use weighting
factors to take into account the relative incapacities
produced by different signs and symptoms, but these do
not tend to be widely used (for example: McDowell *et
al*, 1970; Markham, 1971).

The advantage of subjective assessments is that a
wide battery of signs and symptoms can normally be
rated quickly without the need for complicated
equipment or specialised laboratory facilities. Their
major disadvantage is that they depend upon a
particular individual's assessment of the patient. It
is therefore important that assessments made on
different occasions are carried out by the same
assessor, although even then it may be difficult to
ensure accuracy and precision. If it is necessary to
change assessor then it is vital that clearly defined
guidelines have been laid down (Kennard *et al*, 1984).
Moreover, many of the staging systems are not worded
with sufficient care to allow unequivocal assignation
of every patient to a given category.

Objective assessment

The main advantage of objective assessment is that
it does not depend upon a particular individual's
opinion of the patient. Thus, any assessor familiar
with the test should be able to obtain comparable
results. Moreover, a continuum of results is possible,
allowing the severity of Parkinsonian disability to be
assessed on a continuous scale. A variety of simple
objective tests has been used by investigators. These
tests include measurements of manual dexterity and
walking ability. Although they require no specialised
equipment beyond for example, a stop watch, tape
measure, pegboard, pen and paper, or buttons, the main
disadvantage is that a large battery of tests would be
needed to cover all the clinical signs. Such a
procedure would be too time-consuming, and also tiring
for the patient. It would therefore be better to
choose a few pertinent tests, rather than attempt to
provide a global assessment. For general application,
the selected tests should be quick, easy to perform in
the clinical environment and use equipment that is
simple and cheap. Other more complex tests require
elaborate mechanical, electrical or electronic devices,
and even specialised laboratory facilities. Many of
these techniques could not therefore be employed other
than on a research basis. A selection of both simple
and complex objective tests is shown in Table 1 and
Appendix 4.

Table 1   Examples of objective tests for assessing
           Parkinson's disease

Type of Test	Author	Test
Timed manual dexterity tests	Brumlik and Boshes, 1966	Timed tasks: pick up a series of coins, put on a standard laboratory coat, button and unbutton it
	Walker et al, 1972	Timed tasks: put on a shirt, do up a 1 inch diameter button, do up a 0.5 inch diameter button, open and close a zipper, tie a bow, cut with a knife, use a fork, pour water into a glass, squeeze tooth-paste from a tube, dial a telephone, open and close a door, open an envelope, wash hands, put on gloves
	Broe and Caird, 1973	Timed tasks: put on a sock, do up 3 buttons
	Fahn and Isgreen, 1975	Timed tasks: pick up pins and coins (numbers not specified), place 10 pegs in pegboard, string 10 beads, put on and remove a shirt, do up a button, tie a bow, eat with a spoon, bring a glass to the mouth, cut food, dial telephone numbers, open and close a safety pin, carry a tray
	Mindham, 1976	Time to place 25 grooved pegs into matching holes
Writing tests	Timberlake, 1970	Length of standard sentence measured
	Broe and Caird, 1973	Time to write a sentence of 5 monosyllabic words, and to draw a circle
	Mindham, 1976	Time to write name and address, changes in form, size and area of paper covered also noted

Table 1 continued

Type of Test	Author	Test
Tapping tests		These usually use electronic circuitry to record the number of successful movements in a given time.
	Mindham, 1976	Number of taps in a fixed period of time recorded
	Nutt *et al*, 1984	Number of times 2 keys 20cm apart alternately tapped in 60 seconds recorded
Movement and reaction time tests		Electronic equipment is usually used to record the time taken to react to a given stimulus and that taken to complete a given movement.
	Brumlik and Boshes, 1966	Reaction and movement times recorded when a button 6 inches away is depressed in response to a light. going on using electromyography and accelerometry respectively
	Cassell *et al*, 1973	Tracking task using a line on a screen operated by the assessor and followed with a dot by the subject
Walking and sitting tests	Brumlik and Boshes, 1966	Time to walk 20 feet
	Broe and Caird, 1973	Time to walk 10 yards with one turn and time to rise from a chair
	Mindham, 1976	Time to walk 25 yards with one turn
	Nutt *et al*, 1984	Time to rise from an armless chair, walk 6 metres, turn, return to chair and sit down, 30 seconds allowed to complete task

Further examples of objective tests are given in Appendix 4, of which this table is an abridged version.

Bradykinesia would make a major contribution to the
results of most of the simple and complex tests which
are cited. Other specific tests also exist for
measuring tremor and rigidity but since the work
reported in this thesis concentrates on the assessment
of manual dexterity, blink rate and analysis of gait
they will not be discussed further.

Manual dexterity

Numerous different tests of manual dexterity have
been described (Table 1) using pegboards, threading
beads, stacking washers, tying bows and doing up
buttons etc. Tests involving pegboards and beads may
be seen as childish and insulting and so might not gain
the maximum co-operation of the patient. However,
doing up buttons is an everyday task that involves
complex movements of the hands, including those of
pronation and supination. It may thus be an acceptable
test to an elderly subject as well as being a good test
of dexterity. The test only requires that a standard
set of buttons, a stop watch and a quiet location on
the ward or in the clinic be provided. However, of the
buttoning tests described in Table 1 only those of
Brumlik and Boshes (1966), Walker *et al* (1972) and Broe
and Caird (1973) were found to be discriminatory. In a
test using standard laboratory-coat buttons, Brumlik
and Boshes found that 83 per cent (25 patients) of a
group of 30 Parkinsonian patients exceeded the normal
range of values that had been defined in a group of 30

age-matched controls. Moreover, in a cross-over comparison of amantadine therapy with placebo, Walker *et al* found that a significant difference between treatments could be detected using buttons of 0.5 inch diameter, but not those of 1 inch diameter. Broe and Caird were able to detect a significant difference between pre- and post-treatment periods in an open study of levodopa therapy, but unfortunately did not define button size.

Blink rate

In a study of blink rates of normal subjects, Ponder and Kennedy (1928) found that the rate of spontaneous blinking was relatively constant and unaffected by visual acuity, temperature, darkness, humidity or trigeminal nerve deafferentation, although it was increased by emotional states such as anxiety and anger. They concluded that spontaneous blinking was independent of impulses arising from the retina, cornea, conjunctiva or extra-ocular muscles and must therefore be centrally generated. Furthermore, they proposed that as the almost complete absence of blinking is one of the most pronounced features of postencephalitic Parkinsonism, normal blinking must be dependent on the integrity of the basal ganglia.

Spontaneous blink rates in 448 normal subjects ranging from 2 days to 60 years of age were found to increase from a mean (sd) of 1 (1) blink per minute for infants up to 2 months of age to 18 (7) for adults aged

20 to 25 years, and then remain relatively constant, slightly below this level (Zametkin *et al*, 1979). In agreement with Ponder and Kennedy (1928), Zametkin *et al* (1979) found that the rate of spontaneous blinking remained relatively constant if the conditions of measurement remained unchanged. Karson (1983) studied the blink rates of 49 normal subjects (mean (sd) age 36 (14) years) under five different conditions (silence, casual conversation with the assessor, reading, silent memorisation and spoken memorisation). The blink rates varied from 14 per minute during quiet reading to 32 per minute during silent memorisation, thus showing the importance of standardising conditions if measurement of blink rate were to be used as an assessment. Reported values of blink rates for normal subjects during quiet conversation are shown in Table 2.

Table 2   Blink rates of normal subjects during quiet conversation

	Age (years)	Mean (sd) number of blinks per minute	Author
Range	23 - 57	18 (10)	Karson *et al*, 1981a
Mean (sd)	56 (12)	16 (9)	Karson *et al*, 1982
Mean (sd)	36 (14)	25 (14)	Karson, 1983
Mean (sd)	46 (18)	24 (15)	Karson *et al*, 1984

Karson *et al* (1984) further reported that the mean (sd) blink rate in a group of untreated Parkinsonian patients (mean (sd) age 54 (4) years) was 12 (10) blinks per minute. Karson (1983) also studied blink rates in 15 Parkinsonian patients during periods of levodopa-induced dyskinesia and when no dyskinesia was present. The mean (sd) blink rate for these patients whilst dyskinetic was 24 (16) blinks per minute, and that during the nondyskinetic period was 16 (11) blinks per minute.

Patients who exhibit the most severe symptoms have the greatest reduction in blink rate (Karson *et al*, 1982; Karson, 1983). Moreover, Delwaide and Maertens de Noordhout (1984) reported that in patients with fluctuating akinesia, the severity of akinesia could be followed by, and correlated well with, the reduction in blink rate. It is therefore possible that the assessment of spontaneous blink rate could be an indicator of the dopaminergic status of the Parkinsonian patient at any given time (Karson, 1983; Karson *et al*, 1984; Delwaide and Maertens de Noordhout, 1984).

Other studies support the hypothesis that blinking is mediated by central dopamine activity. Blink rate may be increased in schizophrenia (Stevens, 1978a and 1978b; Karson, 1983), a disorder related to central dopamine hyperactivity, and decreased in Parkinsonism (Hall, 1945; Karson *et al*, 1982 and 1984; Karson, 1983), a disorder related to dopamine deficiency.

Treatment of schizophrenia with neuroleptics, which
block dopamine receptors (Carlsson and Lindqvist,
1963), may decrease blink rates in patients with this
disorder (Karson et al, 1981a). Conversely, blink
rates may be increased in monkeys by the dopamine
agonists apomorphine (Karson et al, 1981b and 1981c;
Karson, 1983) and bromocriptine (Karson, 1983). It has
been claimed that levodopa increases spontaneous
blinking in Parkinsonian patients (Zametkin et al,
1979; Karson et al, 1982; Jankovic et al, 1982)
although this was not studied formally. However,
Karson et al (1984) found that the successful
pharmacologic treatment of two Parkinsonian patients,
with levodopa in one case and trihexyphenidyl in the
other, was associated with an increased blink rate
together with clinical improvement.

Gait analysis

    Walking ability is of great concern to the elderly
patient, and is an important index of clinical
disability.

    It is possible to study the gait cycle in great
detail. Measurable parameters of gait are listed
below.

a) Distance/time measurements which monitor step or
   swing length, step or swing time, support time,
   cadence (number of steps per unit time, usually
   seconds or minutes) and speed.

b) Kinematic data, which are concerned with the ranges

of angular motion in joints and linear displacements of the body in the line of progression.

c) Kinetic data, which are a measure of the causes of motion such as the ground or external reaction forces, the internal forces within the joints, muscle torques, and momentum.

d) Electromyographic data, which assess the phasic activity of muscle groups responsible for gait.

Simultaneous measurement of all these parameters would be ideal for research into the characteristics of gait but, unless sophisticated computers are available, the amount of data generated would be too unwieldy for routine clinical purposes. In most reported studies only one or two of the above types of measurement are made.

Distance/time measurements

Simple methods of gait analysis can be used to measure basic distance/time parameters of gait. Speed can be measured with a stop watch and tape measure, cadence by counting steps during a specific time, and step or swing length from footprints, such as those left by feet covered in talcum powder (Minns *et al*, 1986), or by pads soaked in water soluble dyes attached to the feet (Rose, 1983).

Electrical contact systems are often used to measure the distance/time parameters of gait. Several methods (Grieve, 1969a; Fox and MacDonald, 1974; Wall

et al, 1976; Larsson et al, 1980; Nayak et al, 1982;
Mizrahi et al, 1982) basically involve a walkway
consisting of an open electric circuit in which current
flows when "shorted" by conductive strips attached to
the subject's shoes. The current is proportional to
the distance of the "short" along the walkway, and can
be recorded by an ultra-violet recorder (Fox and
MacDonald, 1974; Wall et al, 1976; Mizrahi et al,
1982). After calibration, parameters of gait such as
swing time, swing length and cadence can be determined.
Alternatively, the signals can be fed into a computer
(Larsson et al, 1980; Nayak et al, 1982).

Kinematic data

A number of photographic and video techniques have
been employed to measure both distance/time and
kinematic data. Gait analysis by interrupted light
photography or stroboscopy requires the subject to walk
in front of a camera with the shutter open, in semi-
darkness and illuminated by a light flashing at a set
rate, usually 20 times a second. Specific anatomical
landmarks on the subject are highlighted by reflective
targets (Levens et al, 1948), and only the serial
positions of each target register on the film, forming
a white stick diagram on a black background. This
method has been used extensively by Murray (et al)
(1964, 1966, 1967, 1969, 1972, 1978), Knutsson (et al)
(1971, 1972, 1979, 1985) and Richards and Knutsson
(1974). Knutsson (1972) supplemented interrupted light

photography by filming subjects during walking. The
resulting cinefilm was then analysed on a frame-by-
frame basis. A method of interrupted light
cinematography was described by Takebe and Basmajian
(1976).

Video recorders now provide a cheaper alternative
to cinefilm with the advantage that replay is
instantaneous and frames can be frozen to allow serial
analysis of the movement pattern (Capildeo *et al*,
1981). Addition of an on-screen digitiser gives the
facility to measure angles and distances, and when
combined with time, approximate velocities and
accelerations (Rose, 1983).

Despite the use of computers for data reduction
(Takebe and Basmajian, 1976; Simon *et al*, 1978 and
1983; Mazur *et al*, 1979) frame-by-frame analysis of
cinefilm or videofilm remains time-consuming and
tedious. This can be overcome using television cameras
coupled to on-line computers that are fast and have
sufficient memory to deal with the large amount of data
generated. Such a system was described by Winter *et al*
(1972). However, both video and television systems
have inferior resolution when compared with
cinematography (Rose, 1983; Olsson, 1986).

Goniometry can be used to measure angular movements
of joints. Goniometers, mounted on an exoskeletal
structure attached to the subject, describe the
position of one body segment relative to another.

There are two types of goniometer, the
electrogoniometer or elgon, and the polarised light
goniometer or polgon. The elgon consists of a
transducer, most commonly a potentiometer, aligned to
the joint axis to be measured. A known constant
voltage is applied to the goniometer, and a fraction of
this is returned as a signal which is proportional to
the angle of movement. Workers who have used this
method include Karpovich and Karpovich (1959),
Kettelkamp *et al* (1970, 1972, 1976), Stauffer *et al*
(1974, 1977) and Gyory *et al* (1976).

In polarised light goniometry, sensors containing
photo-electric cells with polarising gratings in front
of the cells are attached to the subject. The subject
then walks along a pathway illuminated by a beam of
polarised light. As the light polarising materials
move relative to each other, the sensors produce an
electrical signal which can be related to the angular
changes which are responsible. This method was first
described by Grieve (1969b), and has more recently been
used by Johnson and Waugh (1979) and Knutsson and
Lying-Tunell (1985).

Kinetic data

Kinetic parameters of gait can be measured by the
use of force transducers, which change force into an
electrical signal. Force transducers can be attached
directly to the foot, or footwear, of a subject
(Schwartz and Heath, 1947; Hargreaves and Scales, 1975;

Miyazaki and Iwakura, 1978). This has the advantage
that several gait cycles can be recorded, although the
subject's normal gait pattern may be disturbed by the
transducers. On the other hand, force transducers can
be mounted on the floor in the form of force plates, a
system that has been widely used (Carlsoo *et al*, 1974;
Stauffer *et al*, 1974 and 1977; Gyory *et al*, 1976; Nayak
et al, 1982; Simon *et al*, 1983). A disadvantage of
small force plates is that they must be hidden so
subjects do not alter their gait pattern to try to step
on the plate, and since only one step can be measured
at a time it can be difficult to obtain a sufficient
number of measurements. Long force plates, 5 metres in
length, were used by Olsson *et al* (1986) to overcome
this problem, whereas Jansen *et al* (1982) used an
instrumented treadmill consisting of two conveyor belts
supported by a force plate system, thus allowing the
analysis of many consecutive steps.

Ground reaction forces are easily determined from
force plate data, but to determine forces at joints,
such as the ankle, knee and hip, a complete kinematic
picture is also needed. Johnson and Waugh (1979)
described a fully computerised system of suitable
complexity dedicated to the measurement of forces
within the knee joint. It included a walkway with a
force plate, television cameras, and a polarised light
goniometer.

Electromyographic data

The activity of muscles concerned with walking can
be detected using suitable electrodes and recorded
using multi-channel electromyography (EMG). The
electrodes can be inserted into (Carlsoo *et al*, 1974;
Takebe and Basmajian, 1976; Waters *et al*, 1979 and
1982) or attached to the skin over the muscles of
interest (Richards and Knutsson, 1974; Carlsoo *et al*,
1974; Knutsson and Richards, 1979; Mazur *et al*, 1979;
Simon *et al*, 1983). In order to define the gait cycles
in the EMG recording, foot switches, located in shoe
insoles, are often used to signal heel, mid-foot and
toe contacts with the floor (Richards and Knutsson,
1974; Takebe and Basmajian, 1976; Knutsson and
Richards, 1979; Waters *et al*, 1979 and 1982).

Simple methods of gait analysis have been used by
many workers measuring Parkinsonian gait as a function
of the time and/or number of steps taken to cover a
specified distance (Table 1). Such tests have been
claimed to be accurate indices of bradykinesia (Marsden
and Schachter, 1981; Teravainen and Calne, 1980). Of
the simple walking tests described in Table 1, only
that of Broe and Caird (1983) was reported to have
detected any significant difference between treatments.
These workers made an open study of maintenance
levodopa therapy, comparison being made between the
pre- and post-treatment periods. Interestingly, the
age of the group was greater (68 to 85 years) than that

of patient groups used in other studies. It is thus possible that a walking test stresses the older patient more and is thereby more discriminating.

More complex methods of gait analysis have been used (Knutsson and Martensson, 1971; Knutsson, 1972; Murray *et al*, 1978; Gopinathan *et al*, 1981) to study changes in gait patterns in Parkinson's disease. However, few have used this analysis to investigate the outcome of anti-Parkinsonian therapy. Using a mat with sensors, Gopinathan *et al* (1981) carried out a placebo controlled trial using high and low doses of the dopamine agonist lisuride. No difference was found between step length or the number of steps to cover a fixed distance on active or placebo treatment. However there were consistent differences in the time taken to walk that distance. Knutsson and Martensson (1971) used interrupted light photography to study a group of patients on maintenance levodopa therapy. They found significant differences between maximal and free walking speeds, swing length and swing time before and after treatment with the drug. However, cycle duration, double support time and a symmetry factor (the ratio between durations of the shortest and the longest of two successive right and left steps) were not sensitive to treatment.

In the studies reported here, a gait assessment trolley and a pedobarograph have been used to monitor the gait of Parkinsonian patients. The gait assessment

trolley measures distance/time parameters of gait, and the pedobarograph measures the pressure distribution under the weight bearing foot during walking. Further details of these two methods of gait assessment will be given in the methods section.

CHAPTER TWO

THE NIGHT-TIME

Patterns of sleep and bedtime movement vary with age. At night time, Parkinsonian patients sleep lightly, experience abnormal sensory and muscular activity and find it difficult to move in bed. These symptoms, which are often inter-related, cause considerable distress to the patients. There are conflicting opinions as to the effect of anti-Parkinsonian therapy on these problems. In the following sections an attempt is made to distinguish between those factors affecting the sleep pattern and those influencing movement in bed. Since this distinction is somewhat artificial, some overlap of material is inevitable.

2.1   CLASSIFICATION OF SLEEP

Sleep has been classified into rapid eye movement (REM) sleep and non-rapid eye movement (NREM) sleep (Aserinsky and Kleitman, 1953). Rapid eye movement sleep is characterised by synchronous rapid movements of both eyes, which occur in all directions. It is associated with the electroencephalogram (EEG) wave pattern characteristic of stage 1 sleep and a lack of gross body movements (Dement and Kleitman, 1957). The sleep pattern is therefore routinely monitored in experimental studies by recording the EEG, electro-oculogram (EOG) and the electromyogram (EMG) to allow REM sleep (also called stage 1 - REM) to be distinguished from stage 1 of NREM sleep.

Non-rapid eye movement sleep is conventionally classified into four stages, defined by the EEG. This classification was first described by Dement and Kleitman (1957) to replace earlier more complicated classifications. To standardise the scoring of sleep records, a committee of the Association for the Psychophysiological Study of Sleep formulated criteria for the assignation of sleep stages (Rechtschaffen and Kales, 1968). Upon falling asleep stage 1 appears, characterised by a relatively low voltage, mixed frequency EEG pattern without REM. As sleep progresses into stage 2, characteristic wave forms called K complexes, and sleep spindles of 12 to 14Hz, appear. These are superimposed on a background of relatively

low voltage, mixed frequency EEG activity. Further progression of sleep leads to stage 3, characterised by moderate amounts of high amplitude slow wave activity with 20 to 50 per cent of the period consisting of waves of 2Hz or less of peak to peak amplitude of 75μV or more. During the deepest stage of sleep (stage 4), this slow wave activity occupies more than 50 per cent of the period. Sleep spindles and K complexes may or may not be present in stages 3 and 4, which are often referred to as slow wave sleep (SWS). Sleep spindles are thought to occur as a result of thalamocortical connections (Freemon, 1972) whilst K complexes appear as a result of the activation of any of the body's sense modalities (Roth *et al*, 1956).

2.2 EFFECTS OF AGE ON THE SLEEP PATTERN

The sleep patterns of young normal adults have been
well established (Dement and Kleitman, 1957; Williams
et al, 1964 and 1966; Kales *et al*, 1967a; Agnew and
Webb, 1968a). Kales and Kales (1974) summarised a
typical night's sleep in a normal young adult as
follows. After sleep onset, there is a rapid descent
through brief periods of stage 1 and stage 2 sleep to
longer periods of stage 3 and stage 4 sleep. After
about 70 to 100 minutes of NREM sleep, there is a rapid
ascent to the first brief period of REM sleep. This
pattern is repeated at approximately 90 minute
intervals throughout the night, although as the night
progresses the REM periods lengthen and the descent of
sleep may only reach stage 3 or even stage 2. Thus,
whilst stage 2 sleep is evenly distributed throughout
the night, the greatest amounts of stage 3 and 4 sleep
occur in the first third of the night and of REM sleep
in the last third of the night (Williams *et al*, 1964
and 1966). Of the usual 6.5 to 8 hours sleep of the
young adult, 20 to 25 per cent of the night is spent in
REM sleep, whilst 5 to 10 per cent is spent in stage 1,
50 to 60 per cent in stage 2, 5 to 10 per cent in stage
3 and 10 to 15 per cent in stage 4 of NREM sleep
(Williams *et al*, 1964 and 1966; Kales *et al*, 1967a;
Agnew and Webb 1968a).

The sleep pattern described above changes with age.
Both normal "late middle-aged" subjects (mean age 54

years (Agnew *et al*, 1967) and mean age 55 years
(Brezinova, 1976)) and normal elderly subjects (mean
age 75 years (Kales *et al*, 1967b)) have been shown to
have an increased number of awakenings, take longer to
get back to sleep again and hence have a decreased
total sleep time (TST). With increasing years, an
increase in the lighter stages 1 and 2 of sleep has
also been reported (Kales *et al*, 1967b; Agnew and Webb,
1968b). This change in sleep pattern is associated
with a decrease in the deeper stages 3 and 4 of sleep,
the latter stage being particularly affected (Kales *et
al*, 1967b; Agnew *et al*, 1967; Agnew and Webb, 1968b;
Williams *et al*, 1974). Sleep spindles in the elderly
have been found to be infrequent and poorly formed
(Kales *et al*, 1967b). Rapid eye movement sleep
constitutes a fairly constant percentage (20 to 25 per
cent) of the TST throughout adult life but, as TST
tends to be decreased in the elderly, the absolute
amount of REM sleep is in fact slightly to moderately
decreased with age (Kales *et al*, 1967b). However it is
only in the late eighties that there is any clear
indication of a decline in REM sleep (Kahn and Fisher,
1969). The REM periods of the elderly differ from
those of young adults in that they do not increase in
length throughout the night (Kales *et al*, 1967b).
Sleep latency (the time taken to get to sleep) is
affected by age. From the late teens to about 60 years
of age there is a latency period of about 10 minutes
from putting out the light (Agnew and Webb, 1971).

However, a mean sleep latency of 23 minutes was reported in a group of 70 to 79 year old subjects (Williams *et al*, 1974) and of 26 minutes in a group of 71 to 95 year olds (Kahn and Fisher, 1969).

Patients with senile dementia have been shown to have an even more disturbed pattern of sleep than normal elderly subjects. Further decrements in SWS, REM sleep and TST occur in dementia (Feinberg *et al*, 1967; Prinz *et al*, 1978; Allen *et al*, 1983), and stage 2 sleep is poorly organised in that there is a reduced number, or even a complete lack, of sleep spindles (Prinz *et al*, 1978; Allen *et al*, 1983). Allen *et al* (1983) found that sleep was severely fragmented in patients with dementia, with many sleep episodes occurring during the day, although the day/night alternations of wakefulness and sleep could still be recognised.

2.3   EFFECT OF PARKINSON'S DISEASE AND LEVODOPA ON THE SLEEP PATTERN

In Parkinson's disease, the following changes from a normal typical sleep pattern have been reported:

a) decrease in stages 3 and 4 (Kales *et al*, 1971), or stage 4 alone (Bergonzi *et al*, 1974);

b) increase in sleep latency (Kales *et al*, 1971);

c) frequent wakenings after sleep onset (Kales *et al*, 1971; Bergonzi *et al*, 1974 and 1975) with an increase in the time taken to go back to sleep (Kales *et al*, 1971);

d) decreased number of sleep spindles (Ferrari *et al*, 1964);

e) decrease in TST (Kales *et al*, 1971; Bergonzi *et al*, 1975);

f) decrease in absolute REM time due to a decrease in TST, although percentage REM remains the same (Kales *et al*, 1971). However Bergonzi *et al* (1975) found a decrease in percentage REM.

These changes are also common features of the sleep patterns of elderly subjects (page 68). However, Kales *et al* (1971) compared the sleep patterns of six patients with Parkinson's disease, their spouses as one control group, and ten older normal subjects as another control group and concluded that patients with Parkinson's disease were in fact sleeping very poorly in terms of difficulty in falling and in staying

asleep, even when compared with the older normal elderly control group.

Askenasy and Yahr (1983) decided that precise selection criteria were needed to determine reliably whether a specific sleep pattern was associated with Parkinson's disease. They compared a well defined uniform group of ten Parkinsonian patients with a group of ten age matched normal controls. The sleep of the Parkinsonian group was found to have the following characteristics:

a) increased waking state and stage 1;

b) decreased stage 3 and stage 4 (SWS), and REM sleep;

c) low sleep efficiency;

d) abrupt arousal after sleep;

e) increased number of awakenings;

f) long periods of awakening;

g) short periods of sleep.

They considered that observations a) to d) would contribute to a light sleep pattern, whereas observations e) to g) would contribute to a fragmented sleep pattern. On these bases, they described the sleep of Parkinson's disease as "light, fragmented sleep". Unfortunately both untreated patients and those treated with levodopa were included in the study, no differentiation being made between the two groups. However, the same authors found a similar light, fragmented sleep pattern in a later study when five patients with Parkinson's disease had their anti-Parkinsonian medication withdrawn for five days prior

to EEG recordings (Askenasy and Yahr, 1985). Even so, the authors observed that this sleep pattern was not necessarily specific to Parkinson's disease or basal ganglia disorders but could also be found on the first night of adaptation to a sleep laboratory, in the presence of psychiatric disorders or chronic debilitating illness, or could be drug-induced.

EEG studies on the effect of levodopa on the sleep pattern in Parkinson's disease present conflicting results. Problems in interpreting and comparing such studies arise from the use of ill-defined diagnostic criteria, varying and inadequate experimental design and the failure to present either raw data or adequate statistical analysis. It has been variously reported that levodopa may:

a) increase REM sleep (Schmidt and Knopp, 1972; Bergonzi *et al*, 1974 and 1975) or decrease REM sleep (Wyatt *et al*, 1970);

b) decrease REM latency (Bergonzi *et al*, 1975) or increase REM latency (Wyatt *et al*, 1970);

c) increase SWS (stages 3 and 4) (Bergonzi *et al*, 1974) or decrease SWS, although this finding was complicated by the fact that the patients were also taking diazepam (Schmidt and Knopp, 1972);

d) decrease sleep latency (Bergonzi *et al*, 1974) or increase sleep latency (Bergonzi *et al*, 1975);

e) increase the number of sleep spindles (Puca *et al*, 1973);

f) decrease the number of awakenings and wakefulness

i.e. sleep fragmentation (Bergonzi *et al*, 1974 and 1975);

g) improve the cyclical organisation of sleep (Bergonzi *et al*, 1975).

Greenberg and Pearlman (1970) could find no clear effect of levodopa on any sleep parameter. Kales *et al* (1971) found that levodopa had variable effects on REM sleep in the short term but, in the long term, measured values for REM sleep, sleep latency, sleep maintenance and amounts of stage 3 and 4 sleep were comparable to baseline values. They therefore concluded that levodopa neither improved nor worsened the sleep difficulties experienced by patients with Parkinson's disease. However, Askenasy and Yahr (1985) reported that dopaminergic treatment (pergolide and, if needed, levodopa plus carbidopa) improved the sleep pattern when doses associated with clinical improvement were used.

The contradictory findings on the effect of levodopa on some of the sleep parameters may be due to the different doses used. Bergonzi *et al* (1974) found that the improvement in sleep induced by levodopa in average doses (about 3g) was reversed to the pre-levodopa baseline disturbance with higher doses (about 5g). This observation was interpreted as follows. Brain monoamines have been reported to be important in the organisation of the sleep cycle (Jouvet, 1969). These monoamines are known to be pathologically decreased in Parkinsonian patients thus giving rise to

an abnormal sleep pattern. The administration of an adequate dose of levodopa will normalise the levels of brain monoamines, thus normalising both the sleep cycle and extrapyramidal symptoms. On the other hand, administration of higher doses of levodopa could produce an excess of catecholamines thus altering the sleep organisation once again. This phenomenom may also explain further sleep disturbances such as insomnia, nightmares and vivid dreams, restlessness and reflex daytime somnolence that have been reported to occur with high dose or long-term levodopa therapy (Cotzias *et al*, 1969; Muenter, 1970; Sweet and McDowell, 1975; Sharf *et al*, 1978; Nausieda *et al*, 1982). In conclusion, it is evident that no obvious link has been found between levodopa administration and changes in sleep pattern observed in Parkinsonian patients.

2.4 ABNORMAL MUSCLE ACTIVITY AND SENSORY SYMPTOMS DURING SLEEP IN PARKINSON'S DISEASE

Askenasy and Yahr (1983) studied the muscle activity during sleep of a group of ten carefully selected patients with Parkinson's disease and a group of ten age matched controls, using electromyography. Striated muscle activity was markedly increased during sleep in Parkinson's disease. Not only was there an increase in repetitive muscle contractions (RMC) with a rhythm of 360 to 720 cycles per minute (cpm) but also in RMC with a rhythm of 2 to 6cpm (periodic nocturnal myoclonus) and in burst tremor (clinically accompanied by a jerk). A direct correlation was found between the sleep pattern, as measured by EEG, and the muscle activity pattern, with RMC lowest in slow wave sleep. Improvement or deterioration of both patterns occurred concomitantly. In a later study on five patients with Parkinson's disease, the same authors found that with dopaminergic therapy sufficient to produce clinical improvement, normalisation of muscle activity during sleep occurred together with an improvement in the sleep pattern (Askenasy and Yahr, 1985). However, elsewhere, levodopa has been reported to induce myoclonic movements during the waking state (Klawans *et al*, 1975), and also during sleep (Klawans *et al*, 1975; Nausieda *et al*, 1982). The incidence of abnormal muscle activity has therefore been ascribed to both excessive or inadequate levodopa therapy. Further

distressing disturbances to sleep may be caused by abnormal sensations including pain, tingling, numbness and burning that are common manifestations of Parkinson's disease (Snider *et al*, 1976; Koller, 1984; Nutt and Carter, 1984). Studies on patients with painful Parkinson's disease revealed that these phenomena occurred within a certain threshold of dopaminergic stimulation, and could be controlled or abolished either by stopping therapy or increasing it (Quinn *et al*, 1986). These observations emphasize the importance of tailoring the dosage regimen of anti-Parkinsonian therapy to the needs of the patient.

2.5 RELATIONSHIP BETWEEN SLEEP PATTERN AND MOVEMENT

Patients move less when they are asleep (Hinton and Marley, 1959; Hinton, 1961), restlessness tending to increase according to the pattern of wakefulness (Hinton, 1962). There is an inverse relationship between nocturnal mobility and depth of sleep as measured electroencephalographically (Loomis *et al*, 1937; Blake *et al*, 1939). Dement and Kleitman (1957) found that body movements, together with eye movements and the EEG, undergo regular cyclic variations throughout the night with the peaks of eye and body movements coinciding with the lightest phase of the EEG cycle.

Later work has shown that the pattern of movements throughout the night is associated with the distribution of sleep stages. As described earlier (page 67), a typical night's sleep consists of an initial long period (70 to 100 minutes) of stage 3 and stage 4 sleep (SWS), followed by alternating periods of REM and stage 2 sleep with only an occasional short period of SWS. The number of movements occurring at the beginning of the night during stage 3 and stage 4 sleep (SWS) increase later in the night during stage 1, stage 2 and REM sleep (Sassin and Johnson, 1968). It has also been observed that movements are generally followed by the appearance of K complexes on the EEG trace (Gastaut and Broughton, 1965; Sassin and Johnson, 1968).

There is an abrupt cessation of large body movements at the onset of REM sleep and a pronounced increase as REM sleep ends (Dement and Kleitman, 1957; Gardner and Grossman, 1975), the only movements occurring during REM sleep being twitches of the face and extremities (Dement and Kleitman, 1957). Movements in stage 1 and REM sleep are relatively evenly distributed throughout these periods, movements in stage 2 are grouped together at the beginning of the period especially after a change from SWS, and most movements during stage 3 and stage 4 (SWS) occur at the end of the period (Sassin and Johnson, 1968). An absence of body movements just before entering SWS has also been reported (Muzet et al, 1972a).

Sassin and Johnson (1968) found that most of the movements (80 per cent) in SWS were large, involving the head, trunk and extremities simultaneously, whereas stages 1 and 2 contained about equal numbers of large and small movements (involving the head, face or mouth only), with no medium sized movements at all (movements of the extremities alone). The only significant number (10 per cent) of movements of medium size occurred during REM sleep. The hourly frequency of movements has been reported by Sassin and Johnson (1968) to be 25.3, 10.7, 12.1 and 3.6 for stage 1, stage 2, REM and SWS respectively. SWS had a significantly lower frequency of movements than all the other stages, but there was no significant difference between REM and stage 2 sleep. A similar range of frequencies was

reported by Naitoh *et al* (1973), although in this later study the difference between REM and stage 2 sleep was also found to be significant.

2.6 FACTORS INFLUENCING MOVEMENT IN BED

Sleep patterns and bed movement are closely related. The depth of sleep may be influenced by external factors such as noise or the nature of the bedding, and by patient factors such as age, the ingestion of food, drinks and drugs or the presence of Parkinson's disease.

Noise can be particularly disturbing to sleep and its effects have been studied. In one study, a movement was found to be stimulated every 7 seconds after the initiation of a repeated tone pulse (Townsend *et al*, 1973). However, young adults exposed to a tone pulse given every 22 seconds, 24 hours a day, over a period of 30 consecutive days showed no apparent change in the overall number of movements made during sleep, although the distribution of movements throughout the night was altered (Muzet *et al*, 1974). Scott (1972) found that a continuous loud noise during sleep lightened sleep for the first night but a more normal sleep pattern occurred in subsequent nights.

Another important factor is the comfort or otherwise of the bed surface. Suckling *et al* (1957) measured body movements during sleep on hard (plywood), medium (standard mattress) and soft (feather mattress) support surfaces and found that the hard surface promoted an increase in mobility. Bardsley (1977)

assessed the effect of bead (soft), foam on springs
(medium) and foam on board (hard) mattresses on
movement during sleep. There was a significant
difference in the total number of movements during the
night between all subjects sleeping on bead mattresses
and those sleeping on the foam on board mattresses, but
not between all subjects sleeping on spring mattresses
and the other two mattresses.

There have been few studies studies relating age to
movement and most are in neonates and young children.
However, in 1929 Garvey observed that the rate of
movement was greater in children than in adults.
Although Bardsley (1977) studied night-time movement in
young adults, and Wheatley (1982) in elderly patients,
no direct comparison has been made between the two age
groups.

Increasing age has been shown to cause a reduction
in SWS and the absolute amount of REM sleep, and an
increase in stage 1 and stage 2 sleep. Since body
movements occur more frequently in stage 2 than in SWS,
it may be implied that increasing age results in
increasing mobility. However the elderly are more
likely to be suffering from diseases that affect
mobility, such as cerebrovascular disease and
Parkinson's disease, so the relationship between
mobility and age is not straightforward.

Laird and Drexel (1934) reported that fewer movements occurred during sleep in young adults after a light meal of cornflakes and milk, whereas a heavier meal made sleep more restless. Southwell *et al* (1972) compared the effects of a hot milk drink containing Horlicks, hot water and no drink at all taken immediately before bed on movements during sleep in four young adults. It was found that Horlicks reduced the number of small movements made during sleep towards the end of the night. Brezinova and Oswald (1972) confirmed this finding in young adults and also showed that an older group of adults (mean age 55 years) slept longer and had fewer awakenings after a bedtime drink of Horlicks in hot milk.

On the other hand, Wada (1922) noted that body movements during sleep in young adults occurred simultaneously with contractions of the stomach, the majority of movements occurring at the time of maximum stomach activity. McGlade (1942) found that body movements were synchronised with the opening of the pyloric sphincter after certain foods had been eaten.

The general state of nutrition may influence sleep patterns (Crisp, 1967). Patients successfully treated for anorexia nervosa slept longer, with fewer movements, than they did before treatment (Crisp and Stonehill, 1971; Crisp *et al*, 1971). Further work by Crisp *et al* (1973) studied the effect of losing weight on sleep and movement in obese patients. During the

first month of treatment patients slept less well and
moved more.   This pattern was reversed in the following
two months although in the fourth month an increase in
movement and broken sleep was recorded again.

Laird (1935) studied the relationship between the
occurrence of body movements and the urinary bladder
pressure of the subject.   An increase in the number of
movements was observed on the nights that the subject
had an increased urinary output.   However no clear
relationship between the time of movement and a full
bladder could be demonstrated.   This led to the
suggestion that high urine accumulation and increased
mobility may both be due to a common cause, rather than
the bladder pressure itself causing an increase in
movement.

Depressive illness has been found to cause sleep to
be shortened, interrupted more frequently, less sound
and associated with greater nocturnal restlessness
(Hinton, 1962).

Certain hypnotic and sedative drugs such as
barbiturates (Hinton and Marley, 1959; Hinton, 1961),
meprobamate (Hinton and Marley, 1959) and flurazepam
(Crowley and Hydinger-Macdonald, 1979) have been shown
to reduce spontaneous movement during sleep.   However,
when Dobbs *et al* (1986) studied the effect of 192mg and
384mg doses of chlormethiazole on the night-time
movements of 12 elderly patients, no significant

difference was found in the size or number of movements between placebo or drug. Moreover, it was noted that the patients in this study did not experience any significant difference in their subjective assessments of quality of sleep so that the hypnotic effect of the chlormethiazole was probably negligible.

Other drugs that have been studied are alcohol and caffeine (Mullin *et al*, 1933). Whereas caffeine increased the overall mobility during sleep, alcohol was found to redistribute movements, decreasing the number in the first half and increasing the number in the second half of the night.

Stephen and Williamson (1984) reported that, of 95 new cases of Parkinsonism referred to a department of medicine for the elderly, 91 per cent of the 48 patients with drug induced Parkinsonism and 80 per cent of the 47 patients with idiopathic Parkinson's disease experienced difficulty turning over in bed at night. Objective evidence of this was provided by Laihinen *et al* (1987) who monitored the number of "turning over events" during the night period using a static charge sensitive bed (page 91). It was found that nine patients with idiopathic Parkinson's disease (mean age 68 years, seven untreated, and two treated with levodopa) had a reduced frequency of "turning over events" during sleep as compared with a group of age-matched controls. Parkinsonian patients receiving levodopa therapy also often suffer from severe night-

time (Rosenberg, 1969; Lindvall and Olsson, 1984) and
early morning (Laitinen, 1973; Marsden and Parkes;
1976, Lindvall and Olsson; 1984) akinesia, the early
morning hours also being particularly difficult due to
pronounced tremor (Laitinen, 1973). Lesser *et al*
(1979) studied the clinical problems of 131 patients
with idiopathic Parkinson's disease on long-term
levodopa therapy. Ninety-four experienced dressing
difficulties, 79 had difficulty turning over in bed and
65 had difficulty arising from bed. Since little or no
levodopa can be detected in the plasma first thing in
the morning it is possible that the problems are due
to Parkinson's disease unrelieved by therapy, with most
patients requiring their first dose of the day to
achieve mobility (Marsden and Parkes, 1976).
Dopaminergic therapy has been reported to alleviate
difficulty in turning in bed (Lees *et al*, 1977).
However, Lakke *et al* (1980) questioned Parkinsonian
patients about difficulties turning in bed, and whether
or not treatment had improved the complaint. One
hundred and twenty-two patients returned valid
questionnaires. Eighty of the 103 patients receiving
treatment with amantadine, bromocriptine and/or
levodopa reported difficulty in turning over in bed; 58
of the 80 (72.5 per cent) said that treatment had not
helped. Twenty-six Parkinsonian patients were then
tested during the day, when their Parkinson's disease
was optimally controlled with regular doses of anti-

Parkinsonian medication, for their ability to roll over. Of these, 11 showed abnormal axial rotatory movements and 3, who had primarily unilateral Parkinsonism, showed rotational abnormalities with asymmetric qualities. It was concluded that levodopa therapy affected rotation about the longitudinal axis to a much lesser extent than rigidity and bradykinesia.

Conversely, some patients have found that their mobility is restored upon waking from sleep prior to drug intake (Marsden, 1980). Parkes (1983) stated that 10 to 20 per cent of patients with mild to moderate disease are much less disabled for 40 to 60 minutes after waking than for the rest of the day. Sleep benefit can occur in both untreated and treated patients and may be related to the reaccumulation of central dopamine stores during the rest period. However in patients suffering from severe Parkinson's disease the opportunity for such sleep benefit may no longer exist (Parkes, 1983).

2.7 ASSESSMENT OF MOVEMENT IN BED

The simplest method of assessing movement in bed is to watch the subject, noting changes in position and time of occurrence. This approach has the following disadvantages. The size of movements cannot be quantitated, only one subject can be monitored at a time and observer fatigue may result in decreased vigilance.

Filming techniques such as time-lapse cinematography (Southwell *et al*, 1972), movement-triggered infra-red still photography (Muzet *et al*, 1972b; Bardsley, 1977) or infra-red time-lapse video recording (Ryan, 1979) obviate the need for an investigator to sit up all night. However, although the night's recording can be analysed at a convenient time with the additional benefit of replay if required, frame-by-frame analysis, noting each movement, is a tedious, time-consuming process. Furthermore, the normal sleeping environment of the subject may be altered leading to artefacts in the data. For example, Southwell *et al* (1972) required subjects to sleep in dark pyjamas without bed covers. Moreover, unless infra-red or light-intensifying cameras are used, filming techniques require adequate lighting which may disturb a subject used to sleeping in a dark room.

Early work on the effects of drugs on human
mobility used pedometers (Fraser *et al*, 1963) or
modified automatically winding calendar wrist watches
(Schulman and Reisman, 1959; Millichap and Boldrey,
1967) worn by the subject. However, these yielded only
a single count of mobility for the whole recording
period. Small transducers such as weighted electrical
potentiometers (Kresse and Rettenmeier, 1973) or
accelerometers (Korn *et al*, 1974) give an output
related to motion or displacement. If these are
attached to one or more sections of the body (arms,
legs and trunk), they can give more information on the
timing and size of movements. Despite their small
size, sleep may be disrupted by discomfort due to the
transducers, and also by the leads connecting the
transducers to nearby recording equipment. The
necessity for such leads was overcome by using small
cassette recorders attached to the subject in
conjunction with transducers (O'Brien, 1976). Colburn
et al (1976) reduced the size of the equipment attached
to the patient by developing small transducers with
self-contained solid state memories.

The first assessments of body movement during sleep
were based on measurement of mattress displacement. In
1926, Renshaw and Weiss used an electromagnetic device
to monitor the frequency of deformation of a particular
bedspring. Both size and frequency of movement were
measured by Szymanski (1914) using a system in which

flexion of the spring was transmitted by mechanical linkage to a recording lever. In the apparatus designed by Kleitman (1932), a bedspring was attached to the rubber surface of a tambour using a rigid connecting rod. Displacement of the rod initiated a frequency counter and deformed the surface of the tambour. The concomitant pressure change in the tambour then triggered a timing device so that the duration of the body movement could be assessed.

More recently, Cox and Marley (1959) used the vertical displacement of a bed spring at the levels of the subjects' hips and shoulders to actuate a potentiometer. The resulting output voltage was amplified and recorded on a counter and pen recorder. The counter gave a total mobility score for the whole night and the pen recording could be used to assess mobility over hourly intervals during the night. At about the same time, Sherwin *et al* (1961) measured mattress displacement during movement using a ratchet strip attached to the mattress linked to an inertia switch. The switch was in circuit with an electrical impulse counter which recorded the frequency of movement for a whole night.

Another system, involving a long brass tube with slits at specified intervals attached to the underside of the centre of the bed springs, was used by Crisp *et al* (1970) to measure frequency of movement. The tube contained a light source and passed through a collar which was rigidly supported by a steel frame beneath

the bed. Pairs of photodiodes were mounted in the collar wall and if the inner tube, attached to the bedsprings, was displaced sufficiently that one of the slits in the tube passed a photodiode, a voltage pulse was transmitted to the recording apparatus (either electromagnetic counter printers or a time counter with print-out facilities). The authors recognised the fact that the output from the apparatus was dependent upon subject weight and so calibrated the system to allow for this. However, none of these three methods provided information about the duration or absolute size of bed movement, and only that of Cox and Marley (1959) gave information on the timing of movement.

The methods described in the previous section are all designed for beds in which the mattress is supported by a meshwork of bed springs, and cannot be used with the solid based King's Fund beds now used in hospitals. Methods of assessing movement in bed that are applicable to most beds are now descibed.

Dement and Kleitman (1957) monitored patients overnight using electroencephalography (EEG) simultaneously recording body movements by the measurement of the displacement of a bed spring. Movements during sleep, as measured on the mobility record, coincided with artefacts on the EEG record in general, although small limb movements often appeared only on the mobility record and small head movements appeared only as EEG artefacts. EEG can be combined

with other electrophysiological measurements to provide more information (polygraphic monitoring). For example, Brezinova and Oswald (1972) used EEG to measure sleep, and electromyography (EMG) to detect movements, transitory changes in EMG activity being consistent with body movements; Sassin and Johnson (1968) used a combination of EEG, EMG and electro-oculography (EOG); and Coleman *et al* (1980) used EEG, EMG, EOG and also electrocardiography (ECG).

Brocklehurst *et al* (1974) developed a system of measuring restlessness during sleep using the displacement of water to indicate movement. A multi-tubular, water filled sheet was placed on top of the mattress, each tube being fitted with non-return valves. When the subject moved, water was displaced from the tubes into a collecting tank and an equivalent amount replaced in the tubes from a supply tank. A float mechanism connected to a chart recorder continuously monitored the volume of water in the collecting tank. Oswald (1974) used the sound of the bed as an indication of movement, attaching a microphone to the bed springs, amplifying the sound signal and passing it to a recorder. These two methods give information on the timing of moves, and qualitative estimations of the size of moves.

A static charge sensitive bed (SCSB) was used by Alihanka and Vaahtoranta (1979) to record movements during sleep. Two large metal sheets isolated from each other by a stiff insulating plate (wood) were

placed beneath the mattress of the bed. The mattress
formed an "active" layer in which movements of the
subject generated a static charge distribution. These
charges induced a potential difference between the two
metal plates which was recorded using a sensitive
differential AC amplifier. To eliminate charges formed
in the clothing of the subject and in the bed covers
from the recording it was necessary to enclose the
plates and mattress in a shield of conducting material
to form a Faradic cage. This also protected the output
from charges induced by a person moving close by the
bed. Calibration of the system by each subject
performing a given set of typical movements before each
recording was necessary to obtain a reliable measure of
movement. This method was further developed (Alihanka
et al, 1981) to be used for the continuous long-term
monitoring of the ballistocardiogram (BCG), heart-rate,
respiratory rate, respiratory amplitude and body
movements with no electrodes or cables being connected
to the subject. However quantitative measurement of
movement is not possible using this method.

Another approach is the detection of movements by
measuring the loads transmitted by the bed legs. Such
techniques are dependent upon two of the basic laws of
statics, a) that of equilibrium whereby a system of
forces is said to be in equilibrium when the resultant
of all the forces, and of all the moments, at one point
are equal to zero, and b) that of action and reaction,
whereby any load on a support causes an equal and

opposite load to be applied to the support, so that action and reaction are two equal and opposite forces. Any change in position of a load upon a structure (in this case a bed frame) can therefore be calculated using a suitable monitoring device. Fernie (1973) developed a load cell, which when placed under one bed leg measured the force in that bed leg, variations in the force being a direct function of the size of the move made by the patient. Bardsley (1977) extended this technique by using load cells under two of the bed legs which gave a uniform sensitivity over the whole bed. He also used four load cells, one under each leg of a chair, to measure movements of seated subjects. Wheatley (1982) further developed this method using a specially designed load cell (Wheatley *et al*, 1980) under each bed leg. This, combined with special electronic circuitry, gave a system that was independent of the patient's weight. The load cells were designed to be physically robust and stable so that the system was able to be used in the clinical environment (Wheatley, 1982; Barbenel *et al*, 1985).

So far, only Laihinen *et al* (1987) have monitored the movement in bed of Parkinsonian patients in an objective way. They used a static charge senstive bed (page 91) to monitor sleep movements and associated autonomic nervous activities. However, they did not study the effects of drug treatment on their measurements. In the work reported here, the apparatus

used by Wheatley (1982, page 93) has been simplified and used to monitor the movement in bed of elderly patients with and without Parkinson's disease. In addition, the possible effect of levodopa therapy on this aspect of mobility in the latter group has also been investigated.

2.8 ASSESSMENT OF THE QUALITY OF SLEEP

Although EEG measurements (page 65) can demonstrate
the presence of sleep in an objective manner, it is
only surmised that sleep having normal characteristics
is better than sleep that is in some way distorted
(Oswald; 1980). Moreover, the actual perception of the
quality of sleep will vary from person to person. The
assessment of the quality of sleep must therefore
remain subjective, based on the opinion of a particular
individual.

Subjective answers can be rated using a rating
scale or a visual analogue scale. A rating scale
consists of two or more categories, of which the
subject must select one as an answer. For example, the
subject may be asked to rate whether he slept "very
badly", "moderately badly", "averagely", "moderately
well" or "excellently". Although such a scale is easy
to understand, it may not be possible for a single
category to be chosen, and the use of such intervals
may influence the subjects' decisions. Authors who
have used rating scales in sleep studies include Priest
and Rizvi (1976) and Middleton (1978). A visual
analogue scale consists of a horizontal line of
standard length with a statement at one end that the
item being rated could not be better and at the other
end that it could not be worse. For example, one end
may bear the statement "the best nights' sleep ever"
and the other "the worst nights' sleep ever". The

subject is asked to make a mark somewhere along the
line to indicate how he slept that night. The distance
of the mark from one end is then measured and used in
analysis. Such scales may initially be confusing and
will obviously be affected by mental ability. They
require careful explanation before use but once
understood are quick and easy to use. An advantage
over rating scales is that they are continuous.
However, once a ruler is applied to the scale it is
open to question whether the rating becomes interval in
nature (Maxwell; 1978). Authors who have used visual
analogue scales in sleep studies include Hindmarch *et
al* (1977) and Briggs *et al* (1980).

CHAPTER THREE

PHARMACOKINETICS OF LEVODOPA

3.1 ABSORPTION

Levodopa is almost entirely absorbed from the gut
(Peaston and Bianchine, 1970; Morgan *et al*, 1971;
Sasahara *et al*, 1980a) with less than 2 per cent of the
dose appearing in the faeces (Peaston and Bianchine,
1970; Morgan *et al*, 1971). Passive diffusion plays a
very minor role in the transport of levodopa.
Absorption of levodopa occurs by a saturable,
stereospecific, sodium independent, active transport
mechanism for aromatic and branched chain amino acids
(large neutral amino acid, LNAA, system) (Oldendorf,
1971; Wade *et al*, 1973; Wade and Katzman, 1975a).
Competition for the carrier system can therefore occur
between levodopa and other substrates, such as 3-O-
methyldopa (3OMD) (Wade and Katzman, 1975b), endogenous
large neutral amino acids and those from ingested
proteins (Morgan *et al*, 1971; Daniel *et al*, 1976). A
further barrier to levodopa absorption is the presence
of dopa decarboxylase in the gut wall which contributes
significantly to the metabolism of oral levodopa
(Rivera-Calimlim *et al*, 1971; Andersson *et al*, 1975).
After oral and intravenous administration of levodopa
to Parkinsonian patients, observed levels of urinary
levodopa and its non-decarboxylated metabolites implied
that over half the dose was being decarboxylated in the
gut wall (Andersson *et al*, 1975). In addition, after
intravenous administration of radio-labelled levodopa
to rats, 4 to 10 per cent of the radioactivity was

recovered in intestinal tissue. The intestine can therefore metabolise levodopa even after it has reached the blood stream (Landsberg *et al*, 1975; Tyce and Owen, 1979). Although it has been shown in rats that the liver contains high concentrations of dopa decarboxylase and rapidly metabolises levodopa (Tyce, 1971), the liver does not appear to be involved in the first pass effect. It is possible that the residence time of the drug in the liver is insufficient for significant metabolism to occur. This could explain why Sasahara *et al* (1981) found no difference in the area under the levodopa plasma concentration/time curve (AUC) when the drug was injected into dogs via the hepatoportal vein or a peripheral vein.

Whereas in the absence of a peripheral dopa decarboxylase (PDD) inhibitor less than half of the dose reaches the circulation intact (Andersson *et al*, 1975; Sasahara *et al*, 1980a), this fraction is greatly increased when PDD inhibitors are co-administered (Tissot *et al*, 1969; Bianchine *et al*, 1972; Kuruma *et al*, 1972). Further evidence for the influence of decarboxylation on the bioavailability of levodopa was provided by the following observations. Firstly, both the therapeutic and adverse effects of levodopa were diminished by concurrent administration of pyridoxine, a cofactor of dopa decarboxylase (Cotzias, 1969; Abrams *et al*, 1971). Secondly, when present in excess, pyridoxine accelerates the peripheral decarboxylation of levodopa (Abrams *et al*, 1971; Mars, 1974), this

interaction being prevented by co-administration of a
PDD inhibitor (Cotzias and Papavasiliou, 1971; Mars,
1974).

At high doses of levodopa the relationship between
dose and plasma concentration is non-linear: the
absorption as measured by the AUC becoming
disproportionately higher as the dose increases. This
is due to saturation of the PDD enzyme thus allowing
more intact levodopa to be absorbed. Therefore,
although the transport mechanism of levodopa is
saturable, it has a much greater capacity than the
corresponding mechanism underlying PDD metabolism
(Mearrick *et al*, 1974; Sasahara *et al*, 1980b).

Most of the levodopa or its decarboxylation
products are absorbed in the proximal small intestine,
and the instillation of the drug directly into the
duodenum results in the very rapid appearance of
levodopa in the plasma (c_{max} in 15 minutes) (Bianchine
et al, 1971). The stomach has very limited capacity to
absorb levodopa but it can decarboxylate the drug
(Rivera-Calimlim *et al*, 1970a) and, in the absence of a
PDD inhibitor, little unchanged levodopa is presented
to the small intestine of younger patients (Andersson
et al, 1975). The rate of gastric emptying will
therefore have an important effect on the absorption of
levodopa. Moreover, the commonly observed multiple
plasma peaks of levodopa after a single oral dose (Wade
et al, 1974; Evans *et al*, 1980) have been attributed to
erratic gastric emptying (Evans *et al*, 1981).

Gastric emptying is influenced by gastric acidity, less acidic conditions enhancing emptying. An inverse relationship between gastric pH and time to peak plasma concentrations (t_{max}) has been reported (Bianchine *et al*, 1971; Pocelinko *et al*, 1972). Rivera-Calimlim *et al* (1970b) were able to demonstrate that lack of therapeutic response in one Parkinsonian patient was due to excessive gastric acidity which reduced levodopa absorption. The administration of antacids to this patient reduced t_{max}, increased c_{max}, and produced a clinically effective response. However, in a later study, Leon and Spiegel (1972) were unable to use chronic co-administration of an antacid to lower the effective dose of levodopa in three of their Parkinsonian patients.

The co-administration of metoclopramide, a dopamine antagonist that enhances gastric emptying, reduced the value of t_{max}, decreased erratic absorption and increased bioavailability (Mearrick *et al*, 1974). However, the beneficial effects of levodopa would, of course, be antagonised by metoclopramide. Domperidone is a dopamine antagonist that does not cross the blood-brain barrier at normal doses. When domperidone was co-administered with levodopa there was a slight increase in t_{max} and bioavailability of levodopa, and also an increase in the response to therapy (Shindler *et al*, 1984). Conversely, the co-administration of anti-cholinergic drugs reduced gastric motility and

caused a reduction in peak plasma levels of levodopa
(Fermaglich and O'Doherty, 1972; Morgan *et al*, 1975).

When the subject is fasting, peak plasma
concentrations are observed within 0.5 to 3 hours
(Bergmann *et al*, 1974; Wade *et al*, 1974; Evans *et al*,
1980; Rossor *et al*, 1980; Sasahara *et al*, 1980b).
However there is marked interpatient variability in
absorption as described in terms of t_{max}, c_{max} and AUC
(Abrams *et al*, 1971; Wade *et al*, 1974; Tolosa *et al*,
1975; Evans *et al*, 1980). As might be expected, the
intrapatient variability in these parameters is less
(Abrams *et al*, 1971; Wade *et al*, 1974).

In the light of these studies in younger subjects,
the investigations of Evans *et al* (1980, 1981) and
Robertson *et al* (1989) in older age groups are of
particular interest. Using scintigraphic techniques,
Evans *et al* (1980, 1981) demonstrated that elderly
normal controls and Parkinsonian patients had much
slower gastric emptying rates than young normal
controls. However, there was no significant difference
in the rate of absorption (t_{max}) of an orally
administered 500mg dose of levodopa between the young
and the elderly. Furthermore, there was a three-fold
increase in the AUC in both groups of elderly subjects
as compared with young controls suggesting an inverse
relationship between age and relative bioavailability.
The fact that the peak plasma concentrations, the
patterns of multiple plasma peaks and the half-lifes of
elimination were similar for both age groups implied

that the site and mode of absorption were unaffected by age. It was therefore postulated that elderly subjects have a lower gastric activity of dopa decarboxylase than their younger counterparts resulting in a reduction of first pass effect. However, in the absence of intravenous data it is difficult to rule out the possibility that reduction in clearance was responsible for the apparent increase in bioavailability in the elderly.

Robertson *et al* (1989) compared the pharmacokinetics of levodopa administered both with and without the PDD inhibitor carbidopa, after intravenous and oral administration in young and elderly healthy volunteers. The findings of this study are given in some detail in the discussion (page 284) where comparisons are made with the results of the present thesis. A similar age-related increase in AUC in the absence of a PDD inhibitor to that reported by Evans *et al* (1980, 1981) was observed by these authors. This may account for reports that elderly patients require less oral levodopa than younger patients for an equivalent therapeutic response (Broe and Caird, 1973; Vignalou and Beck, 1973; Grad *et al*, 1974).

Levodopa is given with meals to avoid nausea and vomiting, both common side effects of the therapy. However, high gastric acidity and delayed gastric emptying caused by meals have been shown to delay and reduce peak plasma concentrations (Nutt *et al*, 1984). Moreover, if the medication is taken with a high

protein meal, loss of clinical improvement can occur. Conversely, the administration of low protein diets reduces the amount of levodopa needed for a therapeutic response (Mena and Cotzias, 1975). Interestingly, during intravenous infusions of levodopa, a temporary reversal of clinical response occurred when meals high in protein were administered. This reversal in response was not associated with any decrease in plasma concentrations (Nutt *et al*, 1984). Furthermore, for a group of Parkinsonian patients with fluctuations in control or no response to therapy, Pincus *et al* (1987a,b) were able to improve their clinical response to therapy by controlling the timing and amount of protein intake, whilst keeping their oral levodopa/carbidopa regime constant. More recently Tsui *et al* (1989) and Carter *et al* (1989) demonstrated that the improvement in performance in fluctuating Parkinsonian patients on a low protein diet could not be explained by changes in plasma levels of levodopa. This would seem to suggest that competition between levodopa and dietary proteins for the active transport system at the blood-brain barrier (page 105) is of greater clinical importance than that at the gastrointestinal level.

3.2 DISTRIBUTION

Levodopa is widely distributed in the tissues with
an estimated volume of distribution of 0.9 to 1.6L/kg
(Granerus *et al*, 1973; Nutt *et al*, 1985). In the
plasma over 90 per cent of levodopa occurs as the free
amino acid, only 10 per cent being protein bound.

In an *in vitro* study, no significant difference was
detected in the levodopa uptake of red blood cells in
normal subjects as opposed to Parkinsonian patients
(Jiang *et al*, 1983). However, Barbeau *et al* (1975)
reported a defect in the *in vitro* uptake of dopamine in
platelet enriched plasma from untreated Parkinsonian
patients. This defect was partially reversed after
treatment with levodopa. Similar changes in transport
across membranes might also occur in the gastro-
intestinal tract and at the blood-brain barrier
following treatment.

Uptake of levodopa into the brain occurs via the
large neutral amino acid transport system (Wade and
Katzman, 1975a) and as discussed previously (page 104)
the entry of levodopa into the brain may be influenced
by the amino acid content of diet. Studies using
positron emission tomography (Leenders *et al*, 1986a)
found that infusions of large neutral amino acids
reduced brain uptake of ^{18}F-fluorodopa. The amount of
carbohydrate in the diet may also influence the uptake
of levodopa into the brain. A glucose load has been
shown to lower the plasma concentration of branched

chain amino acids thus enhancing the active transport
of aromatic amino acids (Fernstrom and Faller, 1978;
Martin-DuPan *et al*, 1982). Such a process could
explain the observation of an improved clinical
response to levodopa after glucose intake (Muenter *et
al*, 1977).

The behavioural changes, such as depression,
associated with levodopa treatment in Parkinsonian
patients suggest underlying disturbances in 5-
hydroxytryptamine (5-HT) metabolism (Diez *et al*, 1976).
A study by Lehmann (1973) implied that 5-HT synthesis
was depressed in Parkinsonian patients due to the
combined effects of impaired transport of its
precursor, tryptophan (competition for active
transport), and enzymatic changes (reduced activity of
5-OH-indole hydroxylase and increased competition for
5-hydroxytryptophan decarboxylase). Both these effects
could be attributable to levodopa therapy. Using rats
as a model, Algeri and Cerletti (1974) showed that a
single dose of levodopa produced a decrease in brain
tryptophan. It would seem that there is a requirement
for a low but adequate intake of protein to optimise
the effectiveness of the levodopa therapy whilst
minimising the incidence of mental disturbances.
However, it has also been reported that a single dose
of levodopa can increase brain tryptophan levels (Weiss
et al, 1971a), and that chronic levodopa therapy has no
effect on them (Algeri and Cerletti, 1974). It is thus
apparent that the physiological interactions between

levodopa, tryptophan and 5-HT metabolism involve more than the changes in membrane transport and enzymatic activity discussed above.

3.3 METABOLISM

There are four major pathways for the metabolism of
levodopa: decarboxylation, O-methylation,
transamination and oxidation (Figure 3). *In vitro*,
non-enzymatic decarboxylation of levodopa has been
found to occur at physiological pH in the plasma
(Vogel, 1969; Hare *et al*, 1971). However, it is
uncertain whether this pathway contributes
significantly to the formation of plasma dopamine *in
vivo* where most of the metabolic reactions are
dependent on enzyme action.

In vivo, about 69 per cent of levodopa is
decarboxylated to form dopamine which is then
deaminated to dihydroxyphenylacetic acid (DOPAC). The
major metabolite of levodopa is homovanillic acid
(HVA), which is formed by the methylation of DOPAC. A
further 10 per cent of levodopa is methoxylated to 3OMD
by catechol-O-methyltranferase (COMT) (Goodall and
Alton, 1972).

Transamination is a relatively minor pathway
compared with decarboxylation. The enzymes which bring
about such reactions are found in the liver, kidney and
mitochondria. Transamination of levodopa produces
vanillpyruvate, vanillactate and 2,4,5-
trihydroxyphenylacetic acid (Wada and Fellman, 1973;
Sandler *et al*, 1974; Fellman *et al*, 1976). 2,4,5-
trihydroxyphenylacetic acid is in turn subject to
spontaneous oxidation leading to the formation of
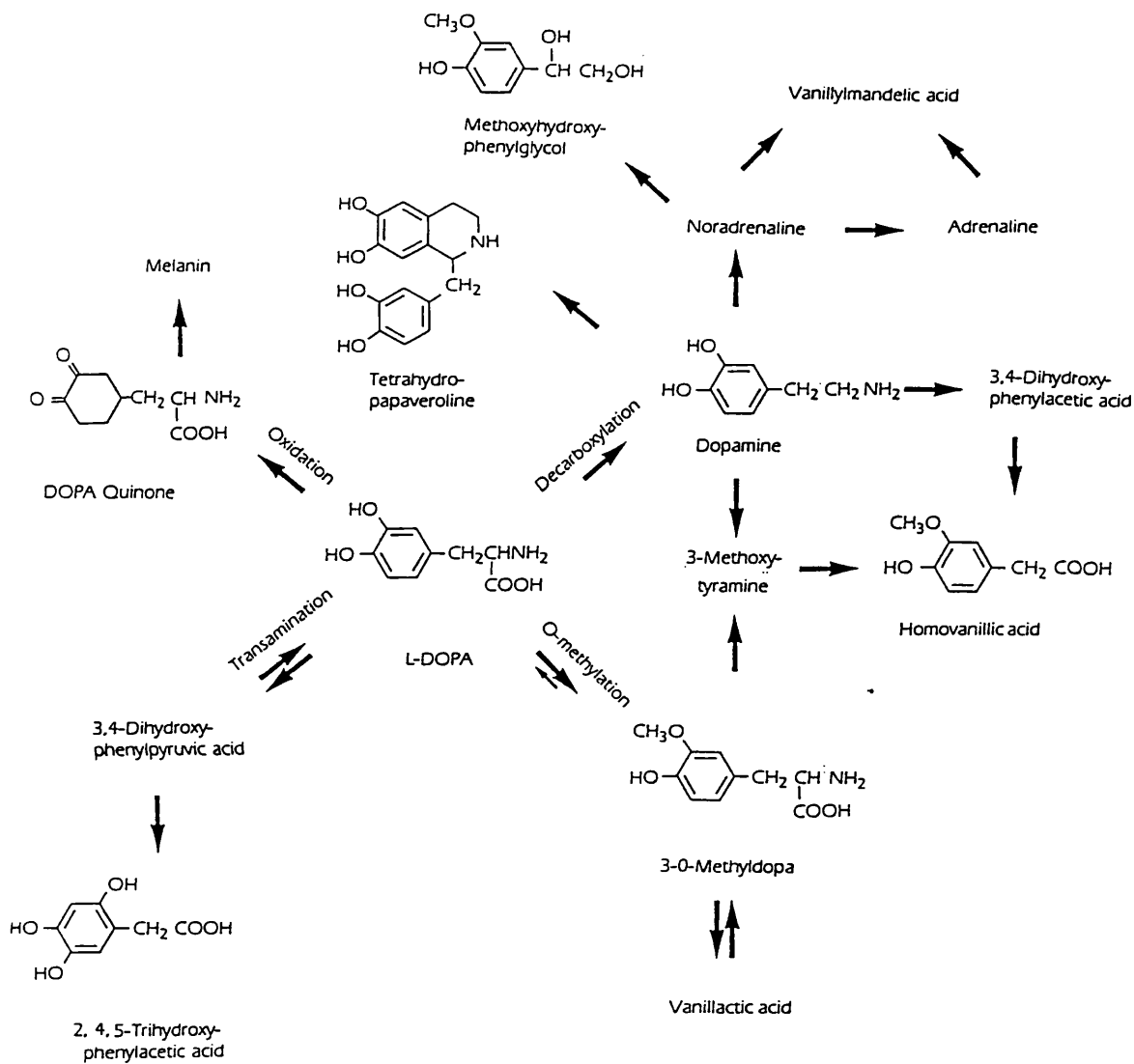
Figure 3 Pathways for the metabolism of levodopa

superoxide, hydrogen peroxide, and a reactive quinone similar to 6-hydroxydopamine (Fellman *et al*, 1976; Nutt and Fellman, 1984). No direct evidence for the oxidation of levodopa in humans has been reported, but the appearance of cysteinyldopa in the urine of Parkinsonian patients suggests that oxidation with a levodopa quinone intermediate does occur (Stewart *et al*, 1983).

A maximum of 5 per cent of dopamine is hydroxylated to noradrenaline by the enzyme dopamine-β-hydroxylase. This is then further metabolised via adrenaline to form vanillylmandelic acid (VMA) (Nutt and Fellman, 1984). Conjugation of levodopa and its metabolites can occur but such complexation appears to be unimportant at plasma levels associated with therapeutic doses (Rutledge and Hoehn, 1973; Jenner and Rose, 1974; Bronaugh *et al*, 1975). Dopamine can also undergo condensation reactions resulting in the formation of tetrahydroisoquinoline alkaloids such as tetrahydropapaveroline (Sandler *et al*, 1973).

All the pathways are irreversible except the transamination pathway. Animal studies have shown that 3,4-dihydroxyphenylpyruvate can act as a precursor for levodopa (Hietala *et al*, 1979; Linden, 1980). A small but detectable demethylation of 3OMD to levodopa has also been reported in rats (Bartholini *et al*, 1971; Tyce *et al*, 1976) and in man (Kuruma *et al*, 1971), occurring particularly in the erythrocytes (Tyce *et al*, 1978).

Considerable effort has been made to elucidate possible metabolic pathways of breakdown of levodopa *in vivo*. However, it remains to be seen whether the accumulation of relatively minor metabolites has any effect on the therapeutic and toxic responses to levodopa therapy.

3.4 ELIMINATION

In the absence of a PDD inhibitor, levodopa is
rapidly cleared from the plasma. Mean values of
clearance range from 0.5L/kg/h during intravenous
infusion of the drug (Nutt et al, 1985) to 1.38L/kg/h
following an intravenous bolus (Sasahara et al, 1980a).
Nutt et al (1985) observed a biphasic elimination curve
after the intravenous administration of levodopa. The
corresponding mean values of the distribution and
elimination half-lives were 5 minutes and 1.3 hours
respectively. The brevity of the distribution phase
probably explains why the elimination of levodopa had
previously been reported as monophasic (Sasahara et al,
1980a). After oral dosing, the elimination of levodopa
has also been descibed as monophasic, with mean
elimination half-lives ranging from 0.77 hours
(Sasahara et al, 1980b) to 1.74 hours (Rossor et al,
1980).

Fifty to 80 per cent of an administered dose is
voided in the urine within 24 hours, the majority being
excreted in the first 6 hours (Morgan et al, 1971;
Goodall and Alton, 1972). Although a small percentage
of the dose is excreted as dopamine, the majority is
eliminated in the form of the dopamine metabolites
(DOPAC and HVA). Goodall and Alton (1972) found that
even after five days about 20 per cent of an
administered levodopa dose had still not appeared in
the urine. They suggested that it may be sequestered,

at least in part, as melanin formed by the oxidation of

levodopa.

3.5 LEVODOPA KINETICS IN THE CEREBROSPINAL FLUID

Levels of HVA in the cerebrospinal fluid (CSF) tend to be lower in Parkinsonian patients than in normal healthy subjects (Jequier and Dufresne, 1972; Gumpert *et al*, 1973; Miachon *et al*, 1974). After administration of radiolabelled levodopa, labelled HVA and DOPAC are detectable in the CSF, although the amount of radioactivity in the CSF is only equivalent to about 10 per cent of the administered dose. Activity peaks in cisternal CSF at 2 to 4 hours, and continues to rise in the lumbar space for up to 8 hours. After 24 hours activity has decreased to 2 to 3 per cent (Pletscher *et al*, 1967). Although a correlation between low pre-treatment levels of HVA in the CSF and subsequent clinical improvement has been found (Jequier and Dufresne, 1972; Gumpert *et al*, 1973), other studies have failed to show such a link (Bowers and Van Woert, 1972; Chase and Ng, 1972; Weiner and Klawans, 1973). Similarly, the relationship between post-treatment HVA levels in the CSF and clinical response is unclear. Some studies suggested that the increase in HVA levels might correlate with therapeutic response (Godwin-Austin *et al*, 1971; Miachon *et al*, 1974) whereas others failed to find any such relationship (Jequier and Dufresne, 1972; Gumpert *et al*, 1973; Weiner and Klawans, 1973). Hare *et al* (1973) analysed the patterns of amino acids occurring in the CSF of normal subjects and Parkinsonian

patients. The amino acid composition differed in only one respect, namely that the methionine content in the Parkinsonian group was depressed. It was proposed that this depletion was the result of increased methylation within the central nervous system (CNS) of these patients.

3.6   EFFECT OF PERIPHERAL DOPA DECARBOXYLASE INHIBITORS ON THE PHARMACOKINETICS OF LEVODOPA

Peripheral dopa decarboxylase inhibitors reduce the amount of oral levodopa required for a therapeutic response by between 60 to 80 per cent (Mars, 1973; Fahn, 1974). In their presence, the plasma half-life of levodopa has been reported to be prolonged (Dunner et al, 1971; Nutt et al, 1983) or unchanged (Rinne et al, 1973; Fahn, 1974). Clinically, there is little evidence for a longer half-life since frequency of dosing was not reduced with the advent of combination therapy (Nutt and Fellman, 1984).

The metabolic profile of levodopa is possibly altered by PDD inhibitors. Less of an administered dose was metabolised to HVA and DOPAC (Bianchine et al, 1972; Sandler et al, 1974), and there was an increase in the amount of the transamination end product, vanillactic acid, and also the O-methylated product, 3OMD. However, when therapeutic plasma levodopa levels were achieved with or without a PDD inhibitor, no difference in the plasma levels of 3OMD was found (Fahn, 1974). Conversely, Kremzner et al (1973) found that CSF concentrations of 3OMD were increased by the concomitant administration of carbidopa and levodopa.

3.7 REDUCTION OF RESPONSE TO LEVODOPA

Even within a single individual, variation in the
timing and content of meals can influence the
bioavailability and therefore the efficacy of a given
dose of levodopa. Moreover, the emergence of
fluctuations in therapeutic reponse have been reported
as affecting 50 per cent of patients treated with
levodopa or levodopa/PDD inhibitor combinations for 5
years or more (Sweet and McDowell, 1974), and 80 per
cent of patients treated for 16 years (Cedarbaum and
McDowell, 1986). A number of studies have investigated
this loss of clinical efficacy during long term
levodopa therapy.

Gancher *et al* (1987) studied the pharmacokinetics
of levodopa using single oral doses and intravenous
infusions in three groups of Parkinsonian patients.
One group consisted of patients who had never been
treated with levodopa, another of treated patients with
relative lack of variation in control of their
Parkinsonism and the other of treated patients with
marked variation in control of their Parkinsonism. All
were pretreated with carbidopa. After oral dosing,
mean values for levodopa for t_{max} , c_{max} , and AUC were
similar for the three groups, AUC being proportional to
dose. After intravenous infusion, elimination half-
life and clearance of levodopa were also comparable in
all groups. Moreover, although concentrations of 3OMD
were considerably lower in the group of patients who

had previously been untreated, they were similar in the groups with marked and with minimal variation in their Parkinsonian signs. On this evidence it was thus not possible to account for fluctuations in control on the basis of pharmacokinetic differences between these patient groups. Similarly, Rinne *et al* (1973), Hare *et al* (1973) and Pilling *et al* (1975) were unable to find any relationship between plasma levodopa concentrations and response.

Other studies showed that on-off fluctuations in individuals were related to an observed variability in plasma levodopa concentrations (Fahn, 1974; Sweet and McDowell, 1974; Shoulson *et al*, 1975; Tolosa *et al*, 1975; Eriksson *et al*, 1984). Moreover, the response of patients with a tendency to marked fluctuations were stabilised by constant rate infusions of levodopa (Shoulson *et al*, 1975; Nutt *et al*, 1984; Hardie *et al*, 1984; Quinn *et al*, 1984). Furthermore, Rossor *et al* (1980), using a placebo control, were able to correlate plasma concentrations following oral levodopa to clinical response, even in patients who did not suffer from rapid swings in performance. On the basis of the latter observations, an oral dosage form which delivers the drug to the plasma at a constant rate would seem to be needed.

Intuitively it might be expected that the clinical efficacy of levodopa would be more closely related to drug concentrations in the CNS rather than those existing in the plasma. The concentration of levodopa

in the CNS is related not only to the existing plasma concentration but is also dependent on uptake and storage within the brain. Hence in patients where there is loss of storage capacity, clinical response might well be more sensitive to changes in plasma concentration.

Reduction in storage capacity for dopamine could account for the on-off syndrome (Marsden, 1980) whilst loss may relate to lack of efficacy. When compared with a control group, Leenders *et al* (1986b) showed that the capacity of the striatum to retain a tracer, L-[^{18}F]fluorodopa, was severely impaired in patients with Parkinson's disease. They stated that: *"Patients with longstanding disease and fluctuating "on-off" clinical response to levodopa treatment had a significantly lower "storage capacity" compared with "early" patients, either treated or showing sustained clinical response."*

It has been shown in animal studies that motor activity is decreased by low doses of dopamine agonists and increased by high doses of the drugs (Stromberg, 1970; Montanaro *et al*, 1983; Bradbury *et al*, 1984). A similar biphasic dose responsiveness may play a part in the motor fluctuations of Parkinsonian patients on chronic levodopa therapy (Paalzow and Paalzow, 1986). This suggestion was investigated by Nutt *et al* (1988) who compared the effects of levodopa infused at different rates with the response to placebo infusions. Rates of levodopa infusion which produced an

improvement in motor function for at least 30 minutes
were associated with motor improvement for 0.5 to 3.5
hours followed by deterioration to below the baseline
score (determined after withdrawal of levodopa
overnight) for 30 to 90 minutes and then spontaneous
improvement to baseline level. They thus suggested
that the worsening of motor function in patients
treated with levodopa may not be simply due to loss of
dopaminergic stimulation and a return to the untreated
state, but may be associated with an inhibitory effect
due to levodopa. Unfortunately they were unable to
predict a mechanism for this phenomenom.

Transient fluctuations in the sensitivity of the
postsynaptic neurons may explain the on-off syndrome
(Fahn, 1974; Teravainen and Calne, 1979). It has been
suggested that patients with Parkinson's disease
partially compensate for neuron loss by developing
denervation supersensitivity (Bernheimer et al, 1973).
In a postmortem study, Lee et al (1978) found increased
binding of radiolabelled haloperidol in the putamen of
patients with untreated Parkinson's disease which
supports the hypothesis of denervation
supersensitivity. Their data from patients with
treated Parkinson's disease suggest that long-term
levodopa therapy decreases this compensatory mechanism.
Resensitisation of receptors may be an alternative
explanation for the improvement seen after a drug
holiday (Direnfeld et al, 1978; Lee et al, 1978).
However, it has also been suggested (Klawans et al,

1977) that long-term treatment with levodopa may itself induce dopamine receptor supersensitivity.

An improvement in performance after reduction or cessation of levodopa has been reported. Sweet *et al* (1972) found an enhanced response to single doses of levodopa following a period of withdrawal in 7 of the 13 patients studied. However, this response to a drug holiday could not be explained by changes in the pharmacokinetics of levodopa in those patients who responded favourably. Similarly, Direnfeld *et al* (1978) described one patient with severe on-off phenomenom in whom a period of reduction in the dosage of levodopa resulted in increased predictability of response to a lower optimal dose. This could be explained by a reduction either of direct toxic effects, or of indirect side effects.

Conversely, the more frequent on-off phenomena observed in patients treated with levodopa/PDD inhibitor combinations (Feuerstein *et al*, 1977) may be due to an increase in toxic metabolites. One metabolite of levodopa that has been suggested to be toxic is 3OMD. In contrast to levodopa which has a half-life of 0.77 to 1.74 hours (page 112), 3OMD has a much longer half-life (15 to 17 hours) and thus will accumulate in the plasma and tissues of patients receiving chronic levodopa therapy, reaching levels higher than those of levodopa (Kuruma *et al*, 1971; Sharpless *et al*, 1972). This accumulation is enhanced by 3 to 10 times in patients concurrently receiving a

PDD inhibitor (Tissot *et al*, 1969; Messiha *et al*, 1972). It occurs despite the reduction in COMT activity during long-term therapy (Weiss *et al*, 1971b) suggesting that decreased breakdown, or reduced elimination of 3OMD is occurring. No metabolites of 3OMD have been found in CSF (Sharpless and McCann, 1971), which implies that 3OMD is derived from the systemic metabolism of levodopa, rather than from its metabolism in CNS tissue. 3OMD, a large neutral amino acid, has a much higher affinity for the active transport system and hence a higher rate of transport into the brain than levodopa and may interfere with the transport of levodopa into the striatum (Wade and Katzman, 1975b). Oral administration of 3OMD has been reported to cause clinical deterioration, decreased response to levodopa and decreased peak plasma levodopa concentrations (Muenter *et al*, 1973; Nutt and Woodward, 1987). Parkinsonian patients who have a poor response to levodopa have higher plasma 3OMD concentrations (Rivera-Calimlim *et al*, 1977) and higher erythrocyte COMT activity than patients with a satisfactory response to therapy (Reilly *et al*, 1980). Fabbrini *et al* (1987) found that the optimal therapeutic doses of levodopa and also the plasma 3OMD concentrations were significantly higher in patients who had on-off syndrome on chronic levodopa therapy than those who did not. However, in view of the long half-life of 3OMD, it was hardly surprising that they found no relationship between fluctuations in motor response and

the circulating 3OMD level. A drug holiday from
levodopa may allow the accumulated levels of 3OMD to
decrease, leading to increased responsiveness to
therapy, at least in the short term. However, more
recently, Cedarbaum *et al* (1988) reported that the
doubling of plasma 3OMD levels long term did not appear
to cause clinical deterioration in the patients
studied. Thus it may be that the high 3OMD levels
reported in patients with response fluctuations merely
reflects the greater levodopa doses taken. It has also
been proposed that other levodopa and dopamine
metabolites formed in the brain, such as
tetrahydropapaveroline, may act as partial agonists,
occupying dopamine receptor sites but producing
inadequate dopaminergic activation (Sandler *et al*,
1973; Dougan *et al*, 1975). Furthermore, Boomsma *et al*
(1989) found that levels of plasma dopa decarboxylase
were raised threefold in patients receiving chronic
treatment with levodopa combined with a PDD inhibitor.
They suggested that this apparent induction of dopa
decarboxylase by PDD inhibitors may be related to the
loss of clinical efficacy of combination therapy in
some patients.

Loss of benefit occurs during chronic levodopa
therapy despite transient improvement caused by a drug
holiday. This may be due to progression of the
underlying pathology of the disease (Marsden and
Parkes, 1976). However, the postulation that the
progressive loss of presynaptic dopaminergic neurons

in the nigrostriatal pathway results in the inadequate conversion of levodopa to dopamine is confounded by the fact that there is no clear relationship between the duration or severity of the disease and the response to treatment (Marsden, 1980). Lloyd and Hornykiewicz (1970) found that, postmortem, the activity of dopa decarboxylase in the striatum of patients with Parkinson's disease was 5 to 10 per cent that of normal subjects. However, because this enzyme is not rate-limiting the small amount remaining in a few intact dopaminergic neurons may be sufficient for adequate dopamine synthesis (Marsden, 1980). Decarboxylase is also widely distributed in non-dopaminergic neurons and cerebral capillaries (Marsden and Parkes, 1977; Marsden, 1980). It is possible however, that further loss of dopaminergic neurons beyond a critical level, or progressive destruction of other neuronal systems may result in a lack of conversion of levodopa to dopamine (Marsden, 1980).

If the above process were responsible for loss of benefit during chronic levodopa therapy then it might be expected that direct dopamine agonists such as bromocriptine, that are not dependent upon conversion for their action, would be of more use in severe Parkinsonism (Calne *et al*, 1974). However, the value of bromocriptine in treating patients with advanced Parkinson's disease, particularly those who are losing, or have lost their responsiveness to levodopa is unclear (Calne *et al*, 1974; Lieberman *et al*, 1976;

Parkes *et al*, 1976; Godwin-Austen and Smith, 1977; Lees *et al*, 1978). A possible explanation for this may be the loss of postsynaptic dopamine receptors (Reisine *et al,* 1977).

3.8   ASSAY OF CATECHOLAMINES AND RELATED COMPOUNDS

A number of methods have been used to measure catecholamines and related compounds in biological fluids and tissues, including gas-liquid chromatography with electron-capture detection (Wong *et al*, 1973; Imai *et al*, 1973), radioenzymatic methods (Da Prada and Zurcher, 1976; Hjemdahl *et al*, 1979), gas chromatography-mass spectrometry (Ehrhardt and Schwartz, 1978; Lhuguenot and Maume, 1980) and high-performance liquid chromatography (HPLC) with fluorescence detection (Nimura *et al*, 1980; Mori, 1981) or electrochemical detection (ECD) (Wenk and Greenland, 1980; Davies and Molyneux, 1982).   Gas chromatographic methods require derivatisation prior to analysis and equipment is expensive.   Radioenzymatic methods are sensitive, enabling analysis of catecholamines in very small volumes of plasma, but sample preparation is complex, time-consuming and expensive (Hjemdahl *et al*, 1979).   High-performance liquid chromatography with ECD is more rapid, less expensive to run, and eliminates the need to use isotopes (Hjemdahl *et al*, 1979; Davis *et al*, 1981), whilst still having the sensitivity to measure circulating levels of catecholamines (Hallman *et al*, 1978).

The separation of levodopa, metabolites such as dopamine, DOPAC, noradrenaline, adrenaline, 3OMD, HVA, and the PDD inhibitor, carbidopa, can be achieved by ion-pair, reversed-phase HPLC.   Under reversed-phase

conditions, catecholamines are generally protonated. This results in poor retention of these compounds on the hydrophobic column. Retentions can be altered dramatically by the addition of ionic surfactants to the mobile phase (Krstulovic, 1982). The presence of anions in the mobile phase enables the formation of uncharged ion-pair conjugates with the catecholamine cations prior to partitioning into the lipophilic stationary phase. Similarly, alterations of pH of the mobile phase can greatly alter retention times (Krstulovic, 1982). Low pH values will result in full protonation of amino groups, whilst carboxyl groups are undissociated and therefore uncharged. Thus, retention of acidic metabolites is greater at low pH values, and the converse is true for amines.

Extraction of catecholamines from plasma for HPLC analysis has been achieved most often by adsorption onto alumina, followed by elution in acid pH (Davies and Molyneux, 1982). More recently, the use of phenylboronic acid (PBA) to separate catecholamines has been described (Kagedal and Pettersson, 1983). The availability of solid phase boronate matrices (Analytichem) allows easier and more rapid separation of catechol-containing compounds than does alumina, and they can be rinsed for re-use several times (Benedict and Risk, 1984).

<u>**EXPERIMENTAL WORK**</u>

CHAPTER FOUR

EXPERIMENTAL METHODS

A number of experimental methods were used to assess the night-time and daytime movement of elderly Parkinsonian patients on levodopa therapy. These are described in this section.

4.1   ASSESSMENT OF MOVEMENT IN BED

Principle of the apparatus

The apparatus used in this study was based upon
that of Wheatley (1982) but with much simpler
electronic circuitry. He used a system with a load
transducer under each bed leg to monitor movement in
bed. Each transducer was instrumented with four
resistive strain gauge elements that were connected in
a bridge configuration so that the out of balance
signal was related to the load applied to the bed leg.
The signals from the four bridges were electronically
processed to produce a signal which was proportional to
the lateral movement of the centre of gravity of the
patient independent of patient weight.

In the present system, each transducer (Figure 4)
consisted of a cantilever whose deflection was sensed
by just one resistive strain gauge.
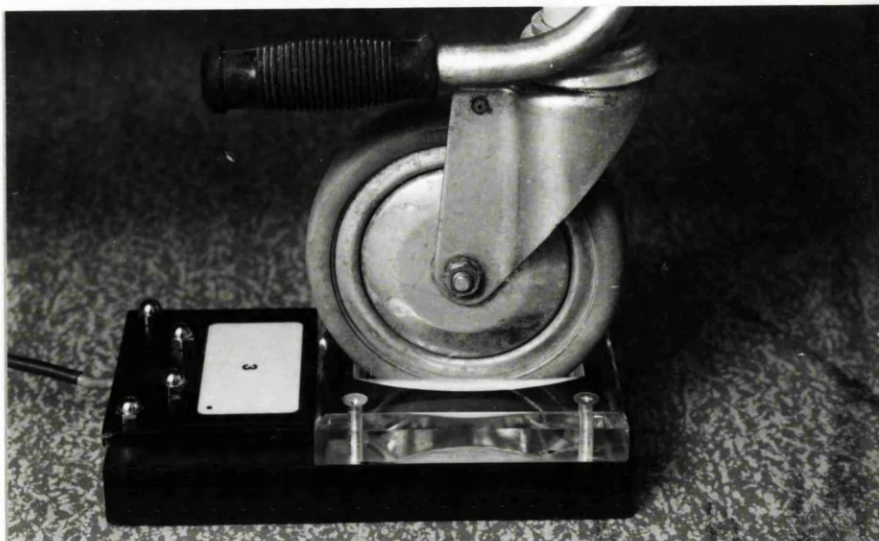
Figure 4   Load transducer in position under bed leg

The four strain gauge resistor elements (one for each load transducer) were connected in a bridge configuration (Figure 5) so that the out of balance signal was related linearly to the position of the patient's centre of gravity across the bed. The use of just one bridge configuration in itself processed the signals which then had to be corrected for the patient's weight. The signal thus obtained was amplified, filtered and displayed on a chart recorder to give a continuous plot of the lateral displacement of the centre of gravity of the patient.
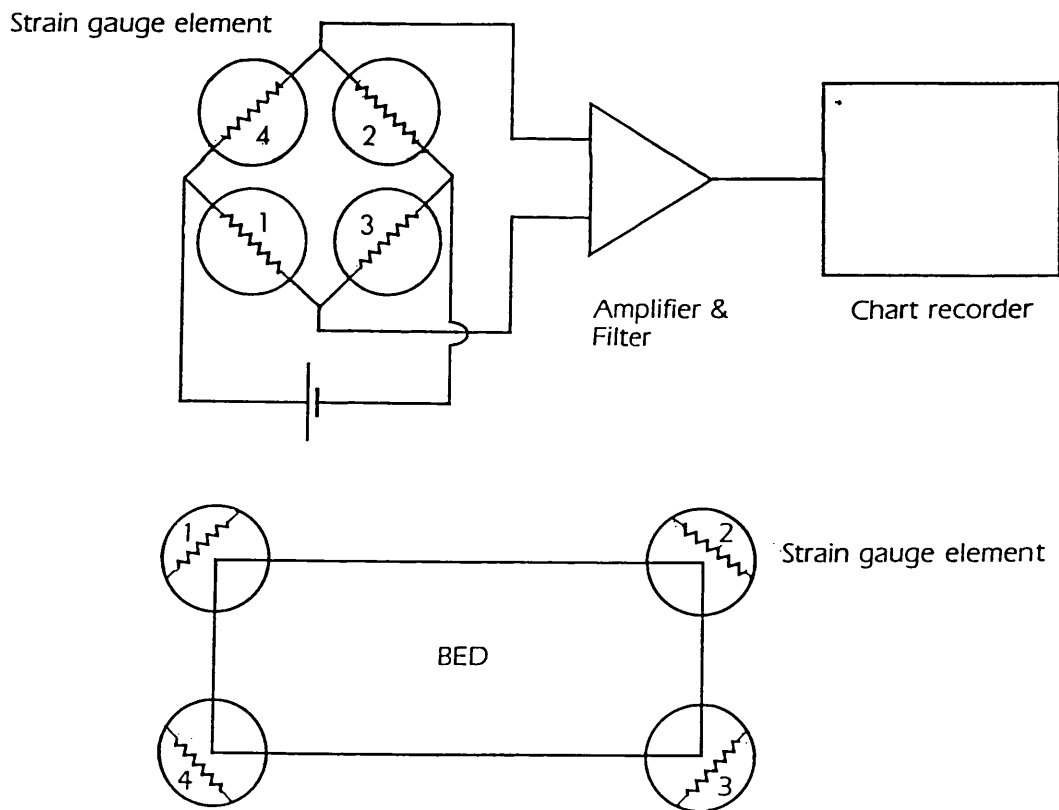
Figure 5   Circuit diagram of bridge arrangement of strain gauge load cells

Use of the apparatus

Each set of apparatus consisted of four load transducers, an amplifier box and a chart recorder. Eight sets were available for use at any one time. So that the system could be set up by the investigator alone, a car jack was modified to fit the bed frame, raise the side of the bed and enable the transducers to be placed under the legs of the bed. Once set up, the apparatus was calibrated as described below. A few patients were found to favour one side of the bed. This preference was accomodated by adjustment of the centreing device of the pen. The apparatus was initially switched on and off manually which necessitated the presence of the investigator but an automatic time switch was later added to the system. Each morning, when the previous night's trace was collected, the apparatus was checked for any inadvertent disturbance by ward staff or patients, a particular problem being disconnection from the electrical supply.

Calibration of the apparatus

On theoretical grounds, the deflection observed on the chart recorder is proportional to the product of the lateral displacement of the centre of gravity of the patient and their weight. If M is the weight of the patient and L the lateral displacement of the centre of gravity of the patient then the resulting

chart deflection (D) will be given by

$$D = kML \qquad \ldots\ldots\ldots(1)$$

where k is a constant for a particular system (bed plus electronics). The validity of this approach was confirmed experimentally by Hayden (1983).

For the current apparatus, from a given deflection of the chart recorder it was thus possible to calculate the equivalent displacement of the patient's centre of gravity provided that the patient's weight was known and the system had been pre-calibrated. This involved measuring the chart deflection caused by the displacement of a known weight. To find the lateral displacement (L) of the patient's centre of gravity from the observed chart deflection, a knowledge of k and M was required. The value of M was available but the value of k had to be obtained by the following callibration procedure.

Calibration weights of 5kg and 10kg were available for use although it became more usual to use the 5kg weight as it was easier for the author to transport. The known weight (m) was placed in turn on the edge of each long side of the unoccupied bed and the resulting deflection (d) on the chart recorder was noted. Since the weight (m) had been moved a known distance (1) equal to the width of the bed the constant k could then

be calculated using the equation

$$d = kml. \quad \ldots\ldots\ldots(2)$$

The calibration procedure was carried out twice each time an apparatus was set up on a bed. In each case there was no detectable difference in the deflection (d) obtained.

An example of a calibration trace and the calculation of the constant k is given on pages 142 and 143.

Analysis of the movement record

When the apparatus was first used in the clinical environment, the types and times of movements made by a patient were observed directly over the course of a night on two occasions. A section of one of the traces obtained with the observed movements annotated is shown in Figure 6. This was one of the first times that the prototype bed movement monitor was used and, as can be seen, the pen produced a thick line. In the bed monitors developed from the prototype, pens of a finer line width were substituted. During the nights of observation, the relationship between observable patient movement and the movement of the pen on the trace was determined. It was found that a deflection of the pen equivalent to a lateral displacement of the centre of gravity of the patient of greater than 4mm was always associated with observable simultaneous

movement of the patient whereas any deflection equivalent to 4mm or less was not (Figure 6, K and L). It was therefore decided that only displacements of the centre of gravity of the patient of greater than 4mm could be detected reliably.

Initially, it was hoped that movements of the various parts of the body (for example arms, legs, trunk) would be distinguishable from the trace. However it was found during the period of direct observation that although small movements of the arms and legs produced smaller pen deflections than those of the trunk, the action of an arm being flung out could produce a deflection equivalent to or greater than the trunk being moved (Figure 6). Using the present apparatus it was therefore not possible to differentiate between movements of the limbs and trunk reliably and thus no attempt was made to do so in subsequent analysis of movement traces.
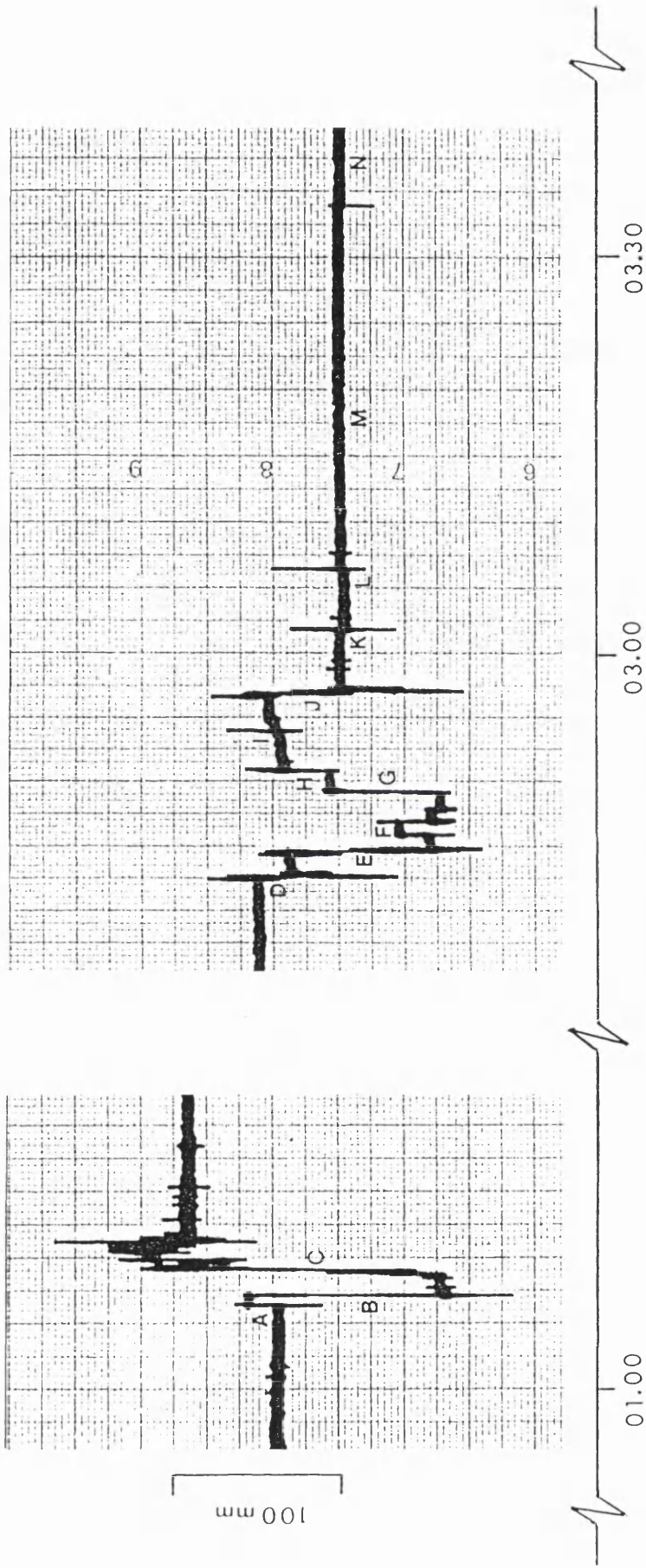
Figure 6   Part of a bed movement trace obtained when movements made by a patient were directly
            observed overnight

Movements:- A - moved arm   G - moved hand to edge of bed
            B - rolled onto back and moved   H - moved trunk
                further down the bed   I - moved hand slightly
            C - threw arm over   J - moved trunk slightly and right hand
            D - moved trunk   to the edge of the bed and then back
            E - moved trunk into the air and   K and L - movement seen on trace but no patient
                then down onto the bed again   movement observed
            F - movement complex of patient   M and N - other people moving in the ward has no
                moving onto their back   observable effect on the trace

Analysis of the movement traces was carried out by hand and proved to be laborious and time consuming. To minimise the influence of artefacts the following procedure was adopted.

The records for the hour after retiring to bed and the hour before rising in the morning were omitted from the analysis to eliminate movement associated with the settling of patients and early morning awakenings. The apparatus was switched on at 22.00 hours (h.) and off at 07.00h. because of the timings of normal ward routines. The hours from 22.00h. to 23.00h. and 06.00h. to 07.00h. were then omitted thus each trace contained 7 hours of movement for subsequent analysis.

Nurses were asked to note any times at which the patient required attention during the night so that these moves, and any in 10 minute periods before and after, could be discarded. This ensured that any moves measured were spontaneous moves of the patient only, not artefacts due to nurses. It quickly became evident that the actions of rising from, and returning to, bed during the night produced characteristic deflections (Figure 7). Also, a few patients exhibited occasional bursts of considerable movement which could possibly be attributed to problems such as periodic nocturnal myoclonus or restless leg syndrome (Figure 8) although these phenomena were not studied in greater detail. Ten minute periods before and after these events were also eliminated from the analysis.
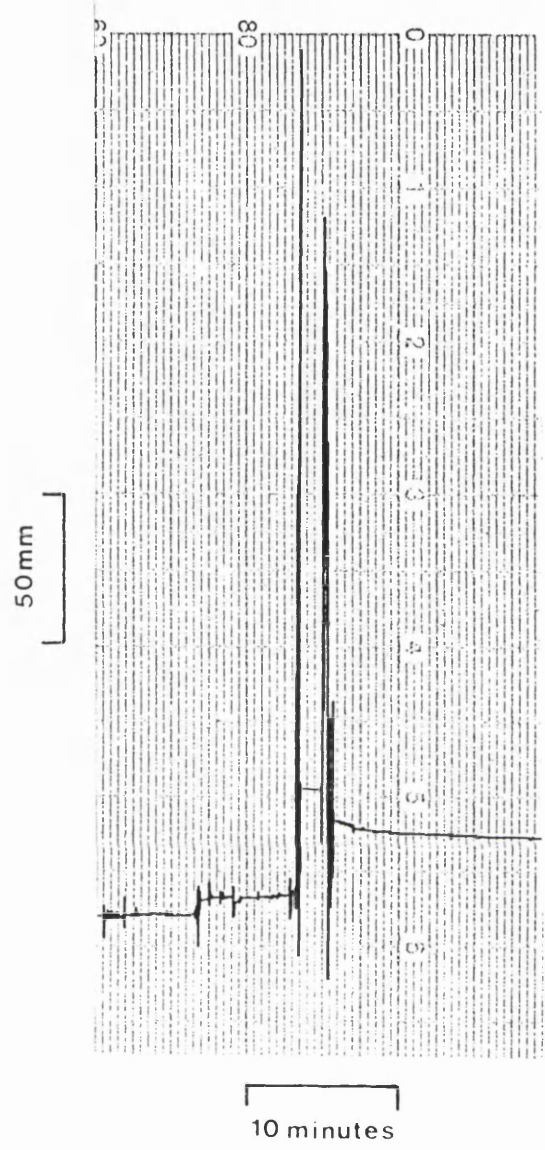
Figure 7   Characteristic trace of rising from and
returning to bed
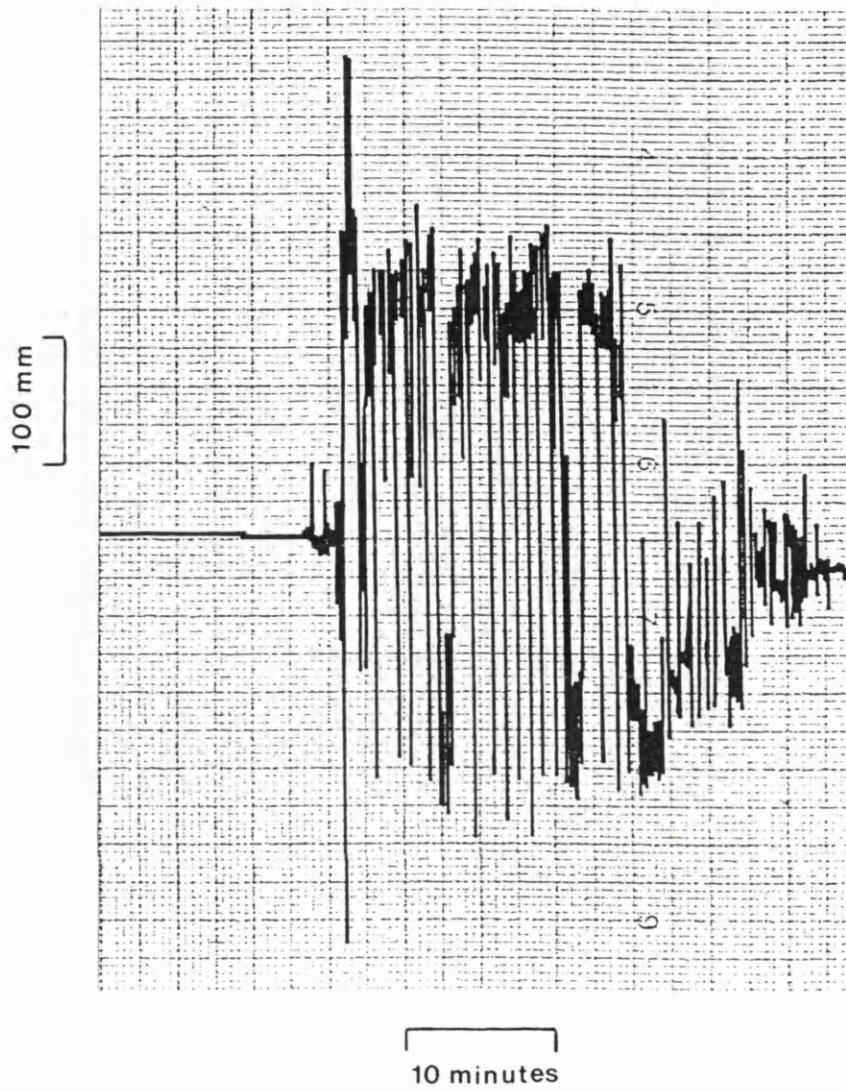
Figure 8   Trace showing an episode of considerable
movement (see text)

Movements were measured from the trace as the
vertical deflection of the pen in millimetres and
converted to absolute values of the movement of the
centre of gravity of the patient using the calibration
procedure described (page 132). The chart paper was
run through at a speed of 2mm per minute thus allowing
the timing of the moves to be calculated. Pen
deflections were only measured if they a) represented a
move of the patient's centre of gravity of greater than
4mm, b) were completed in less than 30 seconds, and c)
were sustained for at least 1 minute. The reasoning
for rule a) has been described above. Examination of
traces showed that occasionally there was a slow
curving movement of the pen which could not be
explained by a time lag of the pen mechanism (Figure
9a)). Experimentation showed that this was due to a
slow sliding of a part of the body from a particular
position once a movement had been completed. This was
considered to be involuntary movement and therefore not
included (rule b) above). Thus in Figure 9a) movement
AB would be measured but not BC. Deflections of the
pen could also occur as quick "blips" on the movement
trace, or as several unsustained movements surrounding
a larger move (Figure 9b)). It was therefore decided
that movements must be sustained for at least one
minute to be measured (rule c) above). In Figure 9b)
movement AB is not sustained for one minute, although
there has been a displacement of the baseline. The
displacement is sustained for at least one minute from

point C, thus the movement is measured as distance AC. Similarly, movement DE is not sustained for one minute and so the resulting displacement is measured as distance DF. An example of a movement trace and its analysis is shown later (page 142).
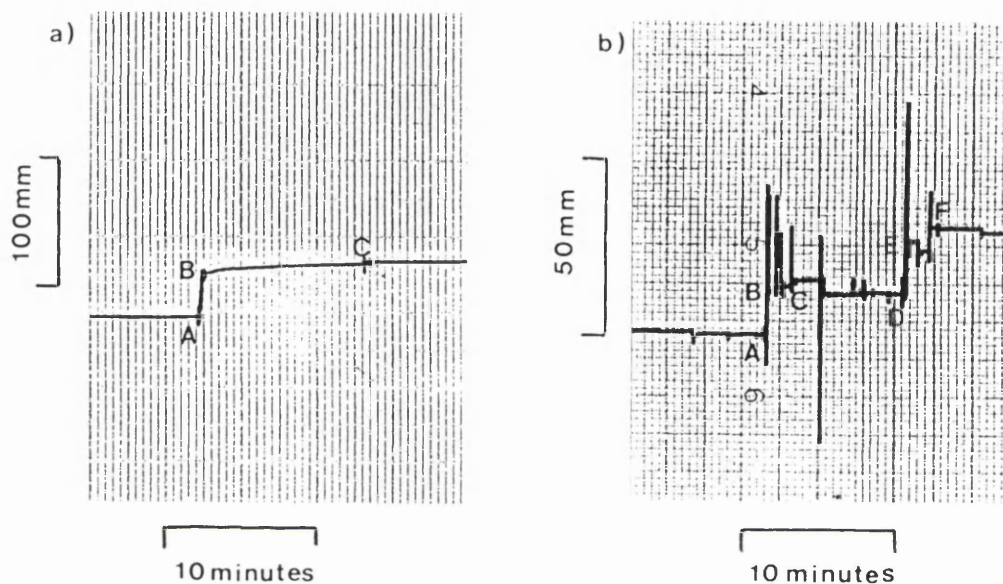
Figure 9   Examples of a) a slow pen deflection and
            b) unsustained movements

Movement data calculated from the record

    For each night studied the following were calculated:

a)   number of movements greater than 4mm per hour;

b)   number of movements greater than 10mm per hour;

c)   number of movements greater than 20mm per hour;

d)   total distance moved (mm) per hour;

e)   mean move size (mm) calculated as

$$\frac{\text{total distance moved per hour}}{\text{number of movements greater than 4mm per hour.}}$$

Example of the analysis of a movement trace

Based on the previous description, an example of the analysis of a movement trace is now given in some detail. The trace chosen is that obtained for patient 1 on the first night of the preliminary bed movement study.

The calibration procedure described previously (page 132) resulted in the trace shown in Figure 10. The calibration weight used in this case was 10kg moved over a distance of 930mm (the width of the bed) giving a pen deflection of 30mm.

Using equation 2 (page 134)

$$k = \frac{d}{ml}$$

$$= \frac{30}{10 \times 930}$$

$$= 3.23 \times 10^{-3} kg^{-1}.$$

Movements of the pen resulting in a deflection equivalent to a movement of the patient's centre of gravity of 4mm or less were not counted (rule a), page 140). Preliminary calculation of the minimum pen deflection to be analysed aided the process of trace analysis and was carried out as follows. In this case, the patient's weight, M, was 44.8kg. Using equation 1 (page 133) the pen deflection D equivalent to a 4mm
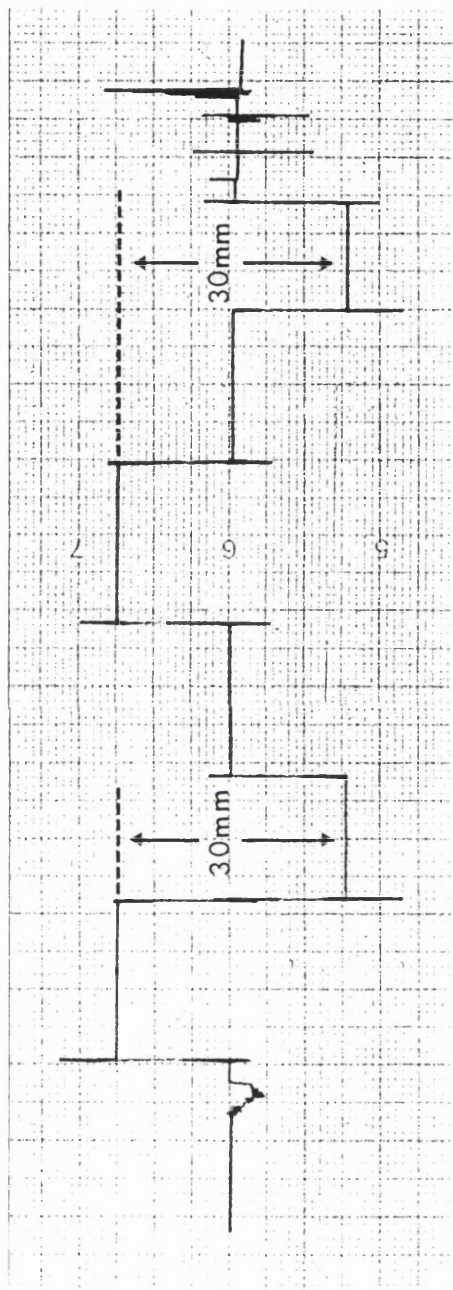
Figure 10   Calibration trace for bed movement monitor for patient 1 of the preliminary bed movement study

movement of the patient's centre of gravity

$$= kML$$

$$= 3.23 \times 10^{-3} \times 44.8 \times 4$$

$$= 0.6mm.$$

Hence, for this patient, only pen deflections greater than 0.6mm should be measured. Since it was only considered feasible to measure intervals of 0.5mm the smallest pen deflection measured in this case was taken as 1mm.

Figure 11 shows the trace obtained by monitoring patient 1 on night 1 beginning at 23.00h. as described on page 137. Move K had resulted from a complex of moves, none of which were sustained for more than 1 minute (rule c, page 140) but which resulted in an overall deflection of the baseline of 1mm. There were two sets of pen deflections (WX and YZ) that were characteristic of a patient getting in and out of bed. These occurred at the same times at which the nursing staff also recorded attending to the patient. Therefore the periods of time equivalent to WX (27.5 minutes) and YZ (25 minutes) were first eliminated (page 137) so the total time of movement trace actually analysed was 6.1 hours. A summary of this bed movement trace analysis is shown in Table 3.
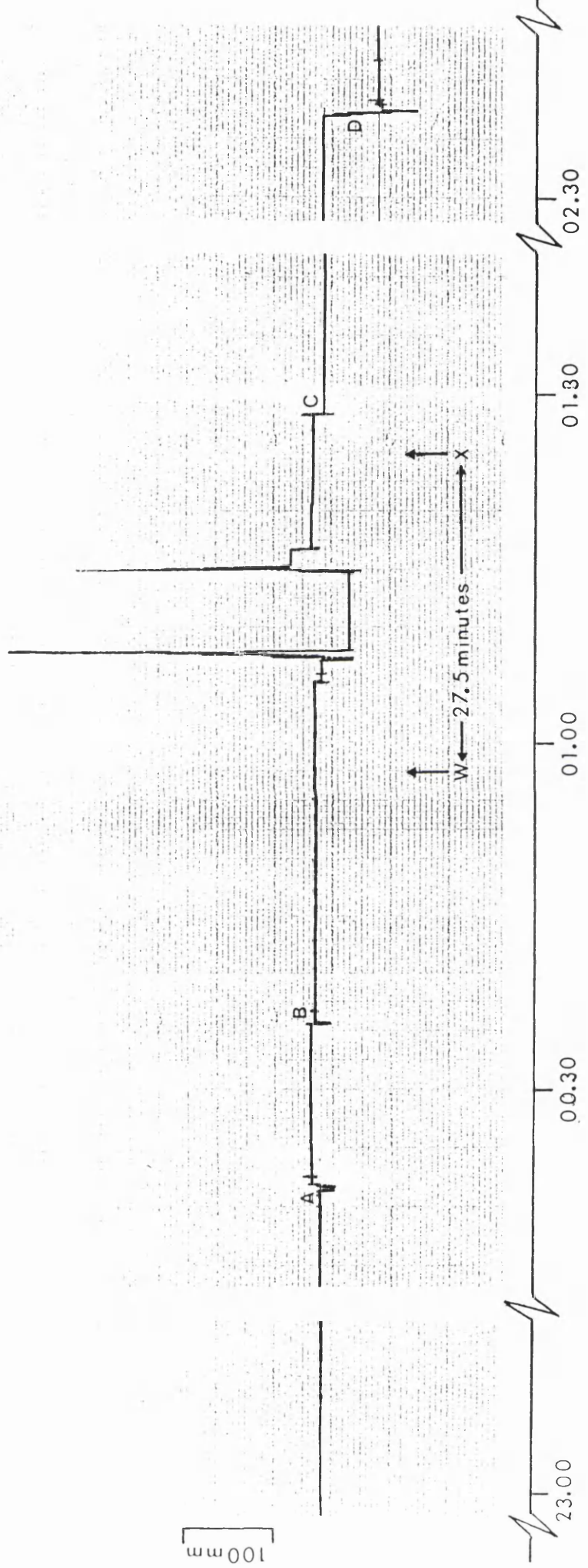
Figure 11   Trace of movement in bed for patient 1 of the preliminary bed movement study on the first night of study
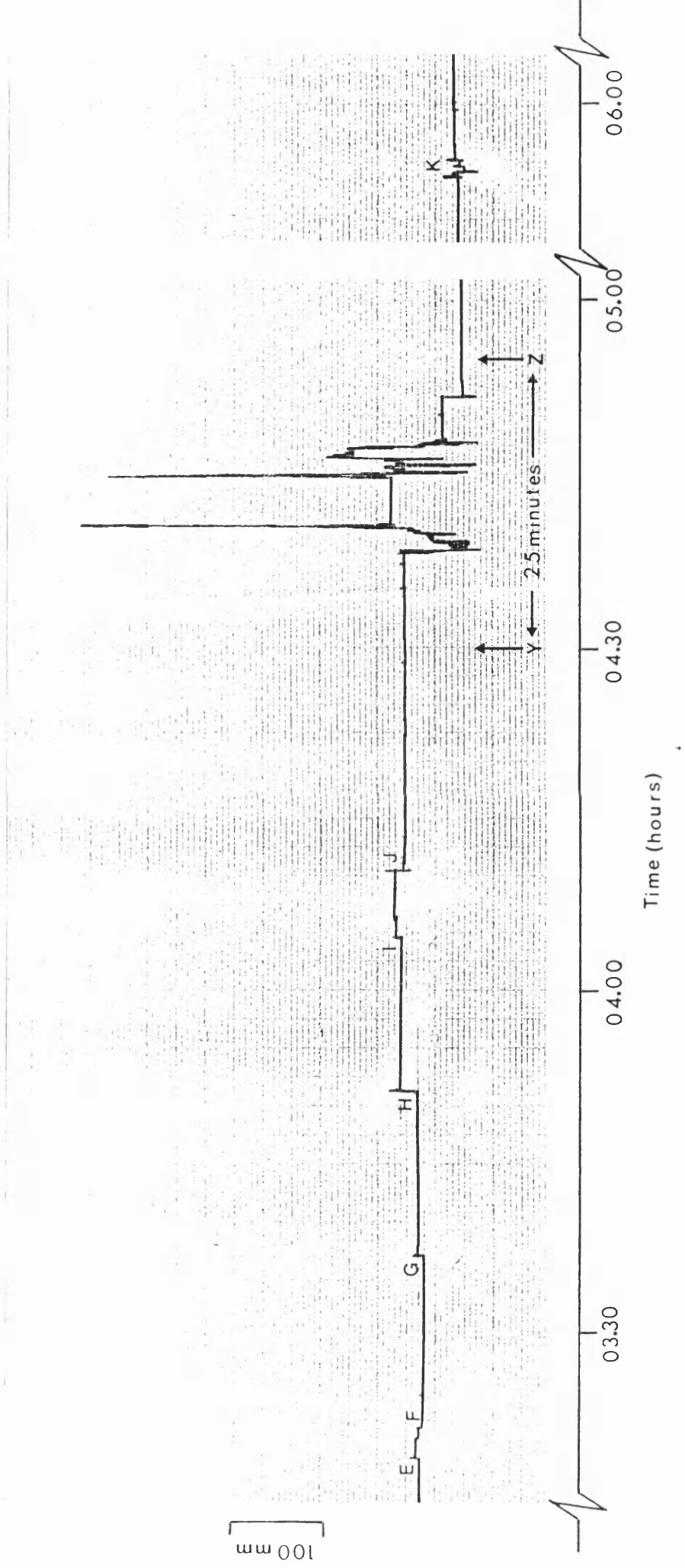
Figure 11 continued

Table 3   Analysis of the bed movement trace shown in
          Figure 11

Move	Pen deflection (mm)	Equivalent move of patient's centre of gravity (mm)
A	1.5	10.4
B	1.0	6.9
C	2.0	13.8
D	9.5	65.7
E	1.0	6.9
F	1.0	6.9
G	1.0	6.9
H	3.0	20.7
I	1.0	6.9
J	2.0	13.8
K	1.0	6.9

The following movement data for patient 1, night 1 (as reported in Appendix 7) could then be calculated.

a) number of movements greater than 4mm per hour

$$= \frac{11.0}{6.1} = 1.8 \text{ movements per hour}$$

b) number of movements greater than 10mm per hour

$$= \frac{5.0}{6.1} = 0.8 \text{ movements per hour}$$

c) number of movements greater than 20mm per hour

$$= \frac{2.0}{6.1} = 0.3 \text{ movements per hour}$$

d) total distance moved per hour

$$= \frac{165.8}{6.1} = 27.2 \text{mm}$$

e) mean move size = $\frac{\text{total distance moved per hour}}{\text{number of movements greater than 4mm per hour}}$

$$= \frac{27.2}{1.8} = 15.1 \text{mm}$$

The above movement trace was particularly straightforward to interpret and has been chosen to facilitate the illustration of the analysis and calculations involved. Many of the other traces produced were such that often just one hour of the trace would produce as many moves as were measured above. An example of an hour of such a trace is illustrated in Figure 12.
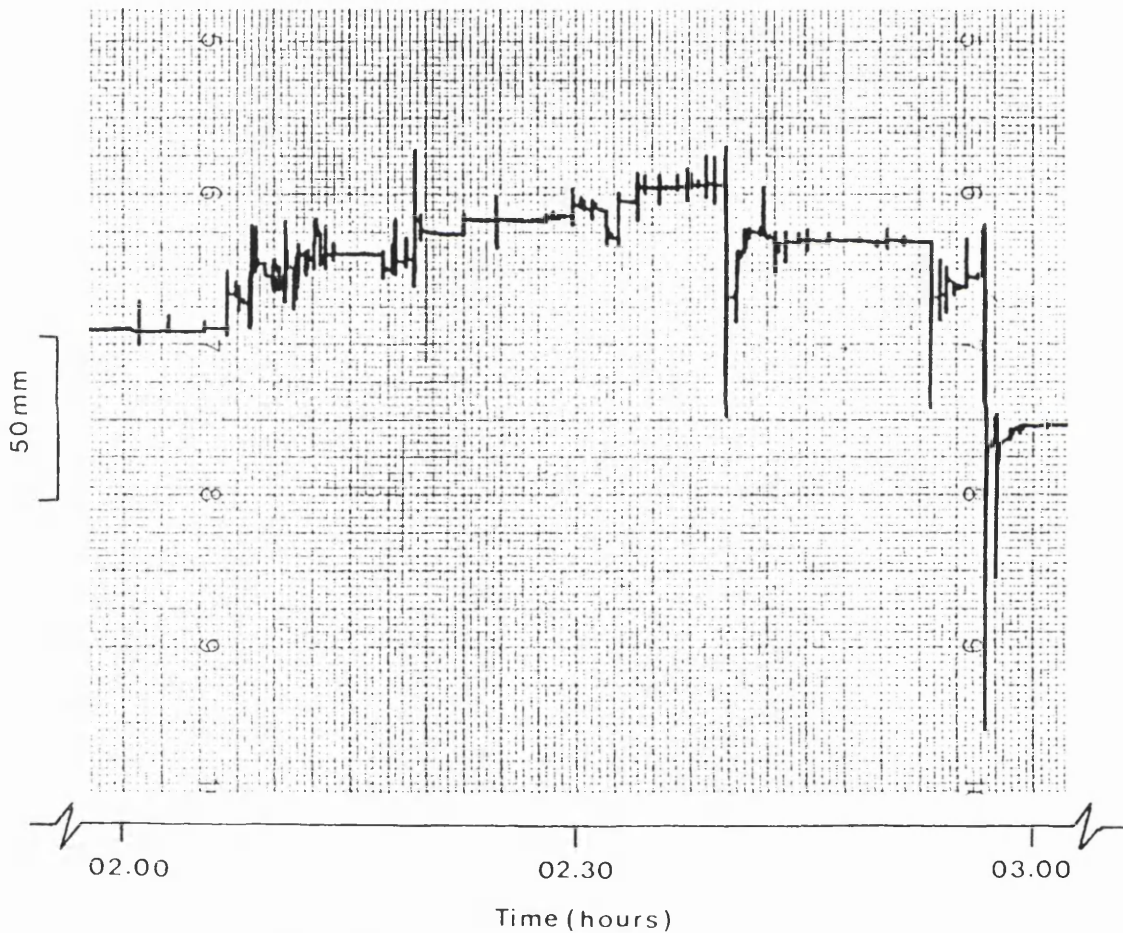
Figure 12   Example of an hour of a bed movement trace with more movement than that in Figure 11. This is part of the trace obtained for patient 22, preliminary bed movement study, night 1.

4.2 QUALITY OF SLEEP

Quality of sleep was assessed using a visual analogue scale consisting of a line from "the worst night's sleep I have ever had" on the extreme left, at zero, to "the best night's sleep I have ever had" on the right at 150mm (Appendix 8). A visual analogue scale was chosen rather than a rating scale because it is continuous in nature (page 96). Careful explanation of the concept of such a scale was given on each occasion it was used. Patients were instructed to mark the middle of the line if they considered their sleep had been normal on the previous night. If the night had been poor or good, the mark was to be made towards the left or right end of the line, at a distance representative of the grading. In addition, the author asked whether the patient had been disturbed by pain during the night.

4.3 TIME FOR TEN BLINKS

Although evidence exists for the dopaminergic control of blinking (page 54), blink rate does not appear to have been used previously as a measure of levodopa efficacy. As mentioned earlier (page 53), the rate of blinking is affected by the conditions under which it is measured. Standardisation of the test is therefore important. In this case patients were isolated from the ward as much as possible by closing the curtains around their bed and the measurements were carried out whilst the patient was engaged in quiet conversation, being asked the same questions in the same order each morning. These were as follows:

What was your night like?

What did you have for breakfast?

What do you think of the weather this morning?

What will you be doing today?

It was also considered important that the patient was not aware of the measurements being made. Although in the literature blink rates are usually quoted in the literature as the number of blinks per minute (page 52), initial experimentation showed that it would be very difficult for one person to count blinks, observe the stop watch and talk to the patient whilst keeping the test as unobtrusive as possible. In order that the author could carry out the measurements without help, the test was adapted so that the time taken for ten blinks was measured. The hand holding the stop watch

was concealed in the hip pocket of a white coat and the fingers were used to keep a tally of the number of blinks up to ten. The period of timing began with a blink and was ended on the tenth blink made by the patient. The time taken was then jotted down quickly on a piece of paper for subsequent transfer to the results sheet.

The initial protocol required four timings, at least one minute apart, to be carried out. However, it usually became necessary to terminate the test because the patient often became aware of being observed closely despite the precautions described above, or occasionally due to disturbances on the ward. In most cases it was possible to carry out three measurements before this occurred.

4.4 MANUAL DEXTERITY TEST

Tests of manual dexterity have been described (page
51). To encourage co-operation, it is necessary for
the elderly person to appreciate the relevance of a
test to their everyday life. For this reason a
buttoning task was chosen. This has the added
advantage of testing movements of pronation and
supination.

A standard set of buttons was manufactured by the
author using a series of buttons graded in size from
very large (36mm diameter) to very small (8mm
diameter). These were sprayed black so that colour
preference would not influence performance, and sewn on
to one long edge of a piece of canvas measuring 500mm
by 200mm. A corresponding series of buttonholes were
made in another piece of canvas of the same size. Both
pieces were lined with parachute material to minimise
stretching of the button holes with use. On each
occasion the set of buttons was laid out in front of
the patient by the author, with matching buttons and
button holes lined up and the largest button nearest
the patient. Patients were asked to do up the buttons
starting with the largest and proceeding down the sizes
to the smallest. After confirmation that the patient
was ready to begin, the following phrase was used to
start the test each time: "You may start". The stop
watch was started on the word "start". The time taken
to do up each button was noted. A maximum time of 2

minutes was set, after which the test was stopped,

regardless of the number of buttons done up. This

helped to avoid overtiring the patients and the

frustration felt by those unable to complete the task.

4.5 TIME TO WALK AN INDIVIDUALLY SET DISTANCE ("TIMED WALKING" TEST)

The use of walking tests has been discussed previously (page 61). The ability to walk is particularly important to the elderly person thus co-operation will be encouraged.

The test involved the measurement of the time taken by the patient to transfer from a chair, walk a set distance, return to, and transfer back into the chair. Each patient was required to walk the same distance on each occasion but because of different abilities the distance set was not the same for every patient. The author's experience of each patient's capabilities had been gained during routine outpatient clinic visits and the distance set was based on this. The test was carried out at the far end of the ward corridor which was mostly unused and therefore quiet. An upright chair with arms was placed at the end of the corridor and the distance to be walked marked by a sticker on the wall. Patients were asked to wear the same footwear and use the same walking aid, if needed, on each occasion. After sitting the patient down in the chair, the test was explained with a demonstration of the distance to be walked before turning round. Once the patient had confirmed that they were ready they were told to start with the phrase "you may start". The stop watch was started on the word "start". The author walked alongside the patient for safety and to

tell them when to turn round. The test ended and the
stop watch was stopped as soon as the patient had
settled comfortably back in the chair.

4.6 MEASUREMENT OF DISTANCE/TIME PARAMETERS OF GAIT
USING A "GAIT ASSESSMENT TROLLEY"

Principle of the apparatus

Objective methods of analysing gait have been discussed previously (page 55). The method of gait analysis used in this thesis was first described by Klenerman and Weller (1987).

A lightweight "gait assessment trolley" was towed behind the patient, by means of a 3 metre length of silk cord attached to the heel of the patient's footwear by two clips (Figure 13). The cord formed a "V" as it passed around a shaft encoder mounted on the trolley. The act of walking simultaneously transferred a length of cord from behind one foot to behind the other, rotated the shaft encoder and pulled the trolley along. The amount of cord transferred represented the distance moved by each foot. This was monitored by the shaft encoder whilst the direction of its rotation indicated whether movements were of the right or left foot. A battery powered infra-red transmitter sent the encoded information to a receiver and chart recorder. Gait on a given occasion was represented by a single trace of distance against time, upward and downward deflections being proportional to distances moved by the left and right foot respectively.

<u>Figure 13</u>   Gait assessment trolley in use

<u>Calibration of the apparatus</u>

Calibration of the trolley by moving the cord
through a known distance enabled absolute distance
measurements to be calculated. The apparatus was set
up as if it were to be used by a patient. Stickers
were laid out on the floor at 20cm and 40cm intervals
(Figure 14) and the clips pulled by hand to these marks
to simulate a step by the patient. As can be seen from
the calibration traces in Figure 14, movement of clip 1
from i) to ii) on the floor resulted in deflection AB
on the trace, movement of clip 2 from iii) to iv)
resulted in deflection CD and finally movement of clip

1 from ii) to v) resulted in deflection EF. This
procedure was carried out three times and the mean
deflection of the pen calculated. Thus for the traces
shown in Figure 14 movement of the cord through 40cm
resulted in a mean deflection on the trace of 35.8mm.
A 1mm deflection of the pen would therefore be
equivalent to a movement of the cord of 1.12cm.
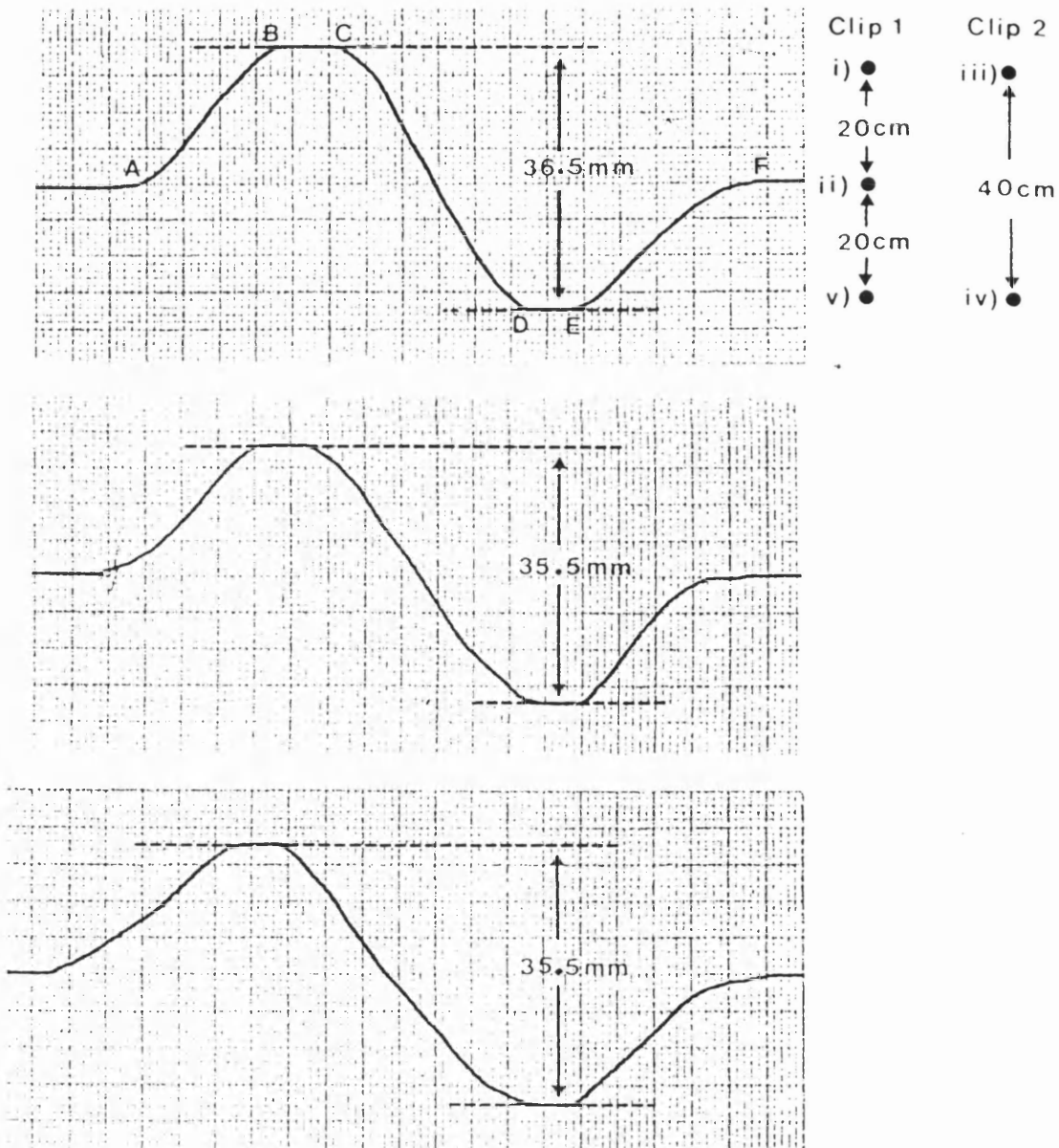
Figure 14   An example of a calibration

Use of the apparatus

The test was carried out at the quiet end of the ward corridor. The apparatus was set up with the gait assessment trolley positioned on the floor in front of the chart recorder and the cord round the shaft encoder on the trolley then stretched out until the two clips were level with each other. The patient was then brought to the test area, the procedure explained and the clips attached to their footwear whilst they were standing with their feet together. Patients were required to wear the same footwear and to use the same walking aid, if needed, on each occasion. Once the patient had confirmed that they were ready they were told to start with the standard phrase "you may start". The chart recorder was switched on as the word "start" was said. The author then walked beside the patient both for safety reasons and to tell them when they had reached the predetermined distance. The clips were then removed from their footwear and the patient was assisted to a nearby chair. The chart recorder was then switched off. The distance walked depended on individual patients' abilities but was constant for each patient as far as possible. Two patients (numbers 1 and 8, daytime Sinemet-Plus study) suffered from severe Parkinson's disease and were not always able to complete even the short distance set for them.

Analysis of the trace

An illustration of a typical trace of distance against time representing gait on a given occasion is shown in Figure 15.
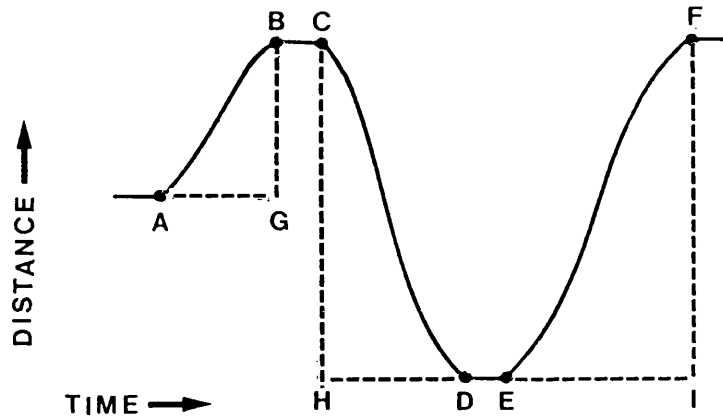
Figure 15 An illustration of a trace representing gait on a given occasion

On the above trace, points A, C and E correspond to the left foot, the right and left again being lifted off the ground and B, D and F, a foot striking the ground. A left step of length BG is followed by a right swing, CH, and then a left, IF. BC and DE are double support times, and HD and EI are swing times. Distance measurements from the trace in mm were converted into the distance in cm moved by the patient's foot by multiplying by 1.12 (see calibration, page 157), and those of time in mm were converted to seconds by dividing by 20, the chart paper being run through at a speed of 20mm per second. In many cases it was noticed that patients took several steps to build up into a regular pattern of gait. This was not

evident when the trolley was used by normal controls of similar age. A period of "steady state" gait was therefore defined by drawing lines to join the points of initial contact of the right and left feet with the ground on the distance/time plot from the time of initiation of gait (W to Z, X to Y, Figure 16) such that the lines were not crossed by any part of the trace. The last foot strike (Z, Figure 16) to touch either of the lines was taken to signal the start of "steady state" gait.

The following parameters were calculated for each trace:

a) swing length (cm) and double support time (seconds) for the entire walk and the first four swings at "steady state";

b) swing time (seconds) for the first four swings at "steady state" only;

c) cadence as the number of swings per minute for the entire walk;

d) speed of walking (cm/second) for the entire walk.

Traces were analysed entirely by hand by the author. It was therefore not considered feasible to calculate swing time for the entire walk as well as swing length and double support time.
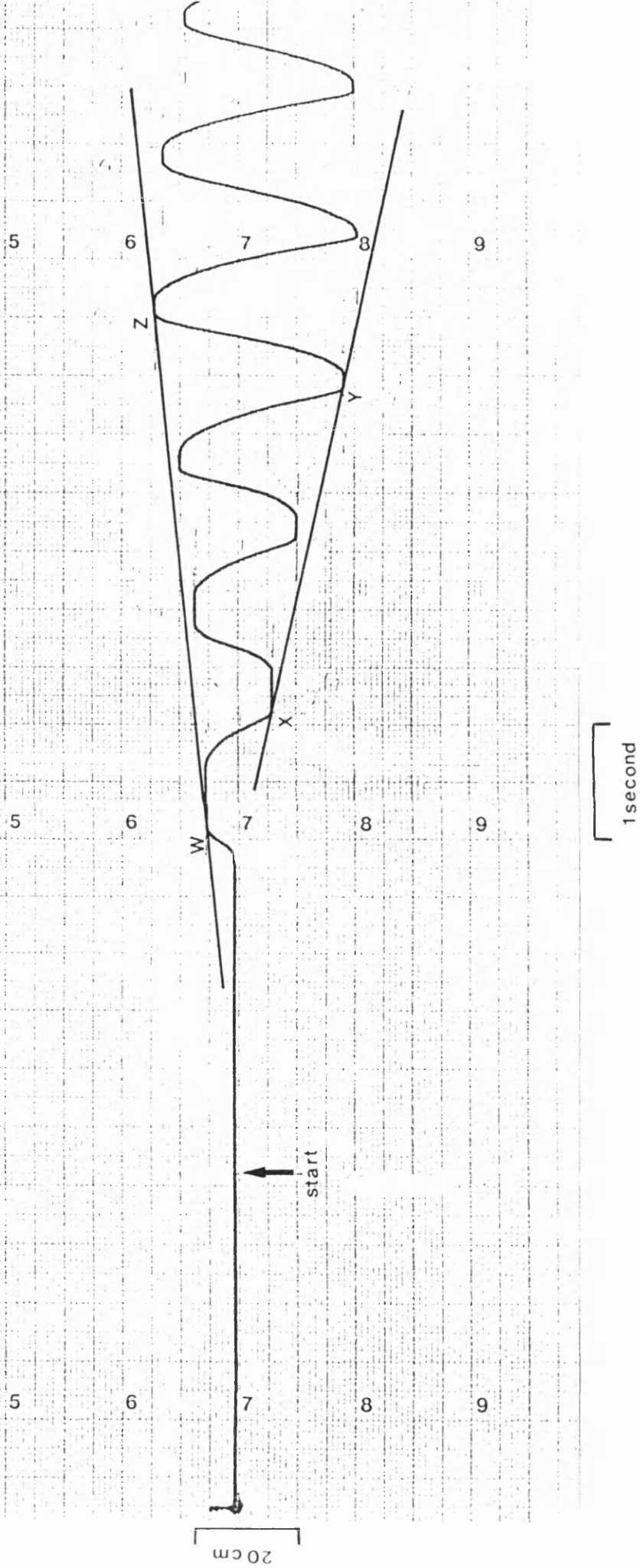
Figure 16 Determination of "steady state" gait. This is part of the trace obtained for patient 9 of the daytime Sinemet-Plus study at the 4 hour post-dose time point on the first day of study.

Example of the analysis of a gait trace

Based on the previous description, an example of
the analysis of a gait trace is now given in some
detail. The trace chosen is that obtained for patient
3 in the daytime Sinemet-Plus study at the 0 hour (pre-
dose) time point on the first day of study and is shown
in Figure 17.

For the purposes of this study, only full swings
were measured therefore the first and last steps were
not counted. The analysis of the entire walk thus
starts at point A on the trace and ends at point k.
Although it was possible to determine whether a left or
right foot was being moved, no distinction between
these was made in this study. As stated previously,
double support time and swing length were calculated
for the entire walk. The analysis of these parameters
for the trace in Figure 17 is shown in Table 4. Double
support time kl was considered to belong to the last
step and therefore was not counted. Distance/time
measurements as represented by deflections on the trace
in mm are reported in Appendix 29.
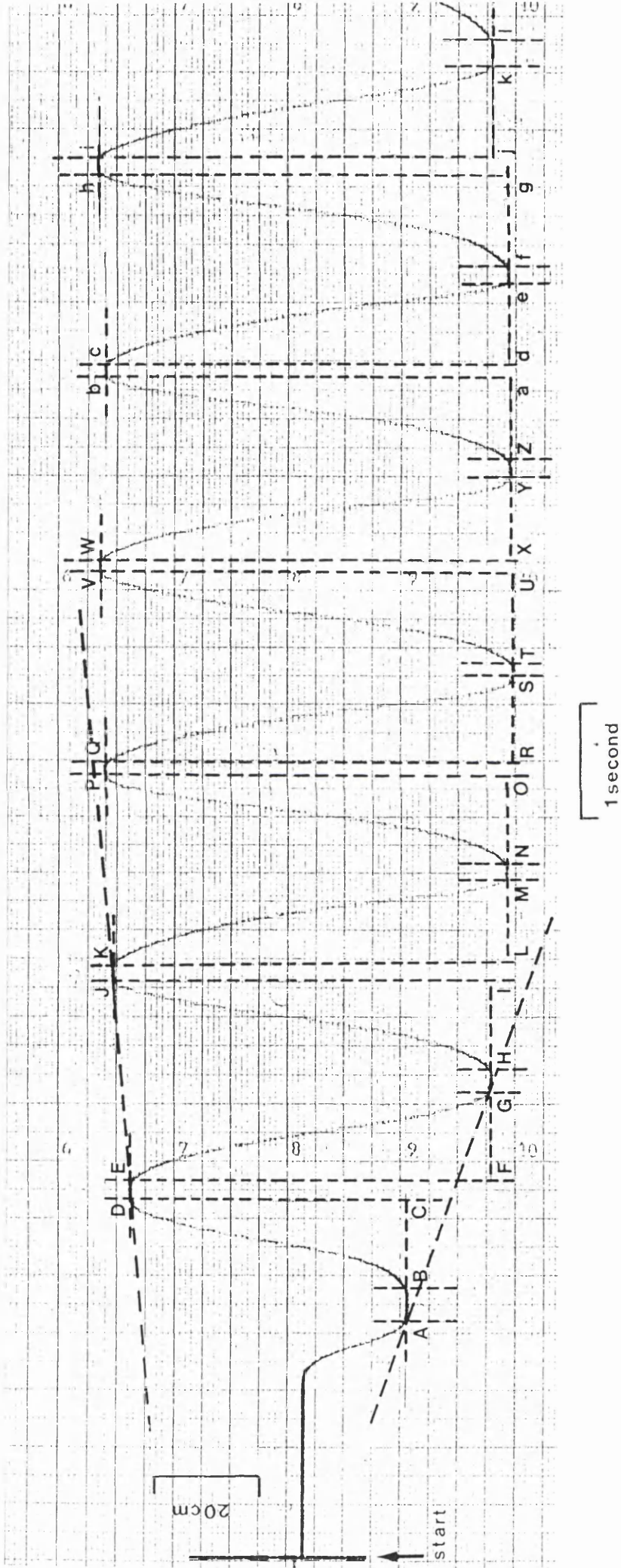
Figure 17 Gait trace obtained for patient 3 of the daytime Sinemet-Plus study at the 0 hour (pre-dose) time point on the first day of study

Table 4   Analysis of double support time and swing
          length for the trace shown in Figure 17 for
          the entire walk

Double support time			Swing length		
Point on trace	mm on trace	Actual value (seconds)	Point on trace	mm on trace	Actual value (cm)
AB	6	0.300	CD	49	54.9
DE	3	0.150	EF	63.5	71.1
GH	4	0.200	IJ	66	73.9
JK	3	0.150	KL	69	77.3
MN	3	0.150	OP	70	78.4
PQ	2	0.100	QR	72	80.6
ST	2	0.100	UV	73	81.8
VW	2	0.100	WX	72	80.6
YZ	3	0.150	ab	71	79.5
bc	2	0.100	cd	71	79.5
ef	3	0.150	gh	71	79.5
hi	3	0.150	ij	69	77.3

Cadence and speed of walking were also calculated
over the entire walk. Cadence (number of swings per
minute) was calculated directly from the trace. For
this trace, the length of trace analysed was 218mm
(distance Ak) which for the given chart speed was
equivalent to a time of 10.9 seconds. The number of
swings in this time was 12 thus

$$cadence = 12 \text{ swings}/10.9 \text{ seconds}$$

$$= 66.06 \text{ swings per minute.}$$

Speed of walking (cm per second) was estimated from
the trace by adding together the swing lengths of one
foot, in this case the left one. For this trace the
actual distance walked by the patient as measured by

the sum of the swing lengths of the left foot (CD + IJ + OP + UV + ab + gh) = 400 x 1.12cm = 448.0cm. The time taken to travel this distance

$$= \frac{\text{distance Ah on the trace}}{\text{chart speed}}$$

$$= \frac{199}{20}$$

$$= 9.95 \text{ seconds.}$$

Thus the speed of walking = 448.0cm/9.95 seconds

$$= 45.03\text{cm/second.}$$

These values are given in Appendix 30.

The mean (sd) double support time, swing length and swing time for the first four swings of "steady state" gait were also calculated from the trace. Applying the method of determination of "steady state" gait as described on page 161, "steady state" gait on this trace starts at point J. Values arising from this analysis are reported in Appendices 31, 32 and 33, and summarised in Table 5.

Table 5　Analysis of double support time, swing length and swing time for the trace shown in Figure 17 for the first four swings of "steady state" gait.

Double support time			Swing length			Swing time		
Point on trace	mm on trace	Actual value (seconds)	Point on trace	mm on trace	Actual value (cm)	Point on trace	mm on trace	Actual value (seconds)
JK	3	0.150	KL	69	77.3	LM	15	0.750
MN	3	0.150	OP	70	78.4	NO	15	0.750
PQ	2	0.100	QR	72	80.6	RS	16	0.800
ST	2	0.100	UV	73	81.8	TU	15	0.750
Mean		0.125			79.5			0.763
(sd)		(0.029)			(2.0)			(0.025)

4.7 PEDOBAROGRAPHY

Principle of the apparatus

The pedobarograph measured the distribution of pressure under a foot when it made contact with the ground. The method used in the present study was first described by Chodera (1957). Changes in pressure during walking were analysed using the computerised system of Betts (1980). The equipment used a simple optical principle. A thick glass plate, with a plastic sheet (elastic foil) over the top surface and pressure transducers under each corner, was illuminated by fluorescent tubes along two opposite edges. A mirror, monitored by a video camera, was inclined at 45° beneath the glass plate (Figure 18).

The light illuminating the glass plate was totally internally reflected within the glass. When pressure was applied to the plastic sheet on top of the glass, the conditions necessary for total internal reflection were destroyed locally. Light therefore escaped, the amount being proportional to the pressure applied (Figure 19). The amount of pressure applied, and the amount of light escaping, were monitored by the pressure transducers and video camera respectively. Signals from these were then analysed by the computer.
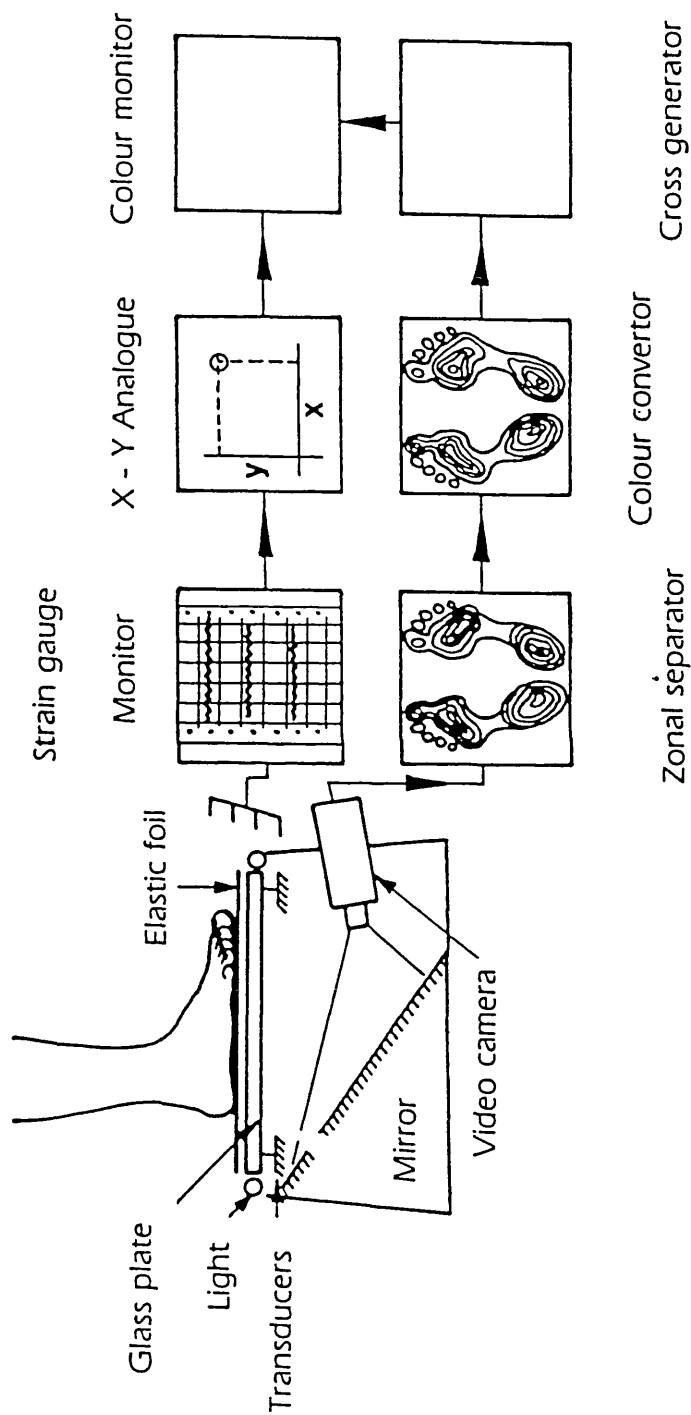
Figure 18   Schematic diagram of the pedobarograph

No pressure

Elastic foil

Pressure applied

Reflected light

No visible light

Glass plate

Totally reflected light

Light source

Shielding
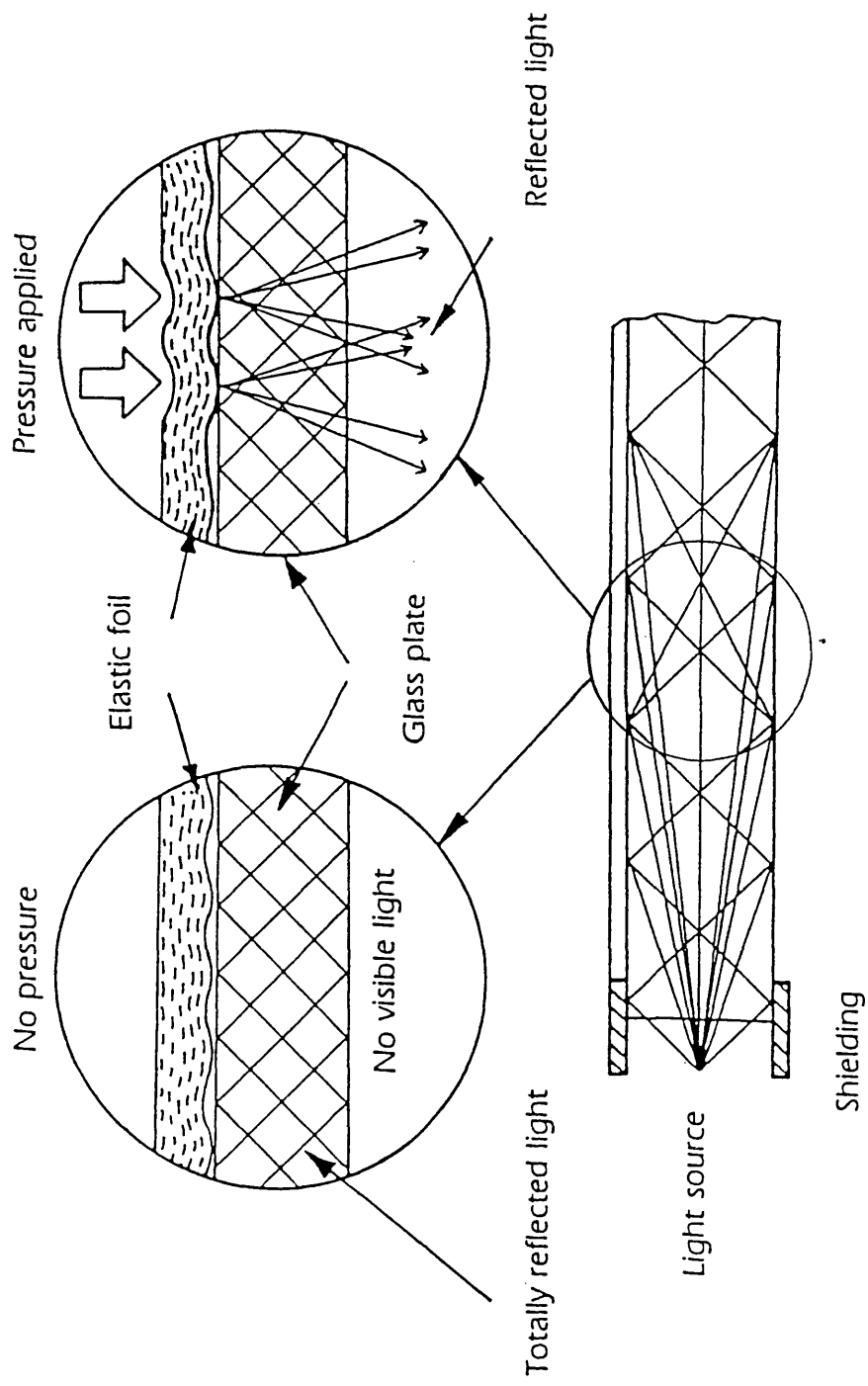
Figure 19   Principle of the pedobarograph

The computer printout of the pedobarograph
displayed frame by frame contour pictures of the
distribution of pressures under the foot throughout the
footstep, and also a combined frames contour picture,
which gave the distribution of the highest pressures
recorded from the time a foot first made contact with
the pedobarograph plate to when it was lifted off.
Various areas of interest could be chosen, and graphs
of pressure against time were drawn for these areas.

Use of the apparatus

A specialist operator was required to operate the
pedobarograph and the video equipment. However the
author was responsible for the explanation, assistance
and supervision which was necessary for the patient to
perform the test successfully bearing in mind that many
of the patients were considerably disabled. Subjects
having pedobarograph assessments are usually asked to
walk over the glass plate in bare feet at their normal
walking speed. Practice walks identify a starting
position from which one foot will land on the plate
without adjustment of gait. However this method could
not be used for the current patients for two reasons.
Firstly, many of the patients were not able to walk
very far and secondly, it was observed that asking
these patients to try to place one foot on the plate
resulted in an inhibition of movement. These patients
were therefore just asked to walk along the walkway in
bare feet with no mention of the glass plate and were

encouraged to look straight ahead rather than at the
floor. After observing two or three walks the
experienced operator was able to adjust the starting
position if necessary to increase the likelihood of a
foot landing on the plate. Recordings were continued
until a maximum of 10 steps had been recorded. Ideally
an equal number of right and left footsteps would be
recorded. In most cases however the test had to be
terminated due to the patient becoming tired.

Analysis of the printout

With the assistance of the operator, the printouts
were interpreted in order that the part of the foot
first making contact with the ground could be
determined. Figures 20 to 23 show examples of the
combined frames picture obtained, the areas of interest
specified and the graphs of pressure against time for
these areas. The closed arrows indicate the time of
heel strike and the open arrows that of forefoot
strike.

The nature of the initial contact between foot and
ground during walking may be affected by Parkinson's
disease. Normally the heel strike preceeds contact by
the forefoot (Figure 20). In Parkinson's disease, heel
strike may occur at the same time as that of the
forefoot (Figure 21), or even succeed it (Figure 22).
At worst, only the forefoot and toes make any contact
with the ground (Figure 23).

COMBINED FRAMES

AREAS OF INTEREST

10

PRESSURE
KG/SQ CM

5

0

0   0.5   1.0

TIME (S)
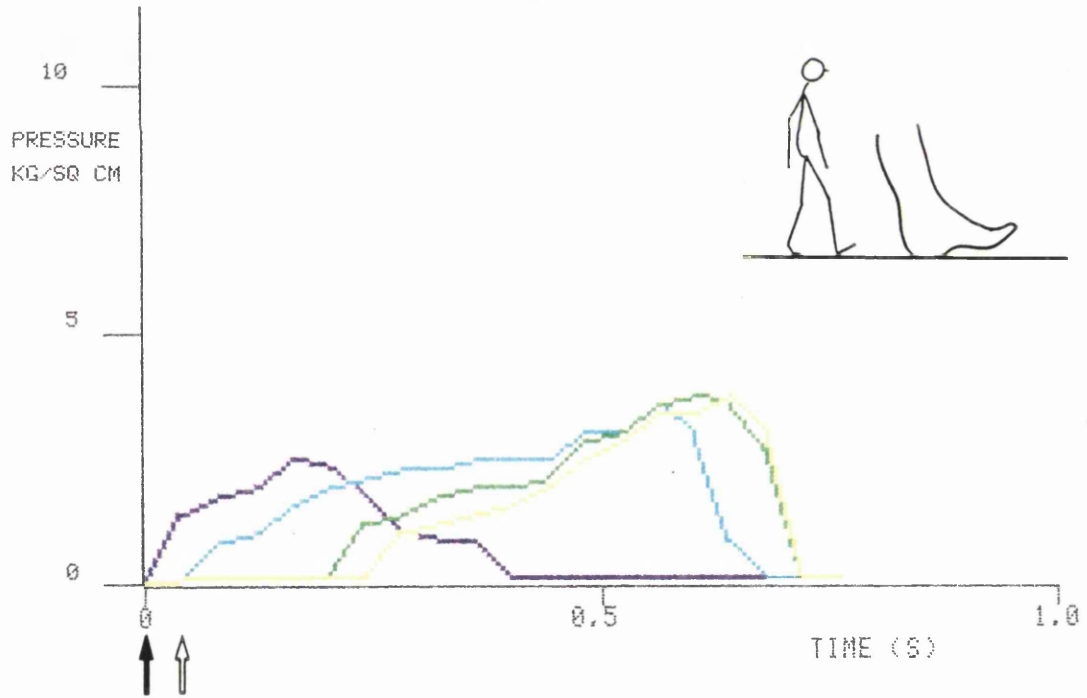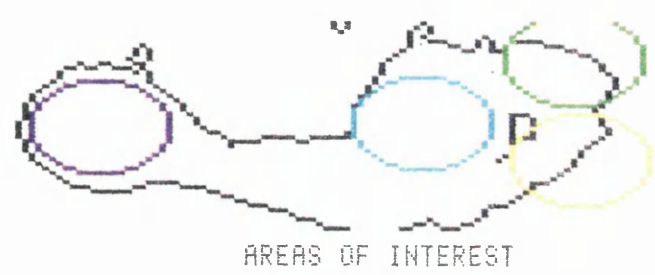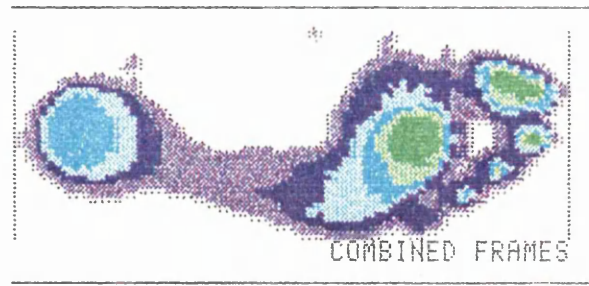
Figure 20   Pedobarograph of the heel striking the
             ground first

COMBINED FRAMES

AREAS OF INTEREST

PRESSURE
KG/SQ CM

10

5

0

0   0.5   1.0

TIME (S)
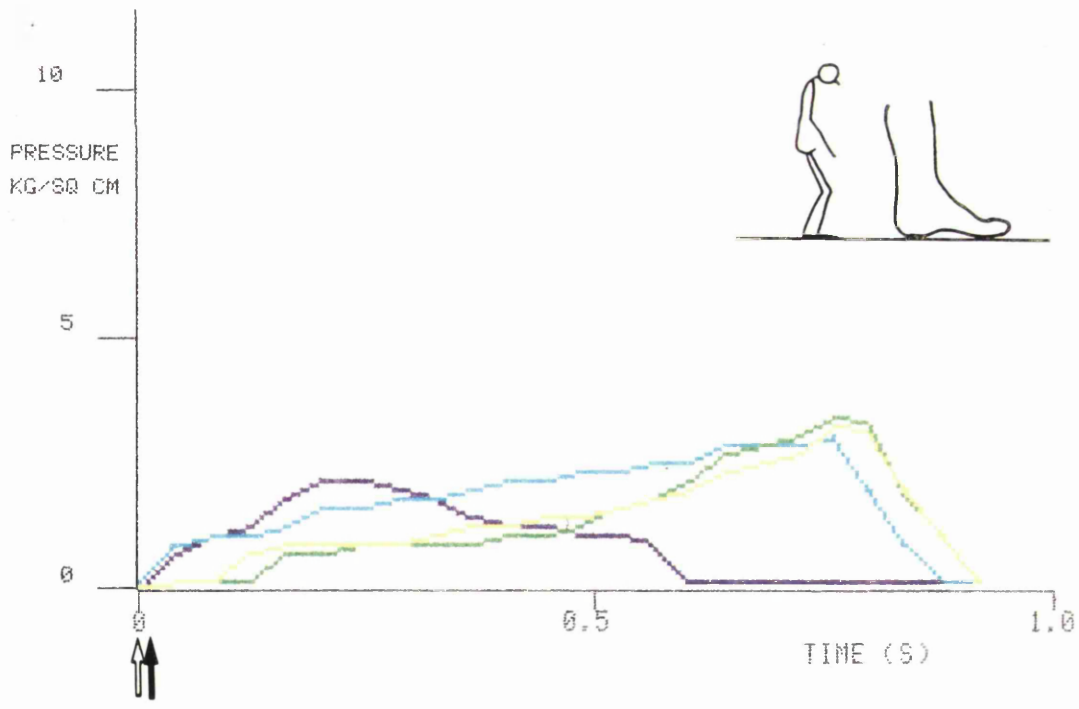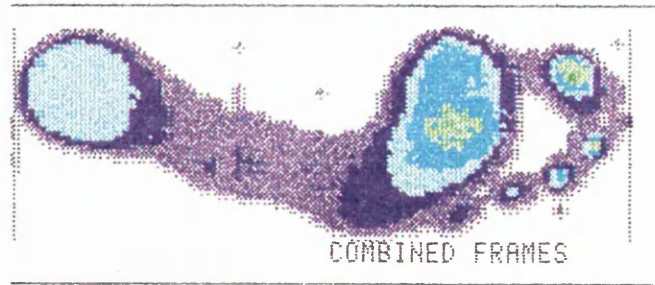
<u>Figure 21</u>   Pedobarograph of the heel and forefoot
striking the ground simultaneously

COMBINED FRAMES

AREAS OF INTEREST

10

PRESSURE
KG/SQ CM

5

0

0   0.5   1.0
                    TIME (S)
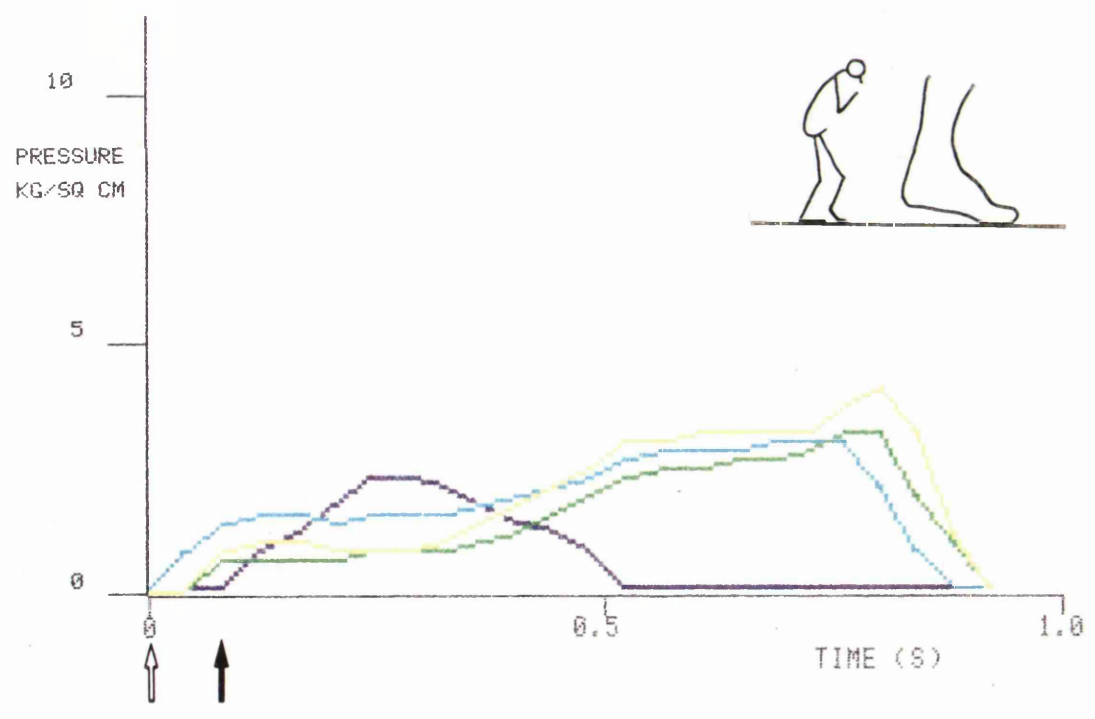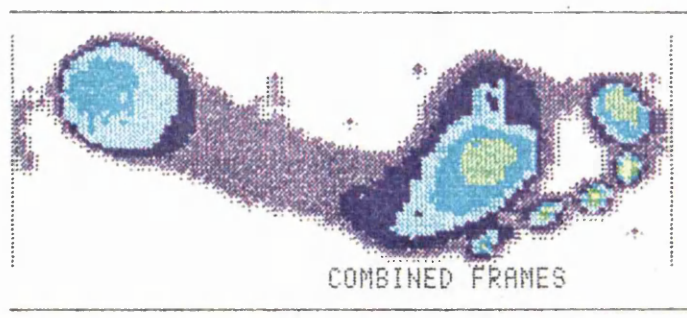
Figure 22   Pedobarograph of the forefoot striking the
            ground first

COMBINED FRAMES

AREAS OF INTEREST

PRESSURE
KG/SQ CM

TIME (S)
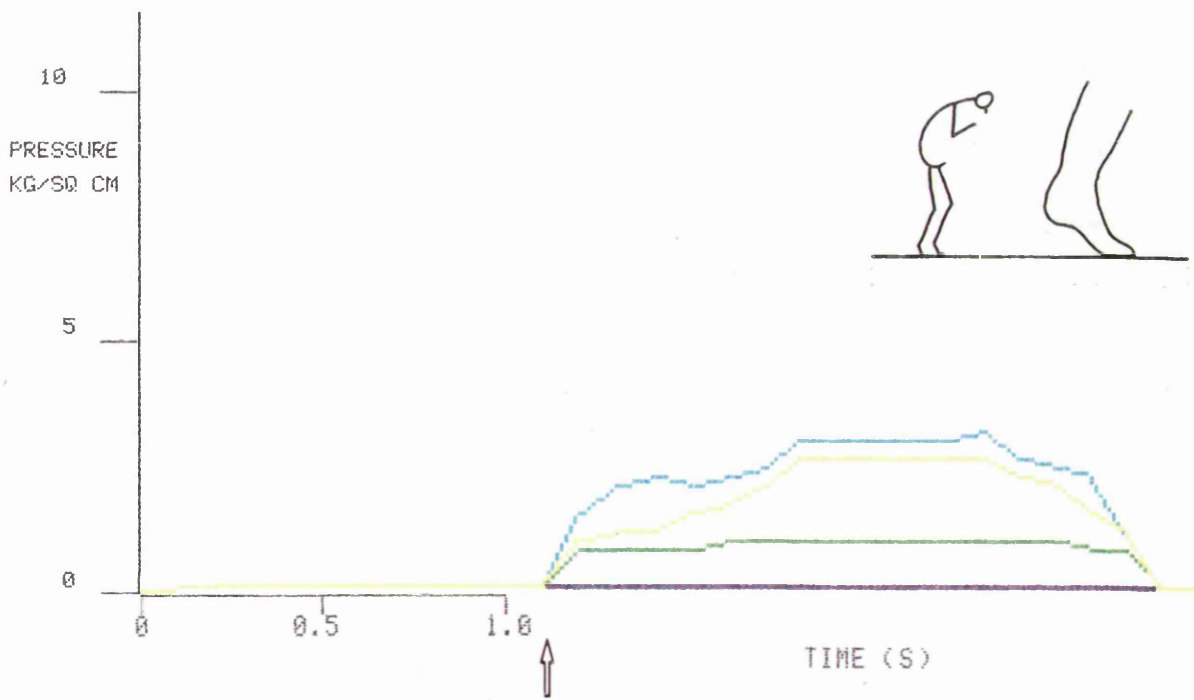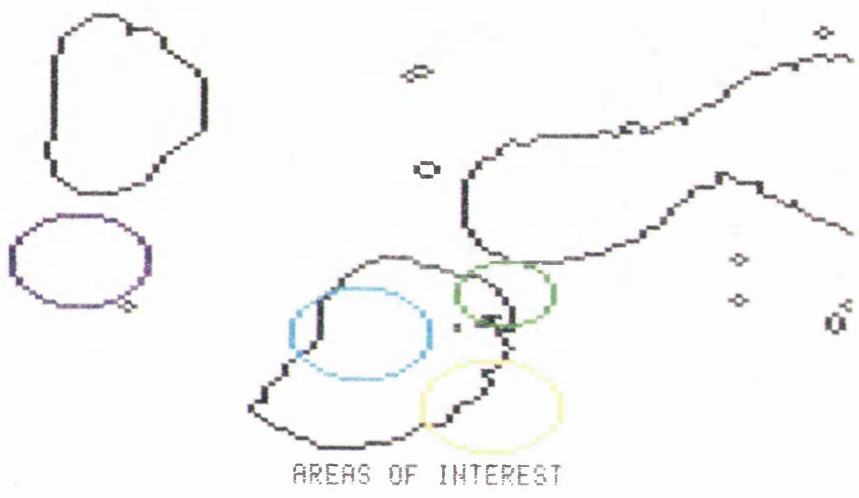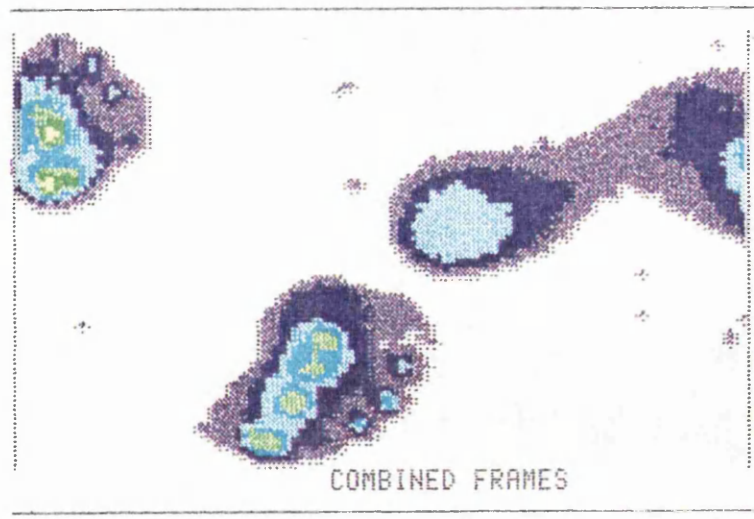
Figure 23   Pedobarograph of only the forefoot and toes
making contact with the ground

A simple index of foot strike was devised by the
author to produce a single value to describe the
"normality" of the patient's gait on each occasion.
Each step was scored according to the nature of foot
strike as follows.

Nature of foot strike	Score
Heel strike	1
Simultaneous heel and forefoot strike	0.5
Forefoot strike	0

The foot strike index was then calculated as:

$$\frac{(\text{number of heel strikes}) + (\text{number of simultaneous heel and forefoot strikes}/2)}{\text{total number of steps studied}}$$

An index of 1 is normal, whereas one of 0 implies the
initial strike is always with the forefoot.

4.8 VIDEO RECORDING

Video recordings were also made of the patient walking in bare feet along the pedobarograph walkway. The camera was positioned at foot level, 2 metres from the patient. The recordings showed the lower half of the body. Patients were not aware of the recordings being made at the time. All recordings were assessed on the same occasion at a later date by an independent assessor blind to the patients' treatment, using a slow playback facility. The patient's overall performance on the two occasions was compared. Scores of 0 or 1 were awarded, a score of unity being given to the better performance. The nature of foot strike for 6 consecutive steps was also independently assessed, and the index of foot strike (page 177) recalculated using this data.

4.9 HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY OF LEVODOPA AND ITS METABOLITES

The method of analysing plasma concentrations of levodopa and its metabolites using ion-pair, reversed-phase high-performance liquid chromatography (HPLC) with electrochemical detection used in this thesis was developed by Dr. S. Bowes, from the method of Benedict and Risk (1984). Although the assay was developed to be capable of analysing other metabolites of levodopa, for the purposes of the present study it was used only to measure plasma concentrations of levodopa and 3-O-methyldopa. Dr. Bowes analysed the plasma samples of four of the patients whilst the author was responsible for analysing the samples of the remaining nine patients in the study of daytime movement.

Materials and reagents

Levodopa and carbidopa were obtained from Merck Sharp and Dohme Limited, Hoddesdon, Hertfordshire. Dopamine (DA), 3,4-dihydroxyphenylacetic acid (DOPAC), adrenaline, noradrenaline, 3-O-methyldopa (3OMD), homovanillic acid (HVA), dihydroxybenzylamine (DHBA), 5-hydroxy-DL-tryptophan (5-HTP) and heptane sulphonic acid (HSA) were purchased from Sigma Chemical Company Limited, Poole, Dorset, and sodium metabisulphite, ethylenediaminetetraacetic acid (EDTA) and ammonium acetate from BDH Chemicals Limited, Poole, Dorset.

Perchloric acid and tris(hydroxymethyl)methylamine

(TRIS) were obtained from Fisons PLC, Loughborough,

Leics. Methanol was of HPLC grade, purchased from

Rathburn Chemicals Limited, Walkerburn, Scotland.

Methods

The extraction from plasma of the compounds of

interest was achieved by deproteinisation with ice cold

perchloric acid, followed by separation of

catechol-containing molecules on phenylboronic acid

(PBA) cassettes (Bond Elut, Analytichem International,

Jones Chromatography Ltd., Llanbradach, Mid-Glamorgan)

as follows. Ten per cent sodium metabisulphite (10µl),

ice cold 4M perchloric acid (60µl) and ice cold

internal standard mixture (600µl; 500ng/ml

dihydroxybenzylamine (DHBA) plus 200ng/ml 5-hydroxy-DL-

tryptophan (5-HTP) in 0.4M perchloric acid) were added

to a 600µl aliquot of plasma. The mixture was vortexed

and left on ice for 20 minutes. The precipitated

protein was removed by centrifugation (MSE Coolspin) at

1720g for 10 minutes at room temperature. An 800µl

aliquot of the supernatant was neutralised (pH 7 to 8)

with 2M tris(hydroxymethyl)methylamine (TRIS; 200µl),

and the neutralised solution applied to PBA cassettes

primed with methanol (1ml) followed by 0.2M TRIS (1ml).

At this pH, molecules containing catechol groups are

bound to the PBA, and the initial eluate from the PBA

cassettes (first extract) contained 3OMD, HVA and 5-HTP

which do not bind. The cassettes were then washed with

methanol (1ml) and 0.2M TRIS (1ml) before elution of
the catechol compounds with 0.2M perchloric acid
containing 0.25 per cent ethylenediaminetetraacetic
acid (EDTA; 1ml). These acid extracts were analysed
separately from the first extracts.

The HPLC system comprised a Varian Vista 5560
liquid chromatograph, with a Rheodyne 7125 injection
valve fitted with a 100μl loop. Separation of
compounds in the acid extracts was effected on a column
(250mm x 4.5mm) packed with 5μl Hypersil
Octadecylsilane (ODS; Shandon Southern Products
Ltd., Runcorn, Cheshire) with a mobile phase of 0.1M
ammonium acetate, 0.27mM EDTA, 0.05mM heptane sulphonic
acid (HSA), adjusted to pH 5.20 with glacial acetic
acid, at a flow rate of 1.2ml/minute. The eluent was
monitored with an ESA Coulochem Model 5100A detector
attached to an ESA Model 5011 analytical cell, at an
applied potential of +0.40V. The mobile phase was
recycled. The first extracts were analysed similarly,
but with a mobile phase of 85 per cent buffer (as
above) and 15 per cent methanol at a flow rate of
1.2ml/minute. This mobile phase was not recycled.
Both mobile phases were filtered through Millipore
0.45μm filters (Millipore (UK) Ltd., Harrow,
Middlesex). Examples of the traces obtained are shown
in Figures 24 and 25.
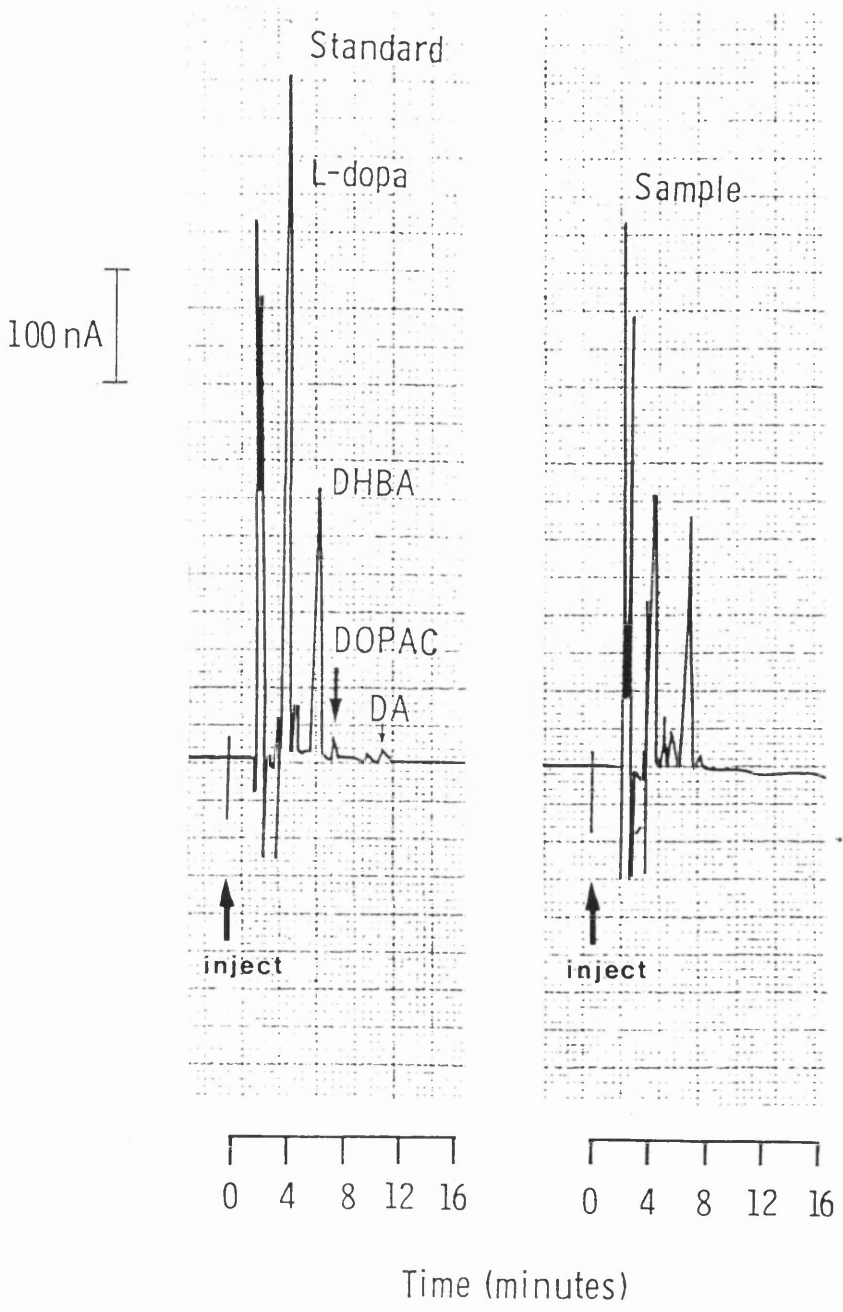
Figure 24   Example of an HPLC trace for levodopa
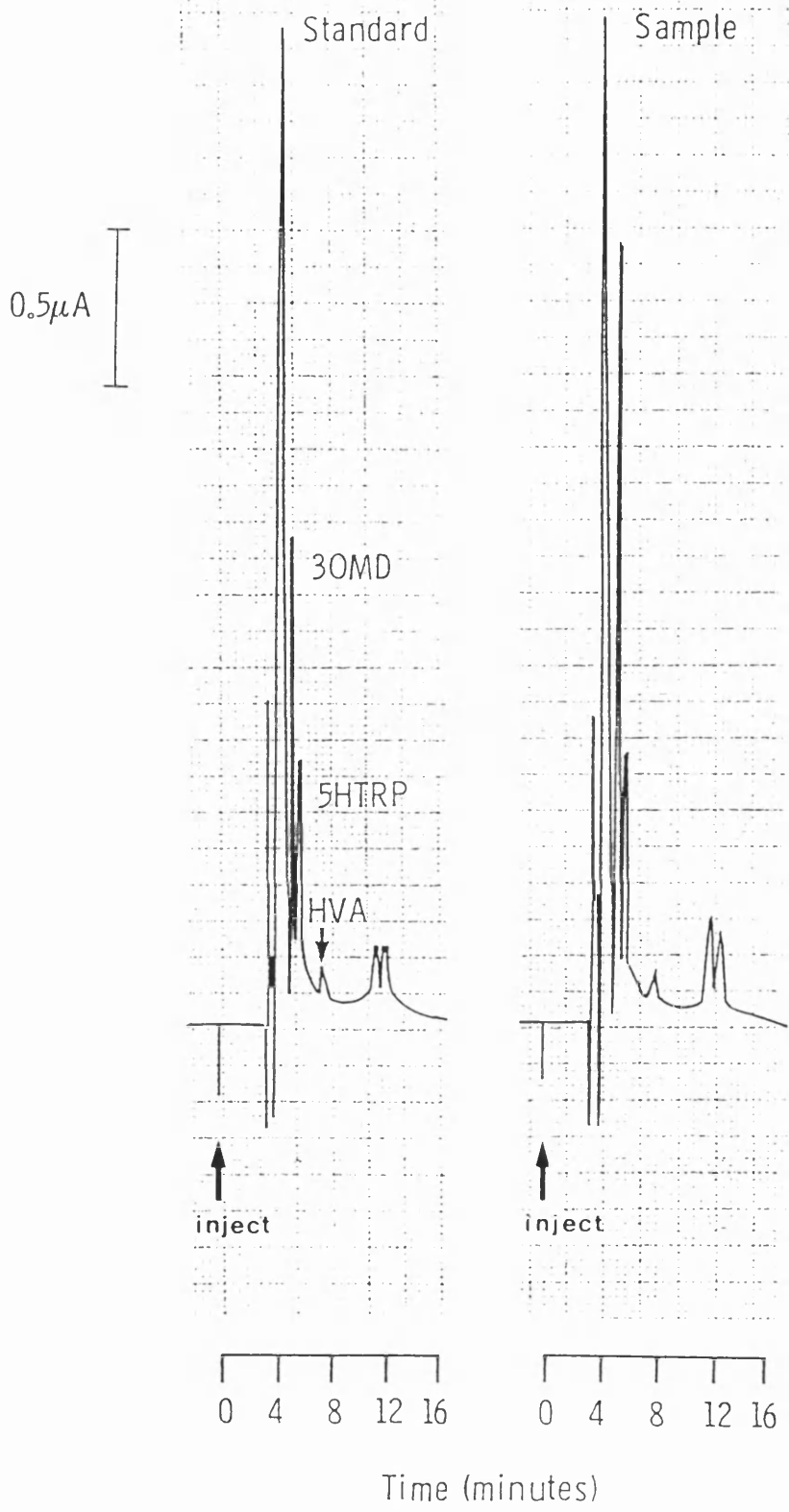
Figure 25   Example of an HPLC trace for 3-O-methyldopa

Quantitation of the compounds was achieved by calculation of the ratio of the peak height to that of 5-HTP (for 3OMD and HVA), or DHBA (for levodopa, dopamine, DOPAC, adrenaline, noradrenaline and carbidopa). The resulting peak height ratios were compared with a standard curve derived from spiked plasma samples which had been subjected to the extraction procedure at the same time as the patient samples. Levodopa standards were linear over the range 0 to 2000ng/ml and those for 3OMD were linear over the range 0 to 15µg/ml. The between and within coefficients of variation for levodopa at a concentration of 500ng/ml were 13.3 per cent and 6.3 per cent respectively, and for 3OMD at a concentration of 3µg/ml the respective values were 3.6 per cent and 2.3 per cent. The recovery of levodopa at a concentration of 1000ng/ml was 19.6 per cent, whilst 3OMD was found to be totally recoverable at a concentration of 1.5µg/ml. The limit of detection of the assay for levodopa was 3.5ng/ml. Since the assay was able to detect ng quantities of levodopa and 3OMD was present in µg quantities, a limit of detection for 3OMD was not carried out.

4.10 DETERMINATION OF MEAN ARTERIAL BLOOD PRESSURE

Determination of the standing and supine diastolic and systolic blood pressures was carried out by the author using a digital blood pressure monitor. The supine measurement was taken after the patient had been lying quietly for 5 minutes, and the standing taken after the patient had been upright for 3 minutes. The standing and supine mean arterial blood pressures were then calculated from these values.

CHAPTER FIVE

PRELIMINARY STUDIES

5.1 PRELIMINARY EXPERIENCE WITH THE BED MOVEMENT MONITOR IN THIRTY CLINICALLY STABLE PATIENTS IN A GERIATRIC UNIT

A preliminary study was carried out with the objectives of testing and gaining experience in the use of the bed movement monitors in the clinical environment and to study the effects of various patient characteristics on night-time movement in bed.

Methods

Clinically stable patients in a geriatric unit undergoing rehabilitation or requiring continuing nursing care were studied, those with hemi-, para- or tetraparesis being excluded. All eligible patients with Parkinson's disease presenting during a six month period were monitored, as were a randomly selected group of other eligible patients from the same wards. Informed consent was sought from all patients.

For each patient, night-time movements in bed were recorded on three consecutive nights using the method described previously (page 130). It has been shown (Wheatley, 1982) that admission to hospital typically results in an increased number of moves on the first night with a reduction on the second night. In this study, therefore, patients were allowed at least three nights to acclimatise to a new environment before movements were monitored.

The following patient data were noted by the author from the clinical files:

a) cognitive function, routinely assessed in the unit using the Modified Tooting Bec Questionnaire, a short test of memory, orientation and concentration in elderly patients which has a maximum (normal) score of 16 points (Denham, 1978; Appendix 5);

b) the Norton score, an assessment of the risk of developing pressure sores based on nursing observation of general condition, mental state, continence and daytime mobility (Norton *et al*, 1962; Appendix 6);

c) the existence of superficial pressure sores;

d) the diagnosis of arthritis of any type;

e) the presence of pain;

f) whether or not a hypnotic was being taken.

The significance of associations between the characteristics of patients and the measures of their movement in bed were assessed by calculating Spearman's non-parametric correlation coefficients. The relationship of mean move size to the cognitive function score and the presence or absence of Parkinson's disease was examined by multiple linear regression analysis. The existence of any systematic change from night to night in any of the variables measured from the bed movement trace was tested using a 2 way analysis of variance.

Results

Patient characteristics

Of the 30 patients studied, 12 had Parkinson's disease, 21 had a history of arthritis, which was a major problem in ten. Seventeen complained intermittently of pain, which was severe in four. The pain was attributed to arthritis, leg ulcers, cellulitis or cramps and was being treated accordingly. Eleven patients were receiving hypnotic or sedative drugs. Seven had superficial pressure sores. The mean (standard deviation) age was 82(7) years and mean (sd) score out of 16 for the modified Tooting Bec Questionnaire was 7(5). It was noted that all 7 patients with superficial pressure sores had Parkinson's disease. The increased frequency of pressure sores in those with Parkinson's disease was highly significant (Fisher's exact test, $P<0.001$). Individual patient characteristics are shown in Table 6.

Influence of patient characteristics on movement in bed

The mean (sd) values of measurements of movements in bed of each patient for the three nights studied are shown in Table 7. Associations between movement in bed and patient characteristics calculated in terms of Spearman's rank correlation coefficient are given in Table 8.

Table 6   Patient characteristics

Patient Number *	Age **	Cognitive function score	Norton score	Super-ficial pressure sore +	Pain ++	Arth-ritis ++	Hypnotic or sedative drugs +++
1	80	16	19	0	2	2	1n10
2	85	0	5	1	1	1	0
3	90	0	13	1	1	1	0
4	79	0	6	1	0	0	0
5	90	2	11	1	0	1	0
6	74	5	11	1	0	0	0
7	78	7	11	1	0	2	0
8	90	7	15	1	1	0	1dc
9	73	6	14	0	0	1	0
10	90	3	12	0	1	1	1th
11	79	14	18	0	2	1	1n5
12	69	14	12	0	0	2	0
13	95	0	10	0	0	0	1c
14	77	0	9	0	0	0	1th
15	83	16	18	0	0	1	0
16	88	2	11	0	0	1	0
17	85	3	10	0	1	2	0
18	84	8	18	0	0	0	1dz
19	84	3	12	0	0	0	1c
20	69	16	17	0	1	0	0
21	79	12	16	0	1	2	1c
22	89	3	18	0	1	2	0
23	81	3	12	0	0	0	0
24	69	12	17	0	1	2	0
25	84	13	14	0	2	2	0
26	73	13	20	0	2	1	1tz
27	84	11	10	0	1	1	1tz
28	93	11	17	0	1	2	0
29	89	5	15	0	1	1	0
30	87	11	14	0	1	2	0

*   - patients 1 to 12 had idiopathic Parkinson's
       disease
**   - in years
+   - scored as absent 0, present 1
++   - scored as absent 0, present 1, major problem 2
+++ - scored as no 0, yes 1

n5   - nitrazepam 5 mg
n10 - nitrazepam 10 mg
dz   - diazepam 10 mg
tz   - temazepam 10 mg
dc   - dichloralphenazone 1300 mg
th   - thioridazine 12.5 mg
c   - chlormethiazole 384 mg

Table 7   Frequency and size of movements in bed. The value
           given in each case is the mean (sd) for three
           consecutive nights.

Patient Number *	Number of moves per hour greater than			Total distance moved per hour (mm)	Mean move size (mm)
	4mm	10mm	20mm		
1	1.6(0.2)	1.1(0.3)	0.6(0.3)	39.2(10.7)	24.8(8.4)
2	10.9(1.2)	2.8(0.8)	0.0(0.0)	96.6(16.3)	8.8(0.6)
3	15.4(3.4)	5.7(0.8)	2.1(1.3)	168.9(30.2)	11.3(2.9)
4	3.6(0.7)	0.7(0.5)	0.2(0.2)	26.4(4.3)	7.4(1.5)
5	3.5(1.1)	1.1(0.4)	0.4(0.3)	38.4(3.5)	11.8(3.8)
6	0.9(0.4)	0.4(0.3)	0.1(0.1)	9.1(4.3)	9.6(2.8)
7	14.5(2.2)	6.4(1.9)	2.4(1.8)	172.4(38.4)	12.0(2.4)
8	4.1(2.6)	1.9(1.4)	0.8(0.7)	62.4(45.1)	14.7(2.4)
9	7.8(4.2)	2.4(1.9)	0.2(0.2)	63.8(38.6)	8.1(1.0)
10	3.4(1.0)	0.7(0.4)	0.3(0.3)	29.4(13.5)	8.4(1.5)
11	5.2(1.0)	2.8(0.7)	1.5(0.4)	110.0(23.1)	21.7(6.4)
12	5.2(2.8)	1.7(0.9)	0.9(0.6)	72.8(47.0)	13.0(2.7)
13	9.3(0.9)	4.2(1.2)	1.8(1.2)	125.5(48.1)	13.6(5.2)
14	20.8(6.4)	14.8(5.7)	4.9(3.4)	336.5(142.3)	16.0(3.2)
15	2.2(0.6)	1.4(0.7)	0.3(0.1)	26.5(7.0.)	12.4(0.1)
16	19.4(9.6)	7.3(6.7)	2.0(2.8)	215.5(161.7)	10.1(3.3)
17	9.5(1.4)	5.0(1.5)	1.2(0.6)	92.7(44.1)	13.1(1.3)
18	3.8(2.0)	2.1(1.0)	1.1(0.8)	74.5(50.1)	18.8(4.4)
19	0.6(0.2)	0.0(0.0)	0.0(0.0)	2.9(1.2)	4.9(0.3)
20	5.2(1.7)	3.0(0.5)	1.5(0.4)	106.1(43.4)	19.9(1.9)
21	1.1(0.4)	0.4(0.2)	0.3(0.1)	18.4(4.7)	17.6(2.7)
22	4.4(1.0)	2.2(0.5)	0.8(0.6)	61.7(22.9)	13.8(1.8)
23	12.0(2.4)	8.4(3.4)	4.5(3.0)	252.9(135.5)	20.1(8.0)
24+	8.0(2.0)	6.6(2.4)	5.2(1.8)	725.5(414.3)	85.9(30.9)
25	3.7(0.6)	1.4(0.6)	0.3(0.6)	47.9(27.6)	12.6(6.3)
26	1.8(1.1)	1.2(0.9)	0.6(0.6)	41.9(31.4)	19.6(9.4)
27	9.6(3.9)	6.7(2.7)	4.4(1.6)	188.0(57.5)	21.0(5.2)
28	5.5(0.9)	1.9(1.0)	0.7(0.8)	58.4(17.5)	10.7(2.9)
29	3.5(3.2)	1.1(1.4)	0.4(0.7)	58.1(79.0)	11.9(8.0)
30	4.7(2.6)	3.3(1.8)	2.4(1.0)	174.5(100.1)	37.0(2.5)

* - patients 1 to 12 had idiopathic Parkinson's disease
+ - extremely obese patient hence axial rotation of the same
    degree would result in a larger lateral movement of the
    centre of gravity than a thinner patient

Table 8   Factors influencing movements in bed.   The relationship between patient characteristics and frequency and size of movements in bed (mean values for three consecutive nights) is expressed in terms of Spearman's rank correlation coefficient.

Patient characteristics	Number of moves greater than			Total distance moved (mm)	Mean move size (mm)
	4mm	10mm	20mm		
Age (years)	0.06	-0.02	-0.05	-0.06	-0.26
Cognitive function	-0.37*	-0.17	0.03	-0.20	0.54**
Idiopathic Parkinson's disease+	-0.06	-0.26	-0.31	-0.13	-0.36*
Arthritis++	0.02	0.03	0.09	0.03	0.20
Pain++	-0.17	-0.06	0.03	-0.09	0.43*
Receiving hypnotic+++	-0.27	-0.15	0.02	-0.15	0.30
Superficial pressure sore+	0.05	-0.15	-0.21	-0.07	-0.41*

* - p<0.05
** - p<0.01
+ - scored as absent 0, present 1.
++ - scored as absent 0, present 1, major problem 2,
+++ - scored as no 0, yes 1. (Eleven patients were receiving nocturnal doses of hypnotic (or sedative) drugs; chlormethiazole in 3, temazepam 2, nitrazepam 2, thioridazine 2, diazepam 1 and dichloralphenazone 1.)

i) Parkinson's disease and cognitive function

Patients with Parkinson's disease or poor cognitive function made relatively small movements. The mean (sd) move size of the 19 patients with Parkinson's disease or a cognitive function score of 3 or less was 13(5)mm. This was approximately half that of the remainder of the group which was 25(24)mm. Those with Parkinson's disease as a group did not have significantly lower cognitive function scores (6(6)) than the rest of the patients (8(6), r=-0.134, p>0.1): thus these two characteristics appeared to have independent influences on movement size. However, when the cognitive function score and the presence or absence of Parkinson's disease were included simultaneously in a multiple regression equation, only the score had a significant (p<0.01) effect on mean move size. Each additional point scored corresponded to an increase of 5 per cent (on average) in the mean move size.

The number of moves made by patients with Parkinson's disease was not significantly different from that made by the other patients. The number of movements greater than 4mm was inversely correlated with the cognitive function score. The 12 patients with a score of 3 or less made nearly twice as many moves per hour than those with a higher score. The trend towards a greater number of moves in patients with poor cognitive function was also seen for moves greater than 10mm, and greater than 20mm, although

these were less frequent, and the difference between the high and low cognitive function groups was not as clear (Table 9).

Table 9 Effect of cognitive function on frequency of movements in bed

	Mean (sd) number of moves per hour greater than		
	4mm	10mm	20mm
Cognitive function score ≤3	9(7)	4(4)	2(2)
Cognitive function score >3	5(3)	3(2)	1(1)

ii) Other patient characteristics

In patients with superficial pressure sores, pain had been controlled by non-narcotic analgesics. These patients had a significantly (p<0.05) smaller mean (sd) move size (11(2)mm) than the rest of the group (19(16)mm). The mean (sd) move size of patients who were suffering pain was significantly (p<0.05) greater (21(18)mm) than that of those who were pain free (12(4)mm). This may well represent an attempt to find a more comfortable position.

Despite the wide age range of the patients (69 to 95 years) no significant correlation was found between age and frequency and size of movements in bed.

Similarly no correlation was found between arthritis and movement in bed even though it was a major problem in ten of the patients.

Quality of sleep was not evaluated in this study but there was no objective evidence in terms of reduction of movement in bed (see Discussion, page 197) to suggest that those who received hypnotics slept better than the rest of the group.

Repeatability of the bed movement measurements

As can be seen from the values for the variance ratios in Table 10 for the bed movement variables calculated, each of three consecutive nights showed no systematic variation. Thus the three nights can be considered to be replications of each other.

Table 10   Repeatability of the measurements

	F value (variance ratio)	degrees of freedom	p value for 2 way ANOVA test for differences between occasions
Mean move size (mm)	0.785	2, 58	$0.25 < p < 0.50$
Total distance moved per hour (mm)	0.840	2, 58	$0.25 < p < 0.50$
Number of moves > 4mm per hour	1.157	2, 58	$0.25 < p < 0.50$
Number of moves > 10mm per hour	0.618	2, 58	$0.50 < p < 0.75$
Number of moves > 20mm per hour	0.208	2, 58	$0.75 < p < 1.00$

Discussion

The present study allowed the author to gain much
experience in the use of the bed movement monitor in
the clinical environment, and in the analysis of the
traces generated.

For the patients studied, the amount of spontaneous
movement exhibited in bed was remarkably small. Since
movement of a limb, not accompanied by movement of the
trunk, can displace the patient's centre of gravity
laterally, many of the small displacements recorded
would not have been accompanied by any useful relief of
pressure on soft tissue in vulnerable areas. Indeed,
patients with pressure sores had a significantly
reduced mean move size compared with those without, but
did not differ from them with respect to number of
moves made or total distance moved.

All those with pressure sores had both Parkinson's
disease and a low cognitive function score. However,
the major determinant of mean move size in the group as
a whole was a low cognitive function score, the
presence or absence of Parkinson's disease having no
additional effect. Increased shearing stress in the
skin, due to tremor or rigidity in the adjacent muscle,
may have added to the susceptibility to pressure sores
of those with coexisting Parkinson's disease.

As discussed earlier (page 77), the decrease in the
total amount of movement in bed during sleep depends
upon the depth of sleep (Loomis *et al*, 1937; Blake *et
al*, 1939; Cox and Marley, 1959). Hypnotics and

sedatives such as barbiturates (Hinton and Marley, 1959; Hinton, 1961), meprobamate (Hinton and Marley, 1959) and flurazepam (Crowley and Hydinger-Macdonald, 1979) have been shown to reduce the total excursion made by individuals during the night. In this study, a different spectrum of drugs for night sedation was in use, which might explain why no difference in movement was detected between the patients who did, and did not receive hypnotic and sedative drugs. The increased frequency of small movements found in those with a low cognitive function score presumably reflected the particularly severe fragmentation of sleep found in dementia in old age (Allen *et al*, 1983).

5.2 PRELIMINARY EXPERIENCE WITH THE GAIT ASSESSMENT TROLLEY IN TWO PATIENTS WITH CLINICALLY OVERT CHANGES IN PARKINSONISM

Prior to its use in the study, the gait assessment trolley (page 156) was tested in two patients with Parkinsonism. In each case, clinically overt changes and fluctuations were compared with the output from the trolley. The diagnosis of the clinically overt changes was carried out by the clinician in charge of the patients.

a) A patient with drug-induced Parkinsonism

One patient was a 76 year old woman (height 155cm), who had been receiving metoclopramide 10mg three times a day for 18 months because of peptic oesophagitis and who had been referred for depression and loss of balance. Following withdrawal of metoclopramide, her gait became less irregular and speed increased (Figure 26). Trace a), taken immediately before withdrawal of metoclopramide, shows hesitancy on starting to walk and as she approached and negotiated a doorway. Two months after withdrawal (trace b)) she was not inhibited by the doorway, but gait was slow and irregular. At eight months (trace c)) her gait was faster but still irregular. The need for normal controls in deciding whether her gait was still affected by Parkinsonism was evident. Her gait was therefore compared at ten months
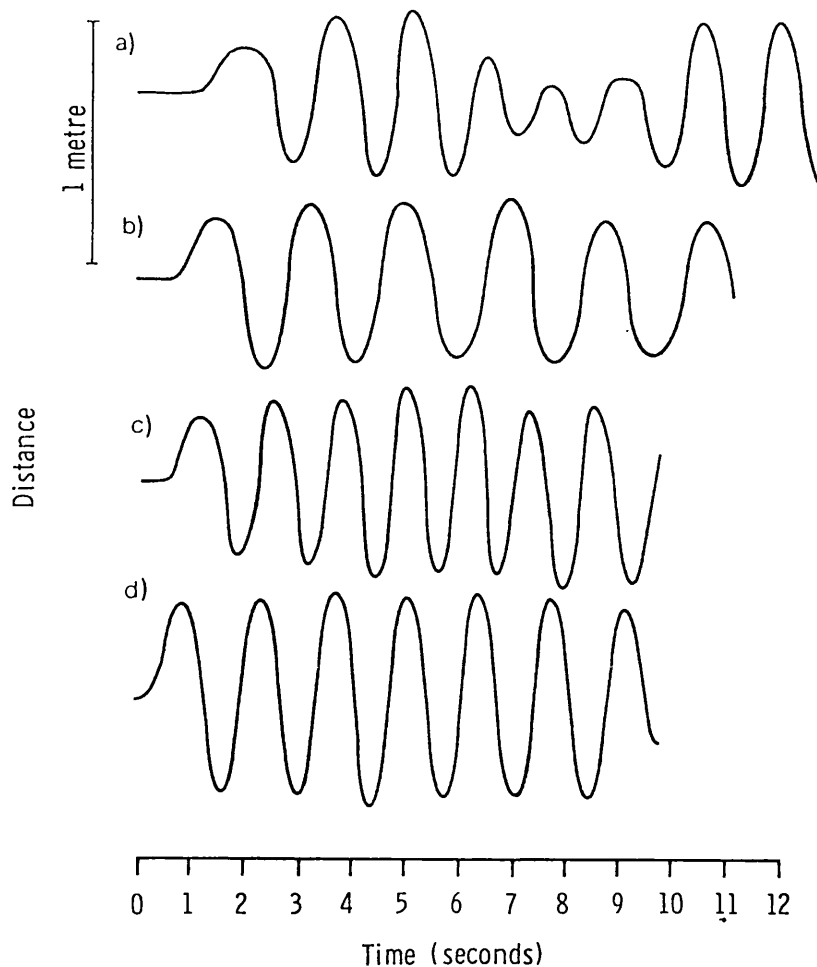
Figure 26 Serial gait assessments in a patient with drug-induced Parkinsonism

(trace d)) with that of a series of normal controls and indeed, at this stage, appeared to be normal for herheight and age. At this time the gait parameters studied (Table 11) did not differ significantly from those of a group of 14 healthy women, aged 66 to 78 years and height 151 to 174cm (Hotellings T^2 test, p=0.45).

Table 11   Gait parameters of a patient with drug induced Parkinsonism 10 months
after withdrawal of metoclopramide and those of a series of normal
controls

Gait Parameter	Patient	Normal controls*
Reaction time (seconds)	0.25	0.55(0.17)
Length of first step (cm)	37	40(9)
Time taken for first step (seconds)	0.55	0.50(0.09)
Mean (sd) length of swing (cm)	80(4)	96(10)
Mean (sd) time taken for swing (seconds)	0.58(0.03)	0.54(0.05)
Mean (sd) double support time (seconds)	0.12(0.03)	0.14(0.03)
Free walking speed (cm/second)	59	76(14)

* - mean (sd) values of a group of 14 healthy women aged 66 to 78 years, height
151 to 174 cm (Individual values are presented in Appendix 28.)

b) **A patient with marked "end of dose" effect**
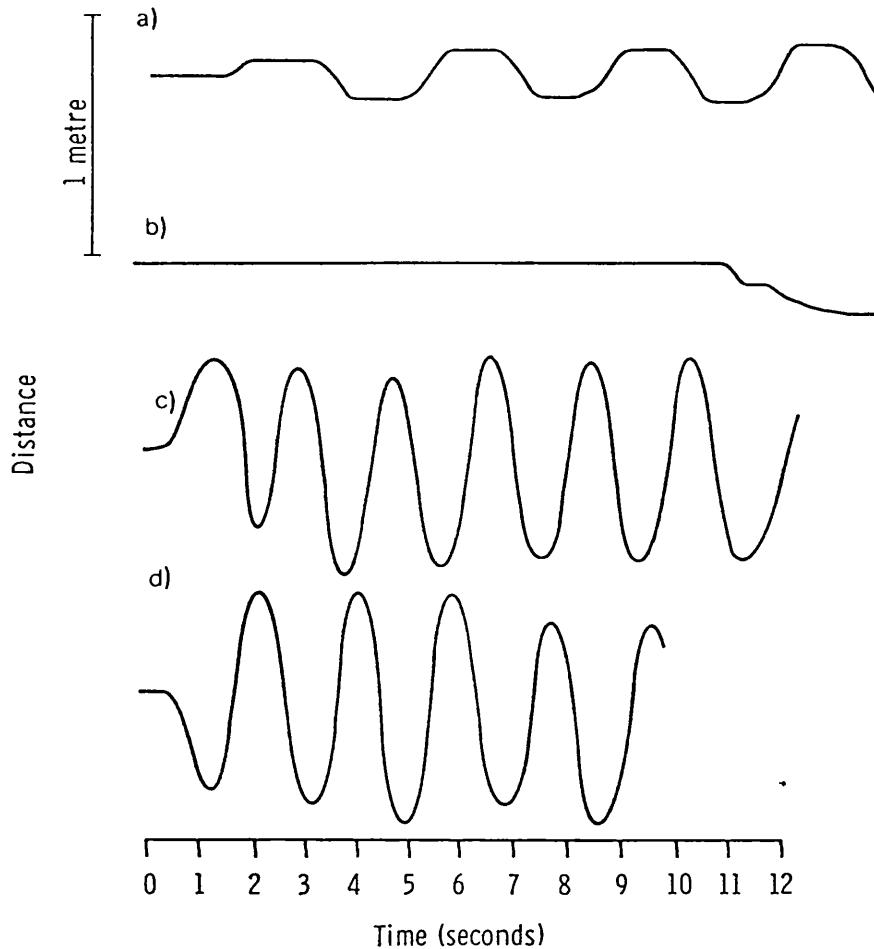
Figure 27   Serial gait assessments in a patient with
            idiopathic Parkinson's disease suffering
            from marked "end of dose" effect and "peak
            dyskinesia"

This patient was a 65 year old man with idiopathic

Parkinson's disease, who had been treated for 11 years

with levodopa/decarboxylase inhibitor combinations and

at the time of referral was suffering from marked "end

of dose" effect and "peak dyskinesia". Figure 27 shows

serial gait assessments that were carried out during a

day of titration of dosage and determination of optimal

spacing of Sinemet-Plus. Trace a) was taken when the

patient had received no anti-Parkinsonian treatment
overnight and shows small, slow steps with a long
double support time. He did not respond to half a
tablet of Sinemet-Plus, only being able to take one
small step forward after great delay (trace b)). One
hour after a whole tablet of Sinemet-Plus, his
neurological deficit had markedly reversed but the gait
was still somewhat irregular (trace c)). Dyskinesia
was observed at one and a half hours. The beneficial
response was maintained for four hours (trace d))
but then faded rapidly.

It was thus concluded that the changes in the gait
assessment traces of these two patients clearly
reflected the changes in gait seen clinically.

CHAPTER SIX

STUDY PROTOCOLS

6.1 NIGHT-TIME SINEMET-PLUS STUDY

Objective

This study was carried out to test whether the night-time dosage regimen of Sinemet-Plus was related to night-time movement in bed and early morning bradykinesia.

Patients

Patients were attending an outpatient clinic for Parkinson's disease in the elderly. Parkinsonism was diagnosed by the clinician in charge according to the presence of two or more of the following signs: tremor, rigidity, hypokinesia and postural abnormality (either flexed posture or impaired postural reflexes). A history of improvement after dopamine replacement therapy was regarded as essential to the diagnosis of idiopathic Parkinson's disease. Alternative causes of Parkinsonism were excluded in a manner similar to that of Quinn and Husain (1986). Patients in whom there were reservations about the diagnosis were excluded. Informed consent was sought from those eligible for the study. For each patient, severity of Parkinson's disease was rated using the Hoehn and Yahr Staging System (Hoehn and Yahr, 1967; Appendix 3). Since in the preliminary study of bed movements (page 187), a cognitive function of 3 or less was found to influence movement in bed, the cognitive function of the patients in this study was also assessed using the Modified

Tooting Bec Questionnaire (Denham, 1978; Appendix 5).
Only those patients with a score of 8 or more out of a
possible 16 were included in the study.

Design of the study

Before entering the study patients were stabilised
on the regime of Sinemet-Plus which appeared to give
optimal control of their Parkinson's disease during the
day. All patients received a night-time dose of two
tablets of Sinemet-Plus at 22.00 hours (h.). They were
receiving no other anti-Parkinsonian agents.

The study was of a double-blind, placebo-
controlled, cross-over design, each patient being given
the three night-time treatments shown in Table 12 in
randomised order. Treatments were for four nights with
an interval of at least three nights between, the
initial regimen of two Sinemet-Plus tablets at night
being resumed between treatments. Daytime medication
remained constant. Active and placebo tablets of
Sinemet-Plus were supplied by Merck Sharp and Dohme
Ltd.

For each night of the study, movements in bed of
the patients were monitored using the method described
previously (page 130). However, in this study the
movement data were not only calculated for the whole
night, but also for the periods of the night before,
and after, the 03.00h. tablet. The following morning,
patients were asked to record their quality of sleep
using a visual analogue scale (page 149), and the

Table 12   Night-time treatments

Treatment	Time		Denoted henceforth as
	22.00h.	03.00h.*	
A	2 placebo	1 placebo	PP.P
B	2 Sinemet-Plus	1 placebo	AA.P
C	1 Sinemet-Plus 1 placebo	1 Sinemet-Plus	AP.A

* - designed to assess whether dividing the nocturnal
    dose between two administration times improved
    sleep and morning performance by overcoming an end
    of dose effect

times taken to walk a set distance (page 154) and to

blink ten times (page 150) were recorded. No morning

anti-Parkinsonian medication was given until these

assessments had been made.

Statistical methods

Analysis of variance was carried out to determine

the effects of treatment (placebo versus the mean of

the two Sinemet-Plus regimes, and the difference

between the Sinemet-Plus regimes), sequence of

adminstration of the three treatments and any

interactions between treatment and sequence. The

analysis took into account any incompleteness of data

on any treatment. Analysis of variance was also used

to determine the night to night, or morning to morning,

repeatability of the tests used in the study. The

association between visual analogue measurements of

sleep and measures of movement and of morning

performance was estimated by calculating the partial

correlation coefficient after allowing for differences

between patients, treatments and sequence of

treatments.

6.2   DAYTIME SINEMET-PLUS STUDY

Objective

The objective of this study was to investigate possible relationships between the daytime mobility of the patient, their dosage regimens and their plasma levels of levodopa and its metabolite 3-O-methyldopa.

Patients

Patients were entered into the study according to the same criteria as described in the night-time Sinemet-Plus study. At the time of study there were no overt fluctuations in the patients' clinical state related to medication. For each patient the severity of Parkinson's disease was rated using the Hoehn and Yahr Staging System (Appendix 3) and the Webster Scale (Appendix 1).

Design of the study

Prior to entry into the study each patient was stabilised on the regime of Sinemet-Plus that appeared to give optimal control of their Parkinson's disease. No other anti-Parkinsonian agents were given. Patients were randomly allocated to receive a tablet of Sinemet-Plus or an identical placebo at 10.00 h., with the alternative treatment being administered at least three days later. The treatments were then repeated starting at least one week later. A light, low protein breakfast was given at least 90 minutes before the dose

so as not to delay or reduce absorption of levodopa,
and to minimise competition with levodopa from other L-
amino acids for active transport into the brain. The
dose was administered with water, with no other drinks
or food allowed for at least another 90 minutes.
Thereafter patients were given normal hospital diets.
No routine doses of Sinemet-Plus were given after the
22.00h. dose on the night before, until 16.00h. on the
treatment day, placebo tablets being substituted as
appropriate. A "timed walking" test (page 154),
measurement of distance/time parameters of gait (page
156) and a manual dexterity test (page 152) were
carried out immediately before and at 2, 4 and 6 hours
after the 10.00h. dose.

Serial blood samples (about 10ml), for assay of
levodopa and its metabolites (page 179) were taken into
heparin immediately before, and at hourly intervals for
6 hours after 10.00h. doses of active and placebo
tablets, given in randomised order, on two further
days. Plasma was separated by centrifugation and
stored in aliquots of approximately 1ml at -20°c until
analysis. Measurements of supine and standing blood
pressures (page 185) were carried out immediately
before and at 2, 4 and 6 hours after the 10.00h. doses
on these days. The only measurements of mobility on
these occasions were pedobarography (page 168) and a
video recording of the patient walking (page 178)
carried out at 12.00h. Although not ideal, it was
considered necessary to carry out the majority of the

response tests on days separate from those upon which
blood sampling took place since it was considered that
the presence of an indwelling venous cannula could have
pronounced effects on the walking ability and manual
dexterity of these elderly patients. Also, for these
patients the tests of mobility took much longer and
proved to be more tiring than they might be in younger
subjects.

Statistical methods

Distance/time parameters of gait, time to walk a
set distance and time to do up the same number of
buttons were analysed using analysis of variance
(ANOVA) controlling for treatment, order, repetition
and session. To control for day to day variation, the
data were standardised by using the changes between the
pre-dose measurement (0 hour) and those at 2, 4 and 6
hours post-dose each day. The difference between pre-
and post-treatment measurements or change expressed as
a ratio was selected in order to give homogeneity of
variance and normal residuals. Analysis of variance
was also used to determine the day to day repeatability
of the tests used in this study. The foot strike index
on active and placebo treatments as measured by
pedobarography was compared using the Wilcoxon signed
rank test. This test was also used to compare the
values of foot strike index obtained by pedobarography
and video recording. Correlations of age, severity of
Parkinson's disease, duration of levodopa therapy and

distance/time parameters of gait with the foot strike

index as measured by pedobarography were tested using

the Spearman's rank correlation test. The probability

of active treatment causing a global improvement as

seen on video recording was calculated using the

binomial distribution. The presence of any

relationships between the parameters of gait, blood

pressure and the plasma concentrations of levodopa and

3-O-methyldopa was tested using an analysis of

covariance.

CHAPTER SEVEN

RESULTS

7.1 RESULTS OF THE NIGHT-TIME SINEMET-PLUS STUDY

Patient characteristics

The characteristics of the 12 patients with idiopathic Parkinson's disease entered into the study are shown in Table 13. Their mean (sd) age was 80(4) years and they had been receiving levodopa therapy for a period of between 5 and 183 months (mean (sd) 44(52) months). The mean (sd) cognitive function score for the group was 13(2) points. Patient 12 withdrew from the study during the first treatment period.

Table 13   Patient characteristics

Patient Number	Age (years)	Hoehn and Yahr staging	Duration of levodopa therapy (months)	Cognitive function score
1	76	4	32	14
2	79	4	94	16
3	79	3	10	10
4	69	5	17	11
5	78	3	11	14
6	81	5	72	11
7	87	4	6	14
8	82	4	183	14
9	81	3	5	14
10	81	4	60	8
11	83	4	16	13
12	79	3	22	12

Effect of nocturnal dosing with Sinemet-Plus on quality
of sleep, movement in bed and morning performance

The within patient variances in number of moves in
each size category, total distance moved, mean move
size, time to walk a set distance and the time for ten
blinks were dependent on the respective mean value in
that patient. Analysis of the data following log
transformation yielded residuals of constant variance.
Statistical results quoted in this section were
obtained using the transformed data.

i) Quality of sleep

Quality of sleep was assessed using a visual
analogue scale. The mean ratings (N=4) of quality of
sleep on each treatment for each patient are shown in
Table 14. Eight patients judged their sleep to be
better on either treatment B or C which contained
Sinemet-Plus than on placebo treatment (A). The mean
ratings on the visual analogue scale for treatments B
and C, 93 and 84mm respectively, indicated a better
than average night, whilst the mean rating on A, 67mm,
indicated a worse than average night. The improvement
in quality of sleep on either treatment B or C as
compared to treatment A was significant (p<0.01),
although the improvement on treatment B as compared to
C was marginal (p=0.06). The improvement was not a
consequence of reduced discomfort during the night as
in fact this was more common on active than on placebo
treatment (Table 14).

Table 14 Quality of sleep and number of interventions during the night. The value given in each case is the mean (sd) for each treatment.

Patient Number	Quality of sleep on visual analogue scale (mm)			Number of interventions per hour		
	Treatment A (PP.P)	Treatment B (AA.P)	Treatment C (AP.A)	Treatment A (PP.P)	Treatment B (AA.P)	Treatment C (AP.A)
1	85(54)	120(14)b	92(22)	0.22(0.06)	0.19(0.13)	0.32(0.08)
2	48(25)b	90(6)cd	84(32)bc	0.38(0.10)	0.25(0.00)	0.35(0.07)
3	126(32)	a	78(60)	0.19(0.07)	a	0.35(0.07)
4	102(27)	a	71(38)	0.19(0.09)	a	0.22(0.09)
5	16(8)	136(3)	146(1)	0.62(0.16)	0.29(0.00)	0.19(0.09)
6	54(23)	63(54)	79(34)	0.25(0.00)	0.25(0.00)	0.25(0.00)
7	68(14)	85(8)c	64(25)	0.25(0.10)	0.25(0.00)	0.25(0.13)
8	69(33)	53(48)	46(31)	0.25(0.00)	0.29(0.08)	0.28(0.07)
9	58(17)	135(20)	123(35)	0.34(0.07)	0.36(0.08)	0.29(0.12)
10	68(11)	81(11)c	77(29)	0.34(0.08)	0.19(0.07)	0.28(0.07)
11	41(20)	75(81)e	67(55)	0.44(0.07)	0.28(0.07)	0.25(0.10)
Mean (sd) 11 patients	67(30)	93(30)	84(28)	0.32(0.13)	0.26(0.05)	0.28(0.05)
Mean (sd) excluding 2 patients (a)	56(20)	93(30)	86(31)	0.34(0.13)	0.26(0.05)	0.27(0.05)

a - final treatment not completed due to intercurrent illness

Discomfort suffered during night:
b - leg cramp
c - "burning" pain in heels
d - paraesthesia in legs
e - pain "like a current running through legs"

ii) Movement in bed

There was no significant difference in the number of "interventions" per hour (N=4), defined as the number of times patients rose from bed or were attended to, on either treatments B or C as compared with A (p>0.1), or on treatment B as compared with C (p>0.5), (Table 14).

However, excluding the above events, patients made fewer spontaneous moves in bed on treatments B and C than on A (Table 15). The reduction reached statistical significance for the mean of the number of moves greater than 4mm measured (N=4, p<0.01) but not for the number greater than 10mm or 20mm (p>0.05, and p>0.1 respectively). Furthermore, the mean of the total distance moved was less on treatments B and C than on treatment A (p<0.01). However, the average mean move size (N=4) was unaffected by treatment. There was no significant difference between treatments B and C with respect to spontaneous movement during the whole night, or the parts of the night before and after the 03.00h. tablet administration time.

Table 15 Frequency and size of movements during the whole night. The value given in each case is the mean (sd) for each treatment.

Patient Number	Number of moves per hour greater than			Treatment A (PP.P) Total distance moved per hour (mm)	Mean move size (mm)
	4mm	10mm	20mm		
1	1.9(0.8)	0.9(0.5)	0.4(0.2)	26.5(10.4)	13.8(2.0)
2	6.5(2.6)	2.9(1.0)	1.3(0.3)	115.7(44.2)	18.9(7.0)
3	2.0(1.0)	1.0(0.4)	0.5(0.3)	32.8(17.4)	15.3(3.8)
4	3.1(1.9)	1.2(0.8)	0.4(0.3)	37.6(25.2)	12.2(3.1)
5	11.2(1.9)	7.9(2.5)	4.1(1.0)	231.5(88.3)	20.1(4.2)
6	2.7(1.1)	1.0(0.5)	0.1(0.2)	24.4(11.1)	9.1(2.9)
7	2.2(1.1)	1.3(1.1)	0.1(0.2)	27.1(14.3)	12.8(2.9)
8	3.8(1.4)	1.8(0.7)	0.7(0.3)	53.7(20.9)	14.3(2.4)
9	3.8(0.7)	2.6(0.7)	1.7(0.6)	86.7(27.1)	22.4(3.7)
10	4.1(0.3)	2.0(0.5)	0.6(0.1)	53.2(7.8)	13.1(1.9)
11	1.6(0.5)	1.1(0.5)	0.9(0.4)	63.5(33.7)	39.4(14.7)
Mean (sd) for 11 patients	3.9(2.8)	2.2(2.0)	1.0(1.1)	68.4(61.0)	17.4(8.3)
Mean (sd) excluding 2 patients (a)	4.2(3.0)	2.4(2.2)	1.1(1.2)	75.8(65.7)	18.2(9.0)

Table 15 continued

Patient Number	Treatment B (AA.P)				
	Number of moves per hour greater than			Total distance moved per hour (mm)	Mean move size (mm)
	4mm	10mm	20mm		
1	2.0(0.3)	0.5(0.4)	0.2(0.2)	19.7(8.7)	9.4(2.6)
2	2.5(0.5)	1.4(0.5)	0.8(0.5)	52.7(11.3)	21.7(1.4)
3	a	a	a	a	a
4	a	a	a	a	a
5	1.9(0.2)	1.0(0.6)	0.4(0.3)	25.7(10.9)	13.3(4.4)
6	2.9(2.7)	1.3(1.2)	0.2(0.2)	29.1(25.8)	10.4(0.7)
7	1.2(0.0)	0.7(0.2)	0.1(0.1)	14.2(1.1)	12.1(0.9)
8	4.6(0.9)	2.7(0.3)	1.6(0.5)	161.1(39.2)	36.2(13.1)
9	2.7(1.0)	1.7(1.1)	1.2(0.8)	62.5(37.4)	21.1(8.0)
10	3.9(0.7)	2.1(0.8)	0.5(0.2)	48.2(12.8)	12.4(1.7)
11	1.8(0.1)	1.2(0.2)	1.0(0.3)	60.0(17.3)	33.3(10.1)
Mean (sd) for 11 patients	2.6(1.1)	1.4(0.7)	0.7(0.5)	52.6(44.4)	18.9(10.0)
Mean (sd) excluding 2 patients (a)	2.6(1.1)	1.4(0.7)	0.7(0.5)	52.6(44.4)	18.9(10.0)

Table 15 continued

	Treatment C (AP.A)				
Patient Number	Number of moves per hour greater than			Total distance moved per hour (mm)	Mean move size (mm)
	4mm	10mm	20mm		
1	1.8(0.7)	0.9(0.6)	0.3(0.2)	22.9(10.2)	12.7(1.6)
2	3.4(1.6)	1.9(0.9)	1.0(0.6)	75.7(47.4)	21.3(5.8)
3	2.6(2.1)	1.4(1.3)	0.5(0.6)	36.8(37.9)	14.1(5.1)
4	7.0(1.9)	3.9(1.0)	1.6(0.2)	116.8(6.0)	17.8(4.9)
5	2.9(0.1)	1.6(0.3)	0.5(0.4)	39.4(10.5)	13.5(3.5)
6	1.7(0.9)	0.6(0.3)	0.1(0.0)	16.9(6.9)	10.5(3.2)
7	1.4(1.4)	0.8(1.1)	0.1(0.2)	17.7(18.7)	10.5(4.8)
8	5.5(2.3)	2.6(1.0)	1.3(0.6)	96.1(46.8)	18.2(5.8)
9	1.7(0.5)	0.8(0.3)	0.4(0.2)	25.2(11.9)	15.0(4.3)
10	5.2(1.8)	3.4(1.5)	1.4(0.6)	84.1(31.8)	16.1(0.8)
11	1.1(0.2)	0.7(0.3)	0.6(0.2)	36.4(13.2)	32.7(8.3)
Mean (sd) for 11 patients	3.1(2.0)	1.7(1.1)	0.7(0.5)	51.6(35.1)	16.6(6.3)
Mean (sd) excluding 2 patients (a)	2.7(1.6)	1.5(1.0)	0.6(0.5)	46.0(30.8)	16.7(6.9)

a – final treatment not completed due to intercurrent illness

iii) <u>Morning performance</u>

a) <u>Time to walk an individually set distance ("timed</u>

<u>walking" test)</u>

The individual distance walked by each patient, and
the mean time taken to walk that distance (N=4) on each
treatment are shown in Table 16. Patients walked
faster (p<0.01) on the mornings following nocturnal
dosing with Sinemet-Plus (treatments B and C) than on
those following placebo (treatment A), (Figure 28).
Dividing the same nocturnal dose of Sinemet-Plus
between the two administration times had no effect on
walking time.

b) <u>Time for ten blinks</u>

There was an indication that the mean time for ten
blinks ($4 \leqslant N \leqslant 16$) was significantly shorter on active
than on placebo treatment (Table 16 and Figure 28).
However, significant (p<0.01) interactions between
sequence and nature of treatment were present, the
implication being that the treatment effect on blink
time was dependent on the order of administration. At
the 1 per cent level, no significant effect of sequence
of treatment or interaction was seen with respect to
the other assessments (i, ii and iii(a)). No
significant difference in the time for ten blinks was
detected between treatments B and C. Since this was
the case for the "timed walking" test and the time for
ten blinks, Figure 28 has been plotted using the mean
of the eight values obtained for treatment containing
active Sinemet-Plus (treatments B and C).

Table 16   Time (seconds) to walk an individually set distance and for ten blinks. The value given in each case is the mean (sd) for each treatment.

Patient Number	Distance (metres) *	Time to walk set distance (seconds)			Time for ten blinks (seconds)		
		Treatment A (PP.P)	Treatment B (AA.P)	Treatment C (AP.A)	Treatment A (PP.P)	Treatment B (AA.P)	Treatment C (AP.A)
1	6	60(11)	35(6)	45(10)	33(7)	36(6)	29(2)
2	6	52(8)	51(9)	39(3)	53(9)	47(11)	53(13)
3	6	29(3)	a	39(4)	28(12)	a	29(12)
4	7	797(61)	a	649(482)	295(254)	a	197(92)
5	6	22(3)	18(3)	19(4)	62(13)	53(5)	47(9)
6	4	292(76)	269(76)	300(94)	52(29)	57(20)	32(6)
7	10	168(17)	141(6)	152(16)	36(4)	34(4)	35(4)
8	6	313(132)	298(109)	202(79)	31(4)	25(3)	26(3)
9	12	84(13)	69(12)	70(8)	64(11)	58(12)	43(5)
10	10	142(11)	149(12)	119(29)	24(5)	17(5)	20(8)
11	12	231(10)	239(45)	176(36)	57(6)	64(6)	69(11)
Mean (sd) 11 patients	8(3)	199(223)	141(106)	165(182)	67(77)	43(16)	53(50)
Mean (sd) excluding 2 patients (a)	8(3)	152(107)	141(106)	125('92)	46(15)	43(16)	39(15)

a - final treatment not completed due to intercurrent illness

* - distance walked by patient each morning measured from chair to turning point and back

Figure 28   Comparison of a) the time to walk a set
            distance and b) the time taken for ten
            blinks following nocturnal dosing with
            active (treatments B and C) and placebo
            (treatment A) Sinemet-Plus. Values given
            are the means for the four mornings studied
            on treatment A and the eight on treatments B
            and C except in the case of patient 3 where
            only data for treatments A and C were
            available. Data from patient 4 were
            excluded from the figure because of the long
            time taken in both walking and blink tests.
            He walked faster on the only active
            treatment completed, treatment C, (649
            seconds to walk a set distance) than on A
            (797 seconds) and took less time for ten
            blinks on C than on A (197 and 295 seconds
            respectively).

Relationship of quality of sleep to movements in bed and morning assessments

There were significant ($p<0.001$) negative partial correlations between the visual analogue rating of sleep and the number of moves in the size categories greater than 4mm, 10mm and 20mm ($r=-0.44$, -0.39, -0.38 respectively) and between the visual analogue rating of sleep and the total distance moved ($r=-0.40$). However, mean move size was not related to quality of sleep ($r=-0.14$, $p=0.16$). Morning performance as judged by walking time and the time for ten blinks was also unrelated to sleep quality ($r=-0.01$, $p=1.0$ and $r=0.04$, $p=0.5$ respectively).

Repeatability of the measurements

The existence of any systematic change from night to night or morning to morning in the variables listed in Table 17 on placebo treatment was investigated using a 2 way analysis of variance. As can be seen from the values of the variance ratio, F, no significant night to night or morning to morning variation could be detected in any of the variables thus the four nights or mornings could be considered to be replications of each other.

Table 17 Repeatability of the measurements

	F value (variance ratio)	degrees of freedom	p value for 2 way ANOVA test for differences between occasions
Mean move size (mm)	0.721	3, 18	0.50<p<0.75
Total distance moved per hour (mm)	0.321	3, 18	0.50<p<0.75
Number of moves > 4mm	0.477	3, 18	0.50<p<0.75
Number of moves > 10mm per hour	0.781	3, 18	0.50<p<0.75
Number of moves > 20mm per hour	1.043	3, 18	0.25<p<0.50
Quality of sleep (mm on visual analogue scale)	0.062	3, 18	0.75<p<1.00
Walking time (seconds)	0.206	3, 24	0.75<p<1.00
Time for 10 blinks (seconds)	0.854	3, 24	0.25<p<0.50

7.2   RESULTS OF THE DAYTIME SINEMET-PLUS STUDY

Patients

A further 14 patients with idiopathic Parkinson's disease were entered into this study.   Their characteristics are shown in Table 18.   Their mean (sd) age was 77(6) years and they had been receiving levodopa therapy for a period of between 6 and 178 months, mean (sd) 51(52) months.   Repeat measurements of response to active and placebo Sinemet-Plus were not possible in two of the patients (numbers 4 and 5) due to intercurrent illness and patient 13 declined to give blood samples for the H.P.L.C. analysis of levodopa and the metabolite 3-O-methyldopa.

Table 18   Patient characteristics

Patient Number	Age (years)	Hoehn and Yahr staging	Webster score	Duration of levodopa therapy (months)
1	81	5	19	78
2	81	3	15	10
3	79	3	13	20
4	88	4	12	12
5	80	4	17	107
6	76	2	4	95
7	77	4	13	100
8	83	5	22	178
9	80	3	13	26
10	75	3	14	6
11	75	3	14	11
12	74	4	17	22
13	66	2	10	8
14	64	2	7	36

Effect of a morning dose of Sinemet-Plus on gait

i) Analysis of the entire walk

The mean values for each walk of the gait parameters double support time and swing length analysed for the entire walk (to a maximum distance of 6 metres) are shown in Tables 19 and 20 respectively. As a measure of the variability, the standard deviation of these parameters is included in parentheses.

Table 19 Values of mean (sd) double support time for the entire walk

Patient Number	Day	Treatment *	Mean (sd) double support time (seconds)** at time (hours)			
			0	2	4	6
1	1	Active	1.209(0.490)	a	a	0.885(0.517)
	2	Placebo	1.300(0.236)	a	a	1.261(0.335)
	3	Active	1.177(0.246)	1.095(0.664)	1.272(0.613)	1.215(0.670)
	4	Placebo	1.168(0.424)	1.159(0.190)	1.051(0.223)	1.078(0.639)
2	1	Placebo	0.144(0.066)	0.099(0.062)	0.159(0.103)	0.093(0.049)
	2	Active	0.140(0.077)	0.114(0.064)	0.087(0.054)	0.059(0.045)
	3	Placebo	0.083(0.038)	0.065(0.025)	0.065(0.024)	0.066(0.042)
	4	Active	0.084(0.033)	0.085(0.032)	0.086(0.073)	0.088(0.082)
3	1	Active	0.150(0.057)	0.148(0.082)	0.084(0.036)	0.152(0.091)
	2	Placebo	0.179(0.078)	0.246(0.056)	0.227(0.067)	0.164(0.043)
	3	Active	0.134(0.065)	0.124(0.039)	0.096(0.021)	0.115(0.031)
	4	Placebo	0.121(0.035)	0.150(0.027)	0.150(0.033)	0.129(0.028)
4	1	Active	0.448(0.397)	0.495(0.436)	0.388(0.313)	0.436(0.325)
	2	Placebo	0.496(0.369)	0.361(0.344)	0.393(0.340)	0.461(0.421)
	3	b				
	4	b				
5	1	Placebo	0.379(0.106)	0.294(0.084)	0.292(0.081)	0.224(0.077)
	2	Active	0.356(0.099)	0.412(0.123)	0.405(0.123)	0.295(0.069)
	3	b				
	4	b				

Table 19 continued

Patient Number	Day	Treatment*	Mean (sd) double support time (seconds) at time (hours)**			
			0	2	4	6
6	1	Placebo	0.118(0.062)	0.134(0.078)	0.134(0.076)	0.128(0.040)
	2	Active	0.117(0.072)	0.084(0.028)	0.084(0.031)	0.090(0.045)
	3	Placebo	0.114(0.037)	0.102(0.063)	0.118(0.047)	0.122(0.045)
	4	Active	0.108(0.038)	0.084(0.045)	0.077(0.039)	0.062(0.017)
7	1	Active	0.150(0.072)	0.100(0.060)	0.115(0.067)	0.113(0.049)
	2	Placebo	0.125(0.033)	0.146(0.056)	0.180(0.052)	0.152(0.061)
	3	Active	0.133(0.042)	0.097(0.050)	0.107(0.036)	0.108(0.038)
	4	Placebo	0.135(0.044)	0.153(0.064)	0.160(0.047)	0.193(0.075)
8	1	Placebo	0.300(0.100)	0.384(0.121)	0.193(0.097)	0.238(0.137)
	2	Active	0.466(0.148)	0.184(0.064)	0.207(0.089)	0.528(0.286)
	3	Placebo	0.257(0.065)	0.297(0.217)	0.513(0.140)	0.529(0.267)
	4	Active	0.496(0.205)	0.088(0.023)	0.288(0.060)	0.197(0.055)
9	1	Active	0.204(0.044)	0.190(0.114)	0.138(0.062)	0.114(0.037)
	2	Placebo	0.186(0.058)	0.156(0.050)	0.166(0.101)	0.123(0.034)
	3	Active	0.245(0.054)	0.202(0.061)	0.203(0.045)	0.177(0.058)
	4	Placebo	0.188(0.062)	0.243(0.085)	0.198(0.075)	0.268(0.079)
10	1	Active	0.146(0.072)	0.117(0.051)	0.103(0.051)	0.181(0.089)
	2	Placebo	0.134(0.044)	0.124(0.044)	0.149(0.052)	0.132(0.037)
	3	Active	0.186(0.095)	0.172(0.070)	0.133(0.042)	0.172(0.049)
	4	Placebo	0.169(0.077)	0.152(0.047)	0.149(0.086)	0.173(0.061)

Table 19 continued

Patient Number	Day	Treatment*	Mean (sd) double support time (seconds) at time (hours)**			
			0	2	4	6
11	1	Placebo	0.125(0.049)	0.084(0.032)	0.095(0.033)	0.080(0.023)
	2	Active	0.098(0.060)	0.078(0.043)	0.070(0.026)	0.068(0.036)
	3	Placebo	0.080(0.029)	0.097(0.032)	0.078(0.030)	0.080(0.033)
	4	Active	0.093(0.027)	0.045(0.017)	0.056(0.037)	0.053(0.025)
12	1	Placebo	0.246(0.062)	0.309(0.185)	0.264(0.106)	0.249(0.082)
	2	Active	0.217(0.079)	0.303(0.258)	0.265(0.096)	0.281(0.124)
	3	Placebo	0.300(0.108)	0.133(0.084)	0.150(0.077)	0.123(0.042)
	4	Active	0.141(0.061)	0.120(0.045)	0.136(0.033)	0.103(0.027)
13	1	Active	0.088(0.032)	0.093(0.038)	0.100(0.036)	0.093(0.029)
	2	Placebo	0.093(0.028)	0.111(0.041)	0.111(0.023)	0.113(0.049)
	3	Active	0.119(0.051)	0.174(0.057)	0.156(0.044)	0.160(0.051)
	4	Placebo	0.154(0.053)	0.141(0.044)	0.143(0.028)	0.152(0.051)
14	1	Placebo	0.057(0.022)	0.050(0.023)	0.053(0.021)	0.050(0.043)
	2	Active	0.061(0.038)	0.044(0.026)	0.047(0.025)	0.044(0.026)
	3	Placebo	0.053(0.031)	0.041(0.019)	0.053(0.020)	0.057(0.029)
	4	Active	0.056(0.028)	0.057(0.022)	0.050(0.022)	0.050(0.022)

* – treatment with one active Sinemet-Plus tablet or one placebo Sinemet-Plus tablet

** – time (hours) following the tablet administration time

a – failure of monitoring equipment

b – treatment not given due to intercurrent illness

Table 20   Values of mean (sd) swing length for the entire walk

Patient Number	Day	Treatment*	Mean (sd) swing length (cm) at time (hours)**			
			0	2	4	6
1	1	Active	9.0(3.2)	a	a	13.2(3.7)
	2	Placebo	15.9(5.0)	a	12.9(3.6)	11.3(3.5)
	3	Active	14.4(2.7)	11.6(2.9)	7.8(1.6)	8.0(1.7)
	4	Placebo	16.8(6.5)	17.9(2.7)	14.6(5.5)	8.7(2.1)
2	1	Placebo	44.2(12.5)	47.8(16.6)	44.1(10.8)	60.1(13.1)
	2	Active	51.2(9.6)	45.8(11.4)	51.4(7.6)	59.5(12.2)
	3	Placebo	71.1(14.9)	77.3(13.4)	71.0(14.4)	56.3(9.3)
	4	Active	62.7(12.9)	74.0(13.0)	80.9(16.1)	79.5(16.7)
3	1	Active	76.2(7.4)	72.8(7.1)	84.9(5.9)	75.2(12.8)
	2	Placebo	66.5(9.9)	63.3(6.5)	67.9(8.5)	68.2(5.0)
	3	Active	70.1(11.2)	64.7(9.7)	82.4(8.2)	80.6(8.4)
	4	Placebo	76.9(8.0)	71.6(6.9)	73.7(4.9)	79.5(9.4)
4	1	Active	14.2(3.4)	18.9(5.5)	20.8(4.1)	20.2(4.0)
	2	Placebo	17.1(3.0)	12.5(5.6)	16.2(4.0)	16.4(4.5)
	3	b				
	4	b				
5	1	Placebo	24.2(3.7)	35.3(3.7)	39.8(4.6)	52.4(7.2)
	2	Active	25.6(3.6)	26.1(4.1)	24.8(2.8)	38.1(3.4)
	3	b				
	4	b				

Table 20 continued

			Mean (sd) swing length (cm) at time (hours)**			
Patient Number	Day	Treatment*	0	2	4	6
6	1	Placebo	75.6(9.7)	73.4(7.5)	75.0(6.5)	73.1(4.9)
	2	Active	73.0(8.5)	87.4(10.1)	88.5(6.9)	84.3(10.0)
	3	Placebo	75.0(8.6)	75.0(11.6)	72.2(6.5)	69.1(7.4)
	4	Active	80.6(9.3)	87.6(14.0)	78.0(9.9)	82.3(8.5)
7	1	Active	56.0(12.3)	69.9(15.6)	67.5(14.3)	72.4(10.1)
	2	Placebo	62.2(7.3)	64.4(6.8)	55.8(9.6)	61.5(13.0)
	3	Active	64.6(11.2)	72.8(12.2)	63.6(10.3)	61.6(13.1)
	4	Placebo	54.0(6.8)	52.0(11.2)	58.6(7.5)	46.9(12.8)
8	1	Placebo	15.9(3.9)	14.4(1.6)	10.5(4.3)	7.7(4.5)
	2	Active	3.6(1.1)	9.1(2.2)	12.1(2.2)	6.2(1.6)
	3	Placebo	14.3(2.9)	15.6(1.8)	6.3(0.8)	6.4(1.6)
	4	Active	10.1(2.1)	56.7(1.8)	10.0(1.0)	10.6(6.0)
9	1	Active	24.0(4.0)	24.9(7.3)	29.6(6.3)	30.5(7.8)
	2	Placebo	28.9(6.6)	38.1(7.7)	36.8(7.4)	35.1(5.3)
	3	Active	23.1(5.7)	25.6(5.9)	23.4(3.4)	26.0(4.8)
	4	Placebo	25.5(4.8)	26.7(6.5)	28.9(5.8)	22.8(5.0)
10	1	Active	42.3(10.2)	47.0(9.6)	53.9(9.4)	37.2(10.3)
	2	Placebo	51.9(9.4)	57.7(8.2)	46.7(11.1)	47.0(9.3)
	3	Active	49.2(5.0)	45.1(7.8)	49.5(5.7)	45.7(6.7)
	4	Placebo	40.2(11.2)	44.6(5.5)	47.7(9.2)	42.1(9.0)

Table 20 continued

Patient Number	Day	Treatment *	Mean (sd) swing length (cm) at time (hours)**			
			0	2	4	6
11	1	Placebo	86.4(5.5)	92.2(10.6)	105.2(7.8)	101.7(13.1)
	2	Active	104.9(9.0)	103.9(6.2)	100.0(3.8)	98.2(5.7)
	3	Placebo	88.5(7.7)	104.0(3.2)	99.0(7.5)	97.2(7.1)
	4	Active	100.1(4.4)	111.0(8.5)	106.6(7.5)	115.5(6.9)
12	1	Placebo	12.0(3.0)	8.0(3.0)	13.7(7.1)	13.0(4.3)
	2	Active	25.8(9.2)	19.3(7.1)	25.0(6.0)	24.8(6.8)
	3	Placebo	39.9(8.6)	34.0(9.2)	29.0(7.1)	36.1(7.0)
	4	Active	38.5(4.9)	38.1(6.4)	39.4(7.4)	37.6(5.7)
13	1	Active	96.1(13.8)	99.3(17.2)	91.2(17.9)	95.5(18.4)
	2	Placebo	88.4(13.1)	81.9(15.7)	81.8(15.1)	81.0(15.1)
	3	Active	75.8(14.8)	66.3(13.4)	71.9(8.6)	66.5(14.0)
	4	Placebo	69.2(15.8)	75.3(12.1)	74.7(10.2)	67.1(13.9)
14	1	Placebo	123.1(8.2)	117.4(6.4)	119.2(8.3)	115.9(16.8)
	2	Active	111.8(11.9)	120.7(18.8)	120.5(10.3)	119.2(10.0)
	3	Placebo	120.5(10.1)	114.5(22.2)	112.9(12.4)	116.8(7.1)
	4	Active	110.4(7.3)	118.6(7.7)	114.1(14.4)	112.8(16.1)

* - treatment with one active Sinemet-Plus tablet or one placebo
     Sinemet-Plus tablet

** - time (hours) following the tablet administration time

a - failure of monitoring equipment

b - treatment not given due to intercurrent illness

In the subsequent analysis, these values were standardised as described on page 211. In each case, the measurement at time 0 hour is a pre-dose value. Negative values could arise if this value was greater than those of the 2, 4, or 6 hour measurements. The grand mean for the standardised double support time on active treatment was -0.037 seconds and on placebo treatment was -0.006 seconds. The mean (sd) percentage change in double support time between active and placebo treatments was -16.4(4.6) per cent. The grand mean of the standardised swing length on active treatment was 38.4mm and on placebo treatment was 2.5mm, giving a mean (sd) difference between active and placebo treatments of 35.9(12.3)mm.

Using analysis of variance a significant difference was detected between active and placebo treatments in mean double support time and mean swing length ($p<0.001$ and $p<0.004$ respectively), (Figure 29). However, there was a highly significant ($p<0.0005$) interaction between nature, order and the repetition of treatment(s) with respect to the mean swing length. Further analysis of the double support time showed no significant difference between the serial (2, 4 and 6 hour) post-treatment measurements.
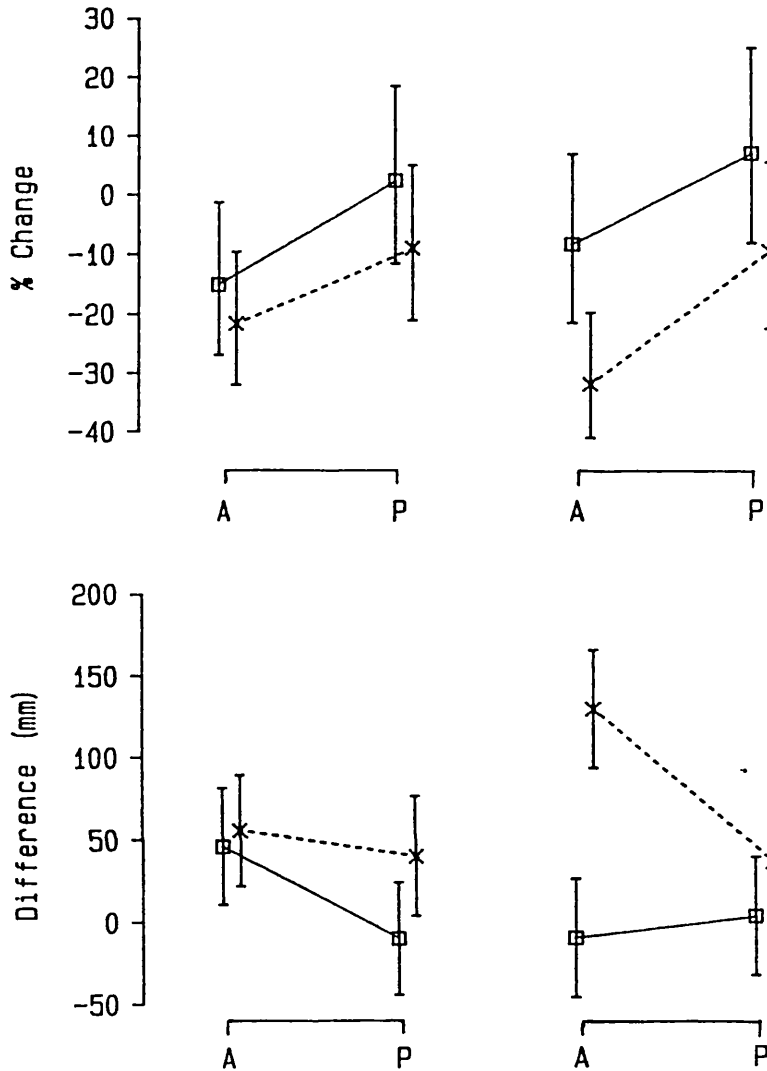
Figure 29   Effect of active and placebo treatment on a)
             the percentage change in mean double support
             time and b) the difference in mean swing
             length. The two administrations of active
             and placebo treatments have been analysed
             separately.
             A - active treatment, P - placebo treatment
             □———□ - mean standardised values of the 2, 4
             and 6 hour assessments of patients receiving
             active treatment then placebo
             x---x - mean standardised values of the 2, 4
             and 6 hour assessments of patients receiving
             placebo treatment then active
             The bars are the 95 per cent confidence
             intervals for these means.

In tables 21 to 25 in this section, the values of gait parameters for three patients with varying degrees of mobility are shown to give an idea of the range of deficits within the patient group. Patient 1 was severely disabled and patient 10 moderately disabled, whilst patient 14 was relatively agile. Values for all the patients are reported in the Appendices.

The values of speed of walking and cadence for the three patients are shown in Table 21. The data for all 14 patients are shown in Appendix 30. No significant difference was detected between treatments using analysis of variance with respect to either of these two parameters, nor to the simple "timed walking" test, values of which are shown in Table 22 and Appendix 34.

Table 21   Values of speed of walking and cadence for the entire walk for three patients

Patient Number	Day	Treatment *	Speed of walking (cm/second)** at time (hours)				Cadence (number of swings/minute) at time (hours)			
			0	2	4	6	0	2	4	6
1	1	Active	2.85	a	a	3.03	36.06	a	a	35.73
	2	Placebo	3.58	a	2.73	2.63	27.63	a	29.45	27.60
	3	Active	2.56	1.83	1.48	1.18	26.92	30.58	28.25	29.58
	4	Placebo	3.01	2.96	2.55	2.05	27.14	24.80	28.31	27.92
10	1	Active	34.06	37.94	44.00	28.53	94.33	94.38	96.20	90.86
	2	Placebo	37.70	43.75	39.44	40.24	98.82	103.64	97.67	102.44
	3	Active	38.44	32.86	36.64	34.67	92.31	85.25	90.84	89.05
	4	Placebo	31.98	37.35	41.63	32.89	96.90	97.32	103.45	91.39
14	1	Placebo	105.65	103.82	105.50	102.63	92.31	94.38	95.45	98.82
	2	Active	87.82	105.00	109.87	110.92	89.26	95.45	96.55	100.00
	3	Placebo	106.56	101.42	98.55	104.00	93.85	94.92	97.74	95.45
	4	Active	93.00	103.32	92.70	97.30	94.32	92.82	92.31	98.18

* - treatment with one active Sinemet-Plus tablet or one placebo Sinemet-Plus tablet

** - time (hours) following the tablet administration time

a - failure of monitoring equipment

Table 22   Time taken to walk an individually set distance ("timed walking" test) for three patients

Patient Number	Day	Treatment*	Distance walked (metres)+	Time (seconds) to walk set distance at time (hours)**			
				0	2	4	6
1	1	Active	6	413	285	130	335
	2	Placebo		225	182	195	165
	3	Active		343	332	691	512
	4	Placebo		244	266	299	310
10	1	Active	10	50	43	43	42
	2	Placebo		36	31	33	39
	3	Active		46	36	36	43
	4	Placebo		42	35	30	36
14	1	Placebo	12	11	11	11	11
	2	Active		11	12	12	12
	3	Placebo		11	12	11	12
	4	Active		11	11	12	12

* – treatment with one active Sinemet-Plus tablet or one placebo Sinemet-Plus tablet

** – time (hours) following the tablet administration time

+ – distance walked by patient measured from chair to turning point and back

ii) <u>Analysis of steady state gait</u>

Double support time, swing length and swing time were analysed for the first four swings and double support times (two gait cycles) of "steady state". The mean (sd) values of these parameters for each walk for the three patients are shown in Tables 23, 24 and 25 respectively. The respective values for all 14 patients are shown in Appendices 31, 32 and 33. Using analysis of variance no significant differences were detected between active and placebo treatments with respect to any of these variables.

Table 23   Values of mean (sd) double support time for the first four swings of
          "steady state" gait for three patients

Patient Number	Day	Treatment*	Mean (sd) double support time (seconds) at time (hours)**			
			0	2	4	6
1	1	Active	1.338(0.682)	a	a	1.075(0.665)
	2	Placebo	1.200(0.173)	a	1.363(0.229)	1.219(0.213)
	3	Active	1.113(0.085)	0.894(0.711)	1.256(0.576)	1.213(0.525)
	4	Placebo	1.006(0.171)	1.375(0.143)	1.156(0.043)	1.356(0.831)
10	1	Active	0.113(0.032)	0.094(0.013)	0.063(0.025)	0.275(0.117)
	2	Placebo	0.150(0.046)	0.081(0.031)	0.106(0.013)	0.119(0.031)
	3	Active	0.144(0.024)	0.188(0.043)	0.131(0.024)	0.125(0.035)
	4	Placebo	0.106(0.013)	0.144(0.024)	0.106(0.013)	0.119(0.055)
14	1	Placebo	0.050(0.020)	0.044(0.013)	0.050(0.000)	0.031(0.013)
	2	Active	0.044(0.013)	0.038(0.014)	0.031(0.013)	0.038(0.014)
	3	Placebo	0.038(0.014)	0.038(0.014)	0.044(0.013)	0.050(0.000)
	4	Active	0.044(0.013)	0.050(0.020)	0.038(0.014)	0.038(0.014)

*   – treatment with one active Sinemet-Plus tablet or one placebo Sinemet-Plus
       tablet

** – time (hours) following the tablet administration time

a   – failure of monitoring equipment

Table 24 Values of mean (sd) swing length for the first four swings of "steady state" gait for three patients

Patient Number	Day	Treatment*	Mean (sd) swing length (cm) at time (hours)**			
			0	2	4	6
1	1	Active	13.0(0.5)	a	a	16.8(0.0)
	2	Placebo	21.0(1.9)	a	16.5(2.5)	17.2(4.1)
	3	Active	17.1(2.4)	15.3(1.5)	8.0(3.1)	8.8(1.0)
	4	Placebo	26.0(1.9)	21.3(1.6)	20.3(1.7)	10.8(1.7)
10	1	Active	46.8(3.4)	53.1(3.0)	62.2(4.0)	30.1(3.2)
	2	Placebo	55.0(2.6)	62.0(3.6)	51.7(6.9)	47.6(7.3)
	3	Active	52.4(2.4)	45.9(3.1)	51.5(4.8)	51.2(2.8)
	4	Placebo	51.2(7.1)	43.0(7.0)	54.6(7.5)	47.0(2.7)
14	1	Placebo	129.1(1.9)	122.2(0.7)	124.3(2.4)	122.9(4.0)
	2	Active	120.4(1.9)	132.2(6.0)	127.7(3.3)	126.0(2.9)
	3	Placebo	128.1(2.9)	128.2(2.8)	122.4(1.1)	121.7(3.0)
	4	Active	115.2(1.5)	123.8(2.6)	123.6(1.1)	124.5(3.0)

* – treatment with one active Sinemet-Plus tablet or one placebo Sinemet-Plus tablet

** – time (hours) following the tablet administration time

a – failure of monitoring equipment

Table 25   Values of mean (sd) swing time for the first four swings of "steady state" gait for three patients

Patient Number	Day	Treatment*	Mean (sd) swing time (seconds)** at time (hours)			
			0	2	4	6
1	1	Active	0.475(0.087)	a	a	0.600(0.129)
	2	Placebo	1.063(0.317)	a	0.700(0.071)	0.838(0.155)
	3	Active	0.838(0.214)	0.731(0.191)	0.563(0.050)	0.469(0.125)
	4	Placebo	1.000(0.079)	0.963(0.085)	0.913(0.118)	0.619(0.189)
10	1	Active	0.506(0.055)	0.538(0.032)	0.506(0.013)	0.481(0.066)
	2	Placebo	0.550(0.041)	0.569(0.063)	0.525(0.029)	0.463(0.032)
	3	Active	0.519(0.024)	0.531(0.024)	0.494(0.055)	0.569(0.055)
	4	Placebo	0.494(0.105)	0.488(0.066)	0.481(0.024)	0.481(0.055)
14	1	Placebo	0.594(0.013)	0.588(0.025)	0.588(0.088)	0.569(0.024)
	2	Active	0.625(0.020)	0.594(0.043)	0.600(0.020)	0.563(0.032)
	3	Placebo	0.588(0.088)	0.569(0.109)	0.563(0.103)	0.575(0.087)
	4	Active	0.581(0.097)	0.569(0.080)	0.581(0.097)	0.563(0.088)

*   – treatment with one active Sinemet-Plus tablet or one placebo Sinemet-Plus tablet

** – time (hours) following the tablet administration time

a   – failure of monitoring equipment

Effect of a morning dose of Sinemet-Plus on manual dexterity

The buttoning test was not completed by all patients in the maximum time allowed of 2 minutes. The number of buttons which a given patient consistently managed on all occasions was therefore taken as the end point of the test. The number of buttons consistently managed and the time taken to do up this number for the same three patients previously selected are shown in Table 26. The relevant data for all the patients are reported in Appendix 35. In addition, the times taken for each button throughout the test are shown in Appendix 36. The times taken to complete the above number were compared for each patient. No significant difference was detected between active and placebo treatments using this test.

Table 26 Time taken to complete a given number of buttons for three patients

Patient Number	Day	Treatment *	Number of buttons consistently done up	Time (seconds) to do up given number of buttons at time (hours)**			
				0	2	4	6
1	1	Active	1+	84	60	a	75
	2	Placebo		30	54	41	30
	3	Active		85	a	a	a
	4	Placebo		120	a	55	a
10	1	Active	5	76	77	59	45
	2	Placebo		70	46	98	52
	3	Active		62	50	42	35
	4	Placebo		34	33	33	76
14	1	Placebo	9	59	46	58	50
	2	Active		67	52	49	53
	3	Placebo		56	41	70	57
	4	Active		41	35	59	40

* - treatment with one active Sinemet-Plus tablet or one placebo Sinemet-Plus tablet

** - time (hours) following the tablet administration time

+ - patient unable to do up even only one button consistently

a - maximum time of 2 minutes exceeded

Repeatability of the measurements

The existence of any systematic change from day to day in the variables listed in Table 27 on placebo treatment was tested using a 2 way analysis of variance. In each case, the mean value of the four time points was tested for each day. As can be seen from the table no significant day to day variation could be detected in any of the variables thus the two days upon which each patient received placebo treatment could be considered to be replications of each other.

Table 27   Repeatability of the measurements

	F value (variance ratio)	degrees of freedom	p value for 2 way ANOVA test for differences between occasions
Mean swing length for entire walk (cm)	0.158	1, 11	$0.10 < p < 0.25$
Mean double support time for entire walk (seconds)	0.461	1, 11	$0.50 < p < 0.75$
Mean swing length for 4 steps* (cm)	0.119	1, 11	$0.50 < p < 0.75$
Mean double support time for 4 steps* (seconds)	0.276	1, 11	$0.50 < p < 0.75$
Mean swing time for 4 steps* (seconds)	0.357	1, 11	$0.50 < p < 0.75$
Speed of walking (cm/second)	0.273	1, 11	$0.50 < p < 0.75$
Cadence (swings/minute)	0.831	1, 11	$0.25 < p < 0.50$
Walking time (seconds)	1.648	1, 10**	$0.10 < p < 0.25$
Buttoning time (seconds)	1.269	1, 11	$0.25 < p < 0.50$

* - calculated for the first four steps of "steady state" gait only

** - the simple "timed walking" test was omitted in patient 12 as a complete battery of tests was considered unfeasible

Effect of treatment with Sinemet-Plus on foot strike as assessed by pedobarography

The mean number of steps analysed was six. However, the number of steps assessed varied considerably between patients, and in some cases, between treatments within patients. This was due to the difficulty in placing the foot in a suitable position with respect to the glass plate. The marked immobility of many of the patients was such that they were not capable of walking for long periods of time, thus a variable number of steps was obtained. More work is obviously needed using constant numbers of steps to obtain comparable foot strike indices.

In 9 of the 14 patients the foot strike index was more abnormal on placebo than on active treatment (Table 28 and Figure 30). A significant improvement in index on active treatment ($p<0.05$) was detected using the Wilcoxon signed rank test. However, this result may have been due to a more favourable distribution of the number of foot strikes assessed. Cochran's weighted test (Armitage and Berry, 1987) was therefore applied. Using this, a highly significant ($p=0.004$) reduction in the number of more normal strikes, i.e. heel strikes plus simultaneous heel and forefoot strikes, was found.

No relationship was detected between age, severity of Parkinson's disease (as rated by the Webster Scale), duration of levodopa therapy, or the distance/time parameters of the gait assessment and the index of foot

strike (p>0.05 in each case). Indeed the patient with

the most abnormal index (0.083) even had a normal

posture.

Table 28   Nature of foot strike as assessed by pedobarography

Patient Number	Order of Treatment *	Total number of steps assessed		Number of heel strikes		Number of simultaneous heel and forefoot strikes		Number of forefoot strikes		Foot strike index **	
		Active	Placebo	Active	Placebo	Active	Placebo	Active	Placebo	Active	Placebo
1	P/A	7	2	0	0	2	1	5	1	0.143	0.250
2	P/A	9	10	1	0	6	3	2	7	0.444	0.150
3+	P/A	5	10	4	9	1	1	0	0	0.900	0.950
4	A/P	3	5	0	0	2	3	1	2	0.333	0.300
5+	P/A	6	5	2	1	4	4	0	0	0.667	0.600
6	P/A	6	6	6	5	0	0	0	1	1.000	0.833
7	P/A	6	8	0	1	6	7	1	0	0.500	0.563
8	A/P	6	4	1	0	4	3	1	1	0.500	0.375
9+	A/P	6	8	2	0	4	6	0	2	0.667	0.375
10	A/P	8	6	0	0	7	4	1	2	0.438	0.333
11	P/A	7	7	1	1	5	2	1	4	0.500	0.286
12	A/P	1	5	1	0	0	1	0	4	1.000	0.100
13+	A/P	8	8	8	8	0	0	0	0	1.000	1.000
14+	A/P	6	6	0	0	1	1	5	5	0.083	0.083

*   -   A - one active Sinemet-Plus tablet, P - one placebo Sinemet-Plus tablet

**   -   <u>number of heel strikes + (number of simultaneous heel and forefoot strikes/2)</u>
                total number of steps

+   -   the first pedobarography did not correspond to the first day on which serial blood
        sampling took place due to the monitoring equipment being unavailable
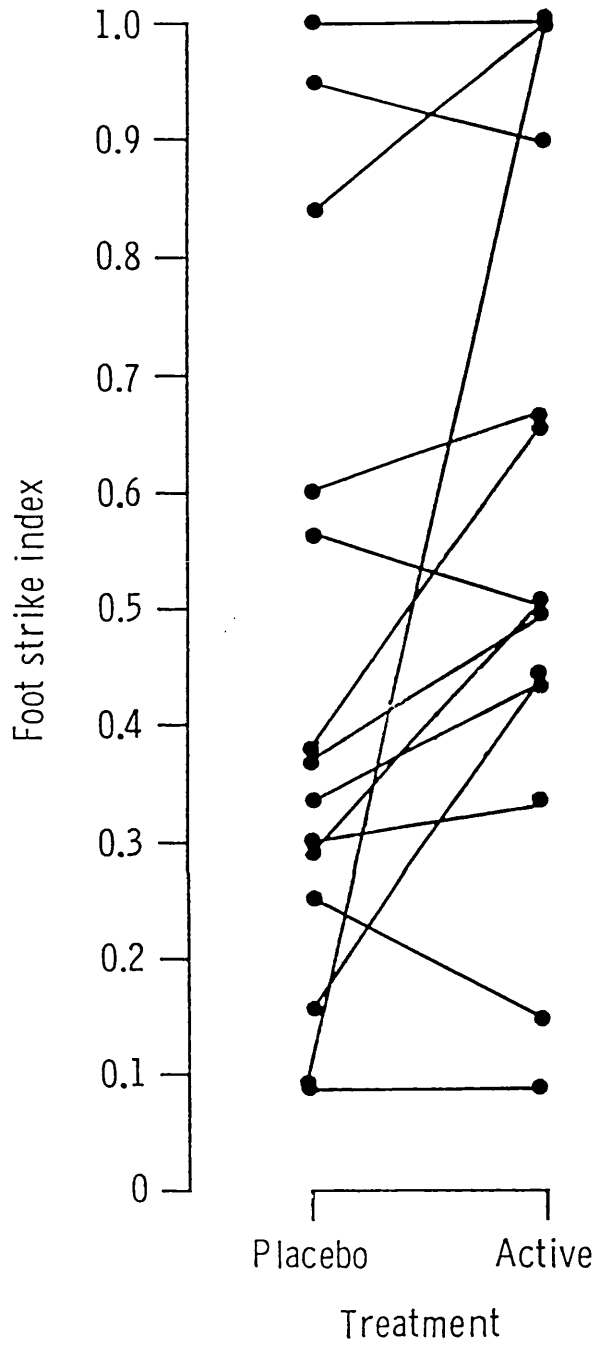
<u>Figure 30</u>   Foot strike index on active and placebo
treatments

Effect of treatment on performance as monitored by video recording

The results of the comparison of each patient's overall performance two hours after the administration of active or placebo Sinemet-Plus as monitored by video recording are shown in Table 29. No significant difference between active or placebo treatment was detected using the binomial distribution.

Table 29 Comparison of the video recordings taken two hours after the tablet administration at 10.00h.

Patient Number	Order of Treatment *	Treatment	
		Active	Placebo
1	P/A	1**	0
2	P/A	1	0
3+	P/A	1	0
4	A/P	0	1
5+	P/A	0	1
6	P/A	1	0
7	P/A	1	0
8	A/P	1	0
9+	A/P	1	0
10	A/P	0	1
11	P/A	1	0
12	A/P	1	0
13+	A/P	1	0
14+	A/P	0	1

 * - A - one tablet of active Sinemet-Plus
     P - one tablet of placebo Sinemet-Plus
** - 1 - the better overall performance of the two
     occasions and 0 - the worst
 + - the first video recording did not correspond to
     the first day on which serial blood sampling took
     place due to the monitoring equipment not being
     available

Characterisation of foot strike: comparative evaluation of video recording and pedobarography

Pedobarography is not commonly available therefore the video recordings were reanalysed paying attention only to foot strike (Table 30). If video recordings were to be as sensitive to the nature of foot strike as pedobarography then the former technique would obviously have universal applicability. For the purpose of this comparison those occasions on which less than three steps were available for analysis on pedobarography or on the video recordings were discarded. Twenty-five pairs of data were then available as plotted in Figure 31.

More abnormal foot strikes were detected using pedobarography than using video recording (Figure 31), but the difference in index (mean (sd) 0.1(0.2)) did not reach significance even at the 10 per cent level (p>0.1) for the 25 comparisons made. However, an obvious problem with the video recording method is that since it is a subjective measurement it is liable to the effects of observer fatigue.

Table 30   Nature of foot strike as assessed by video recording

Patient Number	Order of Treatment *	Total number of steps assessed		Number of heel strikes		Number of simultaneous heel and forefoot strikes		Number of forefoot strikes		Foot strike index **	
		Active	Placebo	Active	Placebo	Active	Placebo	Active	Placebo	Active	Placebo
1	P/A	6	6	0	0	3	1	3	5	0.250	0.083
2	P/A	6	6	2	2	3	4	1	0	0.583	0.667
3+	P/A	6	6	5	4	1	2	0	0	0.917	0.833
4	A/P	6	6	0	0	5	6	1	0	0.417	0.500
5+	P/A	6	6	1	0	3	6	2	0	0.417	0.500
6	P/A	6	6	6	2	0	4	0	0	1.000	0.667
7	P/A	6	6	1	0	5	5	0	1	0.583	0.417
8	A/P	6	6	2	0	4	5	0	1	0.667	0.417
9+	A/P	6	6	0	0	6	5	0	1	0.500	0.417
10	A/P	6	6	0	0	6	5	0	1	0.500	0.417
11	P/A	2***	3***	0	1	2	1	0	1	0.500	0.500
12	A/P	6	6	0	0	3	3	3	3	0.250	0.250
13+	A/P	6	6	6	6	0	0	0	0	1.000	1.000
14+	A/P	6	6	2	4	4	2	0	0	0.667	0.833

* – A – one active Sinemet-Plus tablet, P – one placebo Sinemet-Plus tablet
** – number of heel strikes + (number of simultaneous heel and forefoot strikes/2)
    ──
                              total number of steps

*** – video recording terminated prematurely
+ – the first video recording did not correspond to the first day on which serial blood
    sampling took place due to the monitoring equipment being unavailable
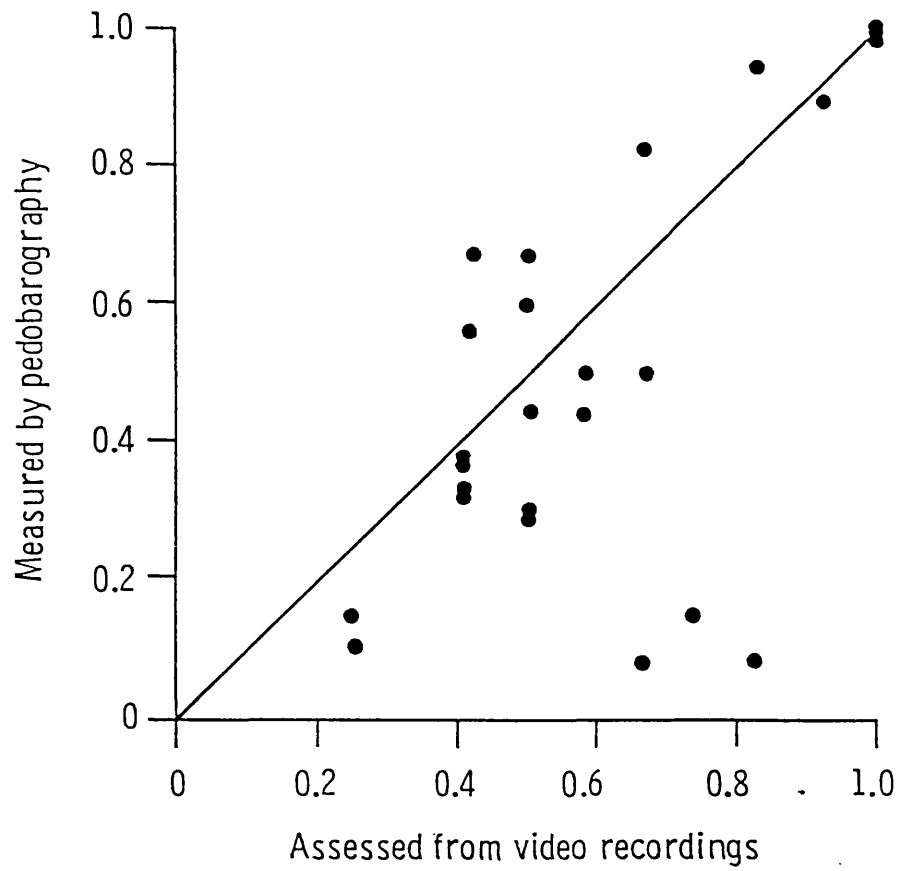
Figure 31   Foot strike index as assessed by two methods

Pharmacokinetics of levodopa in elderly patients with Parkinson's disease

The plasma levels of levodopa and the metabolite 3-O-methyldopa (3OMD) measured at hourly intervals up to 6 hours after dosing each patient with either placebo or active Sinemet-Plus are reported in Tables 31 and 32 respectively. Dr. S.G. Bowes measured the plasma samples from four of the patients, whilst the author was responsible for the assay of the remaining nine. Of the 14 patients who participated in the study of gait analysis, one declined to provide blood samples. For every other patient, except patient 1, the maximum observed concentration of levodopa was associated with a single peak 1 or 2 hours post-dose. Patient 1 had a greatly reduced extent of levodopa absorption and a plasma profile which exhibited two concentration peaks which could be due to her pattern of gastric absorption. The occurrence of multiple peaks has been attributed to erratic gastric emptying (Evans *et al*, 1981) who observed profiles of this type on administration of levodopa in the absence of a PDD inhibitor. Where a PDD inhibitor is not used, delayed gastric emptying itself may result in a smaller extent of absorption, as increased gastric decarboxylation will result in less levodopa reaching the site of absorption in the small intestine. In the presence of a PDD inhibitor, as in the present study, gastric delay should not have this effect. Since diet was

Table 31 Serial plasma concentrations of levodopa following the drug administration at 10.00h.

Plasma levodopa concentration (ng/ml) following:-

Patient Number *	Order of treatment **	ACTIVE treatment Number of hours post-treatment							PLACEBO treatment Number of hours post-treatment						
		0	1	2	3	4	5	6	0	1	2	3	4	5	6
1	P/A	105.3	116.2	121.8	247.0	184.7	253.0	197.6	84.4	76.6	65.4	66.0	54.7	44.0	40.8
2	P/A	42.6	386.2	135.7	147.3	81.5	60.5	40.5	-8.6 ***	-2.0	23.8	-7.3	-3.6	-8.2	-7.9
3	A/P	64.4	950.1	542.5	205.2	169.4	126.0	97.7	-21.8	-33.6	-21.4	-29.0	-28.2	-47.3	-60.8
4	A/P	6.2	393.7	337.6	206.3	94.0	56.2	42.2	2.5 +	-3.9	12.2	-4.1	7.9	-19.6	-4.1
5	A/P	62.5	330.0	149.7	80.7	65.4	72.8	40.7	44.0	19.4	34.5	101.3	239.6	37.8	109.5
6	P/A	17.0 +	560.6 +	252.9	170.4	92.3	30.3	30.8	-0.9	-11.7	9.4	40.3	4.9	10.3	15.7
8	A/P	-12.3	306.9	318.4 +	34.2	57.9	126.7	18.0	-15.1	1.5 ****+	-26.6 +	-21.2	-27.4	-26.6	-33.8
12	A/P	95.8	983.6	438.0	318.1	248.7	193.5 +'	202.2	95.8	95.8	95.8	95.8	95.8	95.8	95.8
14	P/A	112.8	875.3	405.1	265.0	203.6	156.3	106.4	43.4	61.5	99.1	144.6	63.6	39.1	85.3

Table 31 continued

Plasma levodopa concentration (ng/ml) following:-

Patient Number *	Order of treatment **	ACTIVE treatment Number of hours post-treatment							PLACEBO treatment Number of hours post-treatment						
		0	1	2	3	4	5	6	0	1	2	3	4	5	6
7	P/A	-11.8	232.3	202.2	107.5	52.0	4.2	-3.3	-29.5	-31.6	-14.8	10.4	-35.2	-23.3	-28.2
9	P/A	-21.2	588.6	561.8	344.5	131.0	78.9	20.5	-28.2	-20.4	-30.3	-34.8	-27.6	-27.6	-31.8
10	A/P	63.1	679.4	815.9	428.5 +	348.9	233.9	151.5	41.2	15.4	59.8	76.0	49.6	40.8	26.5
11	P/A	80.8	1101.6	472.5	246.1	205.7	152.0	1210.1	31.2	24.5	40.1	33.3	54.0	48.0	84.4

The following samples were analysed by Dr. S. Bowes:-

* - patient 13 declined to give blood samples
** - A - one active Sinemet-Plus tablet, P - one placebo tablet
*** - negative values were obtained in some instances where the regression line
      for the standard curve for that assay had a negative intercept
**** - sample taken at 1.5 hours post-treatment
+ - sample haemolysed

Table 32   Serial plasma concentrations of 3-O-methyldopa following the drug administration at 10.00h.

Plasma 3-O-methyldopa concentration (μg/ml) following:-

Patient Number	Order of treatment	ACTIVE treatment — Number of hours post-treatment							PLACEBO treatment — Number of hours post-treatment						
		0	1	2	3	4	5	6	0	1	2	3	4	5	6
1	P/A	8.16	7.42	7.03	7.01	6.96	6.56	6.72	10.89	7.78	7.85	8.53	8.25	6.25	6.94
2	P/A	4.98	5.41	5.36	5.19	4.94	4.97	4.72	2.66	2.61	2.48	2.48	2.46	2.27	2.06
3	A/P	7.50	6.94	7.15	7.38	7.04	5.55	4.62	7.85	6.63	5.85	5.46	5.55	5.33	5.50
4	A/P	3.90	3.65	3.72	3.57	3.55	3.84	3.34	4.94 +	4.26	4.04	3.63	3.34	3.43	3.02
5	A/P	6.50	6.91	6.76	6.40	6.04	5.50	5.58	6.60	5.80	5.73	5.47	5.16	4.99	5.14
6	P/A	6.40 +	12.51 +	6.21	6.07	5.58	5.69	5.52	4.89	5.12	4.62	4.41	4.32	3.99	3.94
8	A/P	7.25	6.77	10.47 +	6.69	6.14	6.47	6.19	8.12	13.90 *** +	10.45	8.20	7.43	7.40	7.25
12	A/P	4.72	5.00	4.94	4.66	4.71	5.92 +	4.60	5.39	4.99	4.77	4.27	4.17	3.51	3.97
14	P/A	3.57	3.55	3.31	3.38	3.23	3.44	3.23	3.15	2.83	3.03	3.03	2.68	2.43	2.98

Table 32 continued

Plasma 3-O-methyldopa concentration (μg/ml) following:-

Patient Number *	Order of treatment **	ACTIVE treatment Number of hours post-treatment							PLACEBO treatment Number of hours post-treatment						
		0	1	2	3	4	5	6	0	1	2	3	4	5	6
7	P/A	5.20	5.22	5.58	5.35	5.63	5.23	5.22	6.42	7.21	6.40	6.72	5.68	5.35	5.10
9	P/A	2.45	2.75	2.82	3.51	3.35	3.16	3.15	2.97	2.75	2.63	2.22	2.13	2.20	2.17
10	A/P	4.89	4.93	5.06	5.08+	5.41	5.18	4.98	5.32	4.85	5.06	4.38	4.08	4.13	3.96
11	P/A	2.95	2.56	2.88	2.82	2.71	2.78	2.75	3.47	2.94	2.98	2.75	2.83	2.63	2.63

The following samples were analysed by Dr. S. Bowes:-

* - patient 13 declined to give blood samples
** - A - one active Sinemet-Plus tablet, P - one placebo tablet
*** - sample taken at 1.5 hours post-treatment
+ - sample haemolysed

standardised and low in protein, it is unlikely that
differences in absorption could be explained by the
effect of food on gastric emptying, or competition for
active uptake by amino acids in the diet. Patient 1,
whilst showing no clinical signs of fluid overload at
the time of study, suffered from chronic bronchitis and
congestive heart failure and was cyanosed. Is is known
that hypoxia may reduce active transport of levodopa
(Wade *et al*, 1973) and so the data from patient 1 was
excluded from the subsequent pharmacokinetic analysis.

Figure 32 shows the mean plasma levodopa
concentrations at hourly intervals following treatment
with active and placebo Sinemet-Plus for the 12
patients included in the pharmacokinetic analysis. The
plasma profile of patient 1 is also shown.
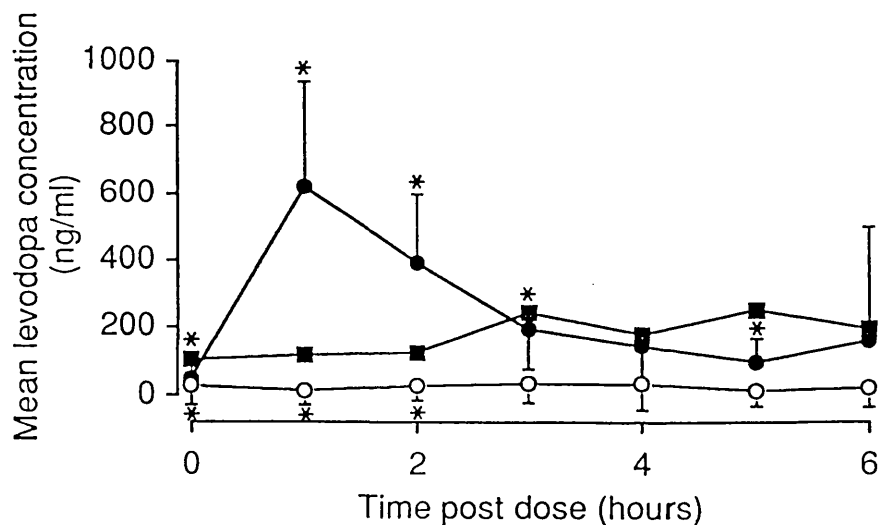
Figure 32   Mean plasma levodopa concentrations on
            active and placebo treatment days. Values
            given as a mean of 11 samples (*) instead of
            12 are due to haemolysis of some samples.
            ● - active treatment, O - placebo treatment
            ■ - patient 1

The decay in plasma 3OMD concentration on active
and placebo treatment days is shown in Figure 33. The
mean half-life of 3OMD in the twelve patients estimated
from the concentration/time plot was approximately 24
hours.
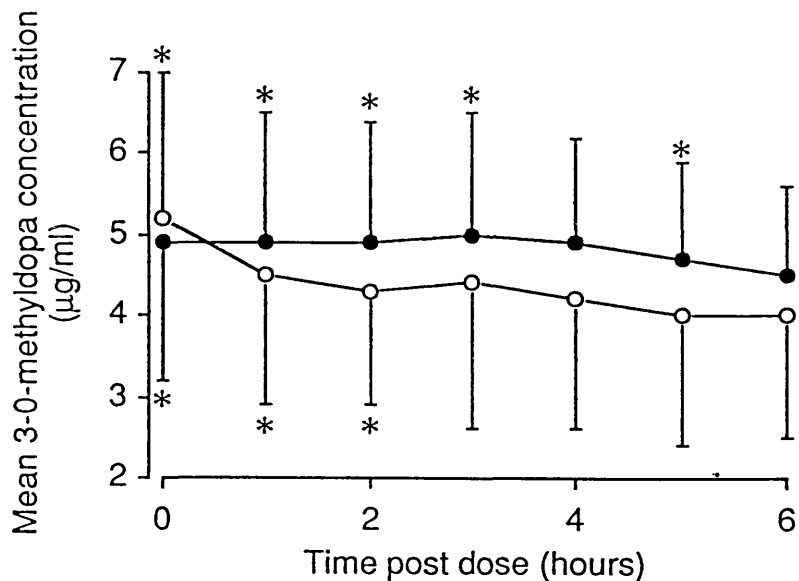
Figure 33   Mean plasma 3-O-methyldopa concentrations on
active and placebo treatment days.   Values
given as a mean of 11 samples (*) instead of
12 are due to haemolysis of some samples.
● - active treatment, o - placebo treatment

The area under the levodopa plasma
concentration/time curve between 0 and 6 hours post-
dose on the active treatment day (levodopa AUC_0^6) was
calculated using the trapezoidal rule after any
appropriate correction for any residual levodopa had
been subtracted.   The values of levodopa AUC_0^6, the
concomitant mean plasma 3OMD concentration (mean

[3OMD]) and the ratio of these two parameters for each

of the 12 patients are shown in Table 33.

Table 33   Values of the area under the levodopa plasma
concentration/time curve, the mean plasma
3-O-methyldopa concentration and the ratio of
these two parameters

Patient Number*	Levodopa AUC_0^6** (ng/mlh)	Mean (sd) [3OMD]*** (μg/ml)	Mean [3OMD] x 1000 / Levodopa AUC_0^6
2	1011	5.09(0.26)	5.03
3	1916	6.57(1.09)	3.43
4	1144	3.64(0.19)	3.18
5	588	6.24(0.56)	10.61
6	1165	5.82(0.31)++	5.00
7	641	5.33(0.19)	8.32
8	862	6.60(0.44)+	7.66
9	1782	3.04(0.38)	1.71
10	2312	5.08(0.19)+	2.20
11	2081	2.79(0.13)	1.34
12	1900	4.77(0.15)+	.2.51
14	1773	3.37(0.15)	1.90

   * - patient 1 had an atypical absorption profile
       therefore this data was excluded; patient 13
       declined to give blood samples
  ** - area under the levodopa plasma concentration/time
       curve for the 6 hour period post-treatment with
       one active Sinemet-Plus tablet
 *** - mean (sd) plasma 3-O-methyldopa concentration for
       the 6 hour period post-treatment with one active
       Sinemet-Plus tablet
   + - data on one haemolysed sample excluded
  ++ - data on two haemolysed samples excluded

The correlations of these parameters with age and

duration of levodopa therapy are shown in Table 34.

Table 34   Effect of age and duration of therapy on the
           pharmacokinetics of levodopa

Correlation co-efficients (r):

	Levodopa AUC $_0^t$ (ng/mlh)	Mean [3OMD] (µg/ml)	$\dfrac{\text{Mean [3OMD]}}{\text{Levodopa AUC}_0^t}$
Age (years)	-0.455	0.256	0.338
Duration of therapy (years)	-0.697*	0.599*	0.782**

Critical r value (DF=10) for p=0.1,   0.497
                          for p=0.05*, 0.576
                          for p=0.01**, 0.708
                          for p=0.001, 0.823

No significant effect of age on mean [3OMD],
levodopa AUC$_0^t$, or the ratio of these two values was
detected. However, there was a tendency for levodopa
AUC$_0^t$ to be less in the more aged patients. A
significant correlation was found between duration of
therapy and levodopa AUC$_0^t$, mean [3OMD] and the ratio of
these parameters. The relationship between duration of
therapy and the ratio of mean [3OMD] to levodopa AUC$_0^t$
is illustrated in Figure 34.
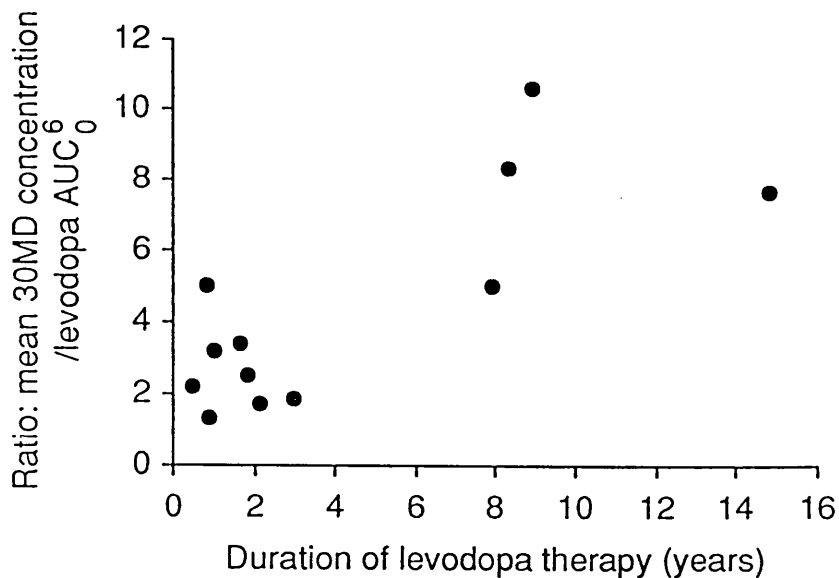
Figure 34   Effect of duration of therapy on the ratio of mean plasma 3-O-methyldopa concentration to area under the levodopa plasma concentration/time curve.

The decay of levodopa in the plasma of the elderly Parkinsonian patients was fitted to a monophasic function using a non-linear regression analysis.   The terminal slopes have been described in terms of an elimination rate constant (k_{el}) and half-life ($t_{1/2}$), which are reported in Table 35.   The mean half-life of 1.7 hours implies that a minimal amount of levodopa would remain in the plasma 12 hours after the administration of the evening dose of Sinemet-Plus. However, in many of the patients, residual and detectable traces of levodopa were found in samples taken just before the morning dose.   The kinetics of drug breakdown may differ between night-time and daytime, but such a difference is unlikely to be of

sufficient magnitude to explain the residuum. It is
possible that levodopa was being formed by other
chemical pathways (for example, by conversion of 3OMD).
The latter could also explain the detection of levodopa
in the plasma of patients after administration of the
placebo form. In this context, Rossor *et al* (1980)
found residual amounts of levodopa (0.3 to 6.1ng/ml) in
the plasma of Parkinsonian patients after their
levodopa therapy had been discontinued for 48 hours.
The values of levodopa AUC_0^∞ in ng/mlh are reported in
Table 35 and were calculated from the plasma data
using:

$$AUC_0^\infty = AUC_0^6 + \frac{1}{k_{el}} \{C_6 \sim C_0\}$$

In the expression, C_6 represents the value of the
measured plasma levodopa concentration at 6 hours post-
dose, and C_0 is the value of any initial pre-dose
concentration. For the sake of completeness a modified
form of Table 34 using these calculated values of
levodopa AUC_0^∞ is given in Table 36. The conclusions to
be drawn regarding the effect of age and duration of
therapy on the pharmacokinetics of levodopa remain
unchanged.

Table 35   Pharmacokinetic parameters of levodopa in
            twelve elderly patients with Parkinson's
            disease

Patient Number	AUC$_0^\infty$po* (ng/mlh)	k_{el} ± 95% confidence limits**	$t_{1/2}$*** (h)
2	1095	0.48 ± 0.05	1.46
3	2315	0.25 ± 0.09	2.80
4	1218	0.58 ± 0.14	1.21
5	718	0.31 ± 0.33	2.26
6	1212	0.65 ± 0.20	1.08
7	641	0.75 ± 0.32	0.93
8	889	0.67 ± 0.25	1.04
9	1814	0.65 ± 0.23	1.08
10	2787	0.32 ± 0.20	2.19
11	2438	0.43 ± 0.42	1.63
12	2596	0.28 ± 0.07	2.50
14	2093	0.33 ± 0.08	2.12

* - area under the levodopa plasma concentration/time
    curve from time zero to infinity post-treatment
    with one active Sinemet-Plus tablet
** - elimination rate constant
*** - plasma half-life of elimination   ·

Table 36   Effect of age and duration of therapy on the
            pharmacokinetics of levodopa (modification of
            Table 34)

	Correlation co-efficients (r):		
	Levodopa AUC$_0^\infty$ (ng/mlh)	Mean [3OMD] (µg/ml)	Mean [3OMD] / Levodopa AUC$_0^\infty$
Age (years)	-0.491	0.256	0.357
Duration of therapy (years)	-0.683*	0.599*	0.815**

Critical r value (DF=10) for p=0.1,   0.497
                        for p=0.05*,   0.576
                        for p=0.01**, 0.708
                        for p=0.001,   0.823

Relationship between plasma concentrations of levodopa
and 3-O-methyldopa, blood pressure and parameters of
gait

The values of the serial measurements of supine and
standing mean arterial blood pressure are reported in
Table 37. For each of the patients, gait and blood
pressure were measured at four time points, namely 0,
2, 4 and 6 hours post-dose, and plasma concentration
data at hourly intervals over the 6 hour period. The
measurements of swing length and double support time
might be related to blood pressure or the plasma
concentrations of either levodopa or 3OMD.
Furthermore, blood pressure itself might be related to
plasma levels of these chemical moieties. The presence
of such relationships was investigated using a within-
patient analysis of covariance. In such an analysis
the data recorded for each patient were fitted to an
appropriate regression line whose slope and intercept
were tested for statistical significance.

Table 37 Serial measurements of mean arterial blood pressure

Patient Number	Day	Treatment *	Position of patient **	Mean arterial blood pressure (mmHg) Number of hours post-treatment			
				0	2	4	6
1	1	P	L	102.7	110.0	110.0	999.9+
			S	93.3	114.0	104.7	999.9
	2	A	L	85.7	94.0	999.9	999.9
			S	87.7	108.3	999.9	999.9
2	1	P	L	96.7	93.3	85.0	101.7
			S	85.0	80.0	73.3	100.0
	2	A	L	86.7	98.7	101.7	100.0
			S	76.7	76.0	93.3	90.0
3	1	A	L	144.3	135.3	128.7	126.3
			S	126.0	140.0	132.7	134.3
	2	P	L	124.0	143.0	136.0	176.0
			S	132.0	127.3	141.3	160.7
4	1	A	L	105.0	113.3	110.0	999.9
			S	95.0	100.0	86.7	999.9
	2	P	L	126.7	126.7	130.0	999.9
			S	113.3	121.3	110.0	999.9
5	1	A	L	120.3	120.3	109.7	118.0
			S	101.1	102.5	101.4	101.2
	2	P	L	118.0	106.7	105.7	120.0
			S	110.7	102.0	89.0	109.7

Table 37 continued

Patient Number	Day	Treatment *	Position of patient **	Mean arterial blood pressure (mmHg) Number of hours post-treatment			
				0	2	4	6
6	1	P	L	142.0	120.7	102.7	119.3
			S	141.0	115.0	93.7	111.0
	2	A	L	130.3	102.0	116.7	134.7
			S	110.0	88.7	114.0	128.0
7	1	P	L	97.3	114.3	108.3	104.0
			S	999.9	103.3	94.7	90.3
	2	A	L	108.0	93.7	91.3	105.0
			S	97.0	100.0	83.3	94.0
8	1	A	L	108.0	83.7	84.7	999.9
			S	70.0	62.7	63.0	999.9
	2	P	L	70.0	108.7	79.7	90.3
			S	57.0	94.7	92.7	82.0
9	1	P	L	114.3	115.0	128.3	123.7
			S	111.7	107.7	112.0	149.3
	2	A	L	122.3	125.0	139.0	140.3
			S	125.0	110.0	138.0	122.7
10	1	A	L	·132.7	150.0	137.7	141.0
			S	105.7	99.3	103.0	102.0
	2	P	L	140.3	133.3	137.7	132.3
			S	131.3	102.0	103.3	96.0

Table 37 continued

Patient Number	Day	Treatment *	Position of patient **	Mean arterial blood pressure (mmHg) Number of hours post-treatment			
				0	2	4	6
11	1	P	L	87.0	105.7	113.7	106.3
			S	75.7	93.7	108.3	101.3
	2	A	L	98.0	97.0	93.7	91.7
			S	95.7	94.3	77.7	85.7
12	1	A	L	152.7	112.7	171.0	156.7
			S	93.7	78.0	113.3	153.3
	2	P	L	120.0	103.3	100.0	105.0
			S	120.0	103.3	100.0	999.9
13	1	P	L	106.7	103.3	98.0	96.7
			S	106.0	98.7	90.7	83.3
	2	A	L	112.7	108.7	102.0	999.9
			S	104.0	92.0	83.3	999.9
14	1	A	L	90.0	98.7	81.7	86.7
			S	88.3	86.7	75.3	90.0
	2	P	L	71.3	86.0	84.7	999.9
			S	76.7	87.3	87.3	999.9

* A – treatment with one active Sinemet-Plus tablet, P – treatment with one placebo Sinemet-Plus tablet

** L – patient in supine position, S – patient in standing position

+ – times when it was not possible to obtain a blood pressure reading due to the frailty of the patient have been denoted by 999.9

Relationships between the following pairs of
variables were examined.

i)   standing mean arterial   vs   [levodopa]*
     blood pressure at
     times 0, 2, 4 and 6   [3OMD]*
     hours post-dose on the
     active day of blood   [levodopa]/[3OMD]
     sampling

ii) the difference between   vs   [levodopa]
     standing and supine
     mean arterial blood   [3OMD]
     pressure at times 0, 2,
     4 and 6 hours post-dose   [levodopa]/[3OMD]
     on the active day of
     blood sampling

iii) mean double support   vs   [levodopa]
     time for the entire
     walk at times 0, 2,   [3OMD]
     4 and 6 hours post-
     dose on each active   [levodopa}/[3OMD]
     day of gait analysis
                                    standing mean arterial
                                      blood pressure

                                    the difference between
                                      standing and supine
                                      mean arterial blood
                                      pressure

iv) mean swing length for   vs   [levodopa]
     the entire walk at
     times 0, 2, 4 and 6   [3OMD]
     hours post-dose on
     each active day of   [levodopa]/[3OMD]
     treatment
                                    standing mean arterial
                                      blood pressure

                                    the difference between
                                      standing and supine
                                      mean arterial blood
                                      pressure

* [levodopa] - plasma concentration of levodopa at the
                respective times
   [3OMD]   - plasma concentration of 3OMD at the
                respective times

In the case of all the pairs of variables studied, no significant (p<0.05) differences between the slopes of the individual regression lines were detected. Consequently, further analysis was based on fitting regression lines with a common slope. Once again, for all the pairs of variables tested, no common slope significantly (p<0.05) different from zero could be detected and thus no evidence of a relationship between any of these pairs of variables within-patient could be inferred.

Further examination of the data was made with a view to uncovering the existence of between-patient relationships between pairs of variables. Accordingly the data was treated in the manner described previously for the ANOVA (page 211). For each patient and for each of the 9 variables listed below, the mean change of the values at 2, 4 and 6 hours compared to the 0 hour value was computed, and the difference in this mean change between active and placebo treatments calculated. Thus a single value for each variable was obtained for each patient. Regression analysis of the following pairs of variables was carried out.

v) Mean double support   vs   plasma levodopa
    time on each pair   concentration
    of active and
    placebo treatments   plasma 3OMD
                                     concentration

                                     ratio between plasma
                                     levodopa concentration
                                     and 3OMD concentration

                                     standing mean arterial
                                     blood pressure

                                     the difference between
                                     standing and supine
                                     mean arterial blood
                                     pressure

vi) Mean swing length   vs   plasma levodopa
    on each pair of   concentration
    active and placebo
    treatments   plasma 3OMD
                                       concentration

                                     ratio between plasma
                                     levodopa concentration
                                     and 3OMD concentration

                                     standing mean arterial
                                     blood pressure

                                     the difference between
                                     standing and supine
                                     mean arterial blood
                                     pressure

No significant relationships at the 0.05 level could be detected between any of these pairs of variables.

In an earlier section, a between-patient comparison was made of foot strike measured by pedobarography on active and placebo therapy (page 247). The existence of a correlation between the following pairs of variables, all measured at 2 hours post-dose, was now investigated. Since for any given patient the

variables were measured only at one time point, a within-patient analysis could not be attempted. To effect a between-patient analysis the corresponding value on the placebo treatment has been subtracted before testing.

vii) $(FSI)_A* - (FSI)_P*$ vs $[levodopa]_A - [levodopa]_P$

$$[3OMD]_A - [3OMD]_P$$

$$[levodopa]_A/[3OMD]_A - [levodopa]_P/[3OMD]_P$$

$$(standing\ BP)_A* - (standing\ BP)_P$$

$$(standing - supine\ BP)_A - (standing - supine\ BP)_P$$

```
* (FSI)  - foot strike index
  (BP)   - mean arterial blood pressure      .
   A     - treatment with one active Sinemet-Plus tablet
   P     - treatment with one placebo Sinemet-Plus
           tablet
```

The resulting correlation coefficients were not significant at the 0.05 level, thus no relationship could be detected between the clinical assessment of foot strike index and mean arterial blood pressure or concentration of either levodopa or 3OMD in the plasma.

CHAPTER EIGHT

DISCUSSION

Working with these patient groups presented a
number of problems. Recruitment of suitable patients
was not easy, and since many of the patients were
infirm it was very difficult to carry out repeat
testing. Because of the wide range of deficits evident
in the patients, it was necessary to adjust tests to
the capabilities of each particular patient. In
certain instances, it may be that tests which take the
patient to the limit of their ability could be more
discriminatory.

There was a wide range of disability within the
patient groups. However, each study was set up such
that the patient acted as their own control. The
repeatability of the parameters measured on placebo
days were tested using an analysis of variance. The
minimal values of the F ratio arising from these
analyses suggest that the within patient variability
was small compared to the between patient variability,
and indeed, that each of the parameters tested on
successive occasions could be considered to be
replicates.

In the study of the effect of Sinemet-Plus on
night-time and early morning mobility, the patients'
night-time movements in bed were measured using a bed
movement monitor, and their early morning performance
evaluated using a simple "timed walking" test and a
test of the time for ten blinks. The patients'
subjective opinion of how well they slept was assessed
using a visual analogue scale.

Spontaneous movement decreases during sleep (Cox
and Marley, 1959), the magnitude of the effect being
dependent on the depth of sleep (Loomis *et al*, 1937;
Blake *et al*, 1939). Thus the observed reduction in the
number of movements in bed in Parkinsonian patients on
levodopa therapy would seem to indicate that the
duration and/or depth of sleep was greater. This was
confirmed by the patients' subjective assessment of
quality of sleep. Hypnotics such as barbiturates,
meprobamate and flurazepam not only reduce spontaneous
movement during the night but can also impair mobility
on the following day (Hinton and Marley, 1959; Hinton,
1961; Crowley and Hydinger-Macdonald, 1979). However,
the beneficial effect of nocturnal dosing with levodopa
on morning performance observed here suggests that its
sleep inducing effect was secondary to improvement in
control of Parkinson's disease. In this respect, Lees
et al (1977) had previously found that difficulty in
turning voluntarily during the night was responsive to
dopaminergic therapy. The patient's improved ability
to turn in bed might allow a more comfortable position
to be adopted. This, together with the knowledge that
position in bed could be changed more easily might
itself be conducive to sleep.

Abnormal sensations of pain, tingling, numbness and
burning are themselves common and distressing
manifestations of Parkinson's disease (Snider *et al*,
1976; Koller, 1984; Nutt and Carter, 1984). These
phenomena have been ascribed both to excessive and to

inadequate doses of levodopa (Klawans *et al*, 1975; Nausieda *et al*, 1982; Askenasy and Yahr, 1985; Quinn *et al*, 1986). Discomfort and pain were, in fact, more common accompaniments of active than of placebo treatment in the present study, thus the improved sleep on levodopa could not be explained by a diminution in these symptoms.

In the preliminary study of bed movements in elderly patients in a geriatric rehabilitation unit (page 187), a reduction of movement in bed was found to be associated with a low mental test score and the presence of pressure sores. However, it is unlikely that the administration of bedtime doses of levodopa would have, in the longer term, predisposed the second patient group (page 226) to pressure sores. Although their improved quality of sleep resulted in less spontaneous movement in bed, these outpatients, despite being frail, were considerably less infirm than the inpatients of the former study.

The patients' performance of the "timed walking" test was found to be significantly better on active Sinemet-Plus than on placebo, despite the long interval between nocturnal dosing and the morning assessment. The ability in this study to discriminate between active and placebo treatments using a "timed walking" test is attributed to standardisation of the environment in which the test was performed, familiarity of the patient with both assessor and test procedure prior to entry into the study, and the

selection of a distance to be walked which was tailored
to the capabilities of each subject. Without this
attention to detail a "timed walking" test could be
even less sensitive to drug effects than a global
rating of disease severity (Mindham, 1976). However,
no difference was found between the results of the
"timed walking" test for the two spacing options of
active treatment. It remains unclear whether this
indicates that the test was not sensitive enough to
detect a difference or whether there was indeed no
difference in response.

Reduction in blink rate has been reported to
correlate well with severity of akinesia in patients
with fluctuating akinesia (Delwaide and Maertens de
Noordhout, 1984) and it was therefore surprising that
blink rate had not previously been documented as a
measure of the efficacy of levodopa therapy. Although
this test has the advantages of being quick and of
requiring no co-operation from the patient, in the
present study, blink rate was found to be too labile to
serve as a reliable index of treatment effect.

It might be that the improvement in morning
performance seen on active treatment was due to the
reaccumulation of central dopamine stores during sleep
(Parkes, 1983). Since active treatment resulted in a
better nights sleep, it is possible that a greater
degree of reaccumulation occurred on active than on
placebo treatment. No difference in the movement in
bed or quality of sleep could be detected between the

two spacing options of the active treatment. This
suggests that either the reaccumulation of dopamine
stores during rest smoothes out the effect of levodopa
administration or the test was insufficiently sensitive
to detect a difference.

In the study of the effect of Sinemet-Plus on
daytime mobility the objective tests used were video
recording, gait assessment, a test of manual dexterity,
pedobarography and a simple "timed walking" test.
Serial plasma concentrations of levodopa and 3-O-
methyldopa, and blood pressures, following active and
placebo treatments were also measured.

Video recording on active and placebo treatments
confirmed that there were no overt fluctuations in
clinical state in response to treatment. The method of
gait assessment was inexpensive, quick to perform and
suitable for use in clinic or on a ward. Moreover, the
technique of measurement was simple enough to learn
without special training. Patients wore their ordinary
clothing and walked with the use of an aid or personal
assistance if necessary. Moreover, analysis of the
double support times during a short walk allowed a
response to the test dose to be detected in these
patients. Despite the imprecise method of measuring
double support time from the trace, the difference
between treatments was highly significant. However,
over the short distance walked, swing length was
confounded by the order of treatment and therefore was
not a reliable index of treatment effect. This may be

because swing length was more influenced by voluntary control than double support time. Although a short walk is more practicable in clinic, a longer one may be accompanied by a more automatic pattern of gait. It is possible that under these conditions swing length might then become a reliable index of the treatment effect.

The analysis of two gait cycles (four steps) at steady state showed no significant differences between treatments for any of the variables studied. This may reflect the limited amount of data analysed. Speed, cadence, the "timed walking" and manual dexterity tests did not show any significant difference between treatments. Again, the effect of treatment on these parameters may have been confounded by voluntary control. For example, the manual dexterity test appeared to be influenced by the patient's emotional state.

The index of foot strike revealed a significant ($p<0.05$) difference between active and placebo treatments. This difference was confirmed using an analysis that allowed for the variable number of steps measured ($p=0.004$). However, there was no relationship between age, severity of Parkinson's disease, duration of treatment with levodopa, or the distance/time parameters of gait and this index of foot strike. Pedobarography thus showed abnormalities of foot strike which were not evident from other observations. It may therefore provide a useful instrument for objective evaluation prior to therapy, and for assessing

progress. Indeed, the use of a larger pedobarograph plate may increase the sensitivity of the test in such comparisons.

Gait may have been more profoundly affected had withdrawal of medication been longer (the maximum period without medication in these studies was 18 hours). The duration of response to treatment could not be defined in the patients studied except to say that there was no significant difference between the improvements seen at 2, 4 and 6 hours post-treatment: a longer post-treatment follow up would be required to define the duration of response. In other words, although the patients were responsive to levodopa, unlike figure 35a), further work is required to determine whether that response was in the longer term (figure 35b)), the short term superimposed on a longer term effect (figure 35c)), or the short term (figure 35d)).
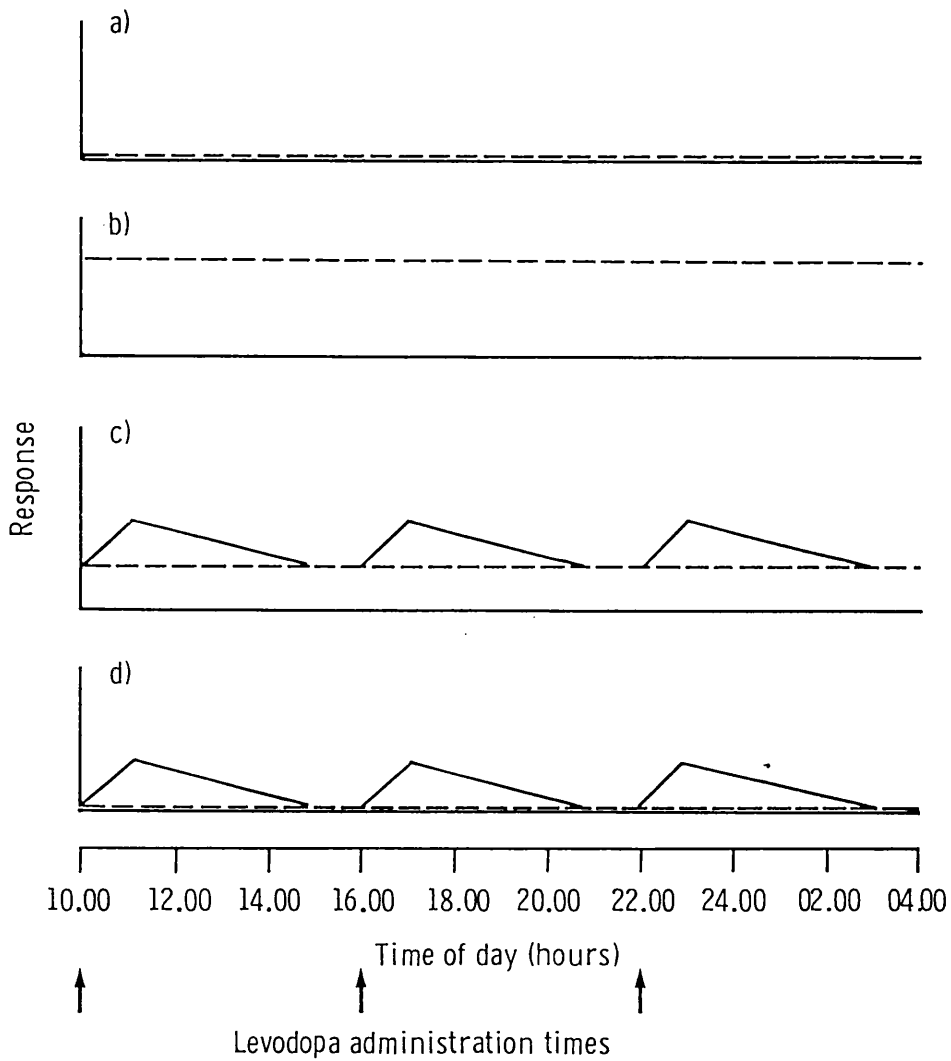
Figure 35 Hypothetical response/time profiles of symptoms of Parkinson's disease during levodopa therapy

a) - no response to treatment occurs
b) - storage capacity in the presynaptic neurones is sufficient to produce a flat response curve
c) - storage capacity is limited and some fluctuation occurs against a background of longer duration response
d) - storage capacity is reduced so that there is only a short and no long duration effect

Most of the literature on the pharmacokinetics of levodopa relates to the manner in which "young" subjects handle the drug moiety itself. However, as discussed earlier, Evans *et al* (1980, 1981) administered oral levodopa without a PDD inhibitor to elderly Parkinsonian patients, and elderly and young controls without Parkinsonism. On average, when each group of elderly subjects was compared to the young cohort, there was a three-fold increase in levodopa AUC$_g$ (subsequently denoted in this section as AUC). Robertson *et al* (1989) compared the pharmacokinetics of levodopa after intravenous and oral administration in a group of young (age 20 to 23 years) and a group of elderly (age 68 to 75 years) healthy volunteers. They found a similar age-related increase in AUC, but more importantly, they were able to demonstrate that this increase was associated with a 40 per cent reduction in plasma clearance. Furthermore, the bioavailability in the elderly group compared to that in the young group had increased from 0.4 to 0.6. They also compared the effect of carbidopa on the pharmacokinetics of levodopa in a group of young (age 21 to 22 years) and a group of elderly (age 69 to 76 years) healthy volunteers. In both groups, 100mg of carbidopa was given 1 hour prior to the oral administration of 125mg of levodopa. A further 50mg of the PDD inhibitor was then given 5 hours later. The mean AUC of 4530ng/mlh in the elderly group was 35 per cent greater than that observed in the case of the younger cohort. A comparison with levodopa

IV data in the same volunteers showed that although the clearance in the elderly group was again reduced by 40 per cent, the bioavailability in each age group was now essentially the same (0.85 in the elderly group, 0.86 in the young group). Since they had now demonstrated that the co-administration of carbidopa had abolished the between group age-related difference in bioavailability which had previously been observed, they concluded that decarboxylation was the age dependent variable in the first pass metabolism of levodopa.

In the present study of elderly patients with Parkinson's disease, no such increase in the AUC with age was detected, and indeed there was a tendency for the AUC to decrease with age. Moreover, it was observed that AUC decreased as duration of therapy with levodopa increased. The mean value of the AUC was 1651ng/mlh which is only 36 per cent of the corresponding value (4530ng/mlh) reported in the work of Robertson *et al* (1989) for their healthy elderly group given levodopa together with carbidopa. In this study, a 100mg quantity of levodopa has been administered with carbidopa in a 4:1 ratio. Although the pharmacokinetics of levodopa has been shown to be dependent upon the proportions of PDD inhibitor present (Kaakkola *et al*, 1985), the relatively low value of the AUC suggests either that the first pass effect was more marked in this relatively aged group or that the efficacy of transport processes from intestine to

plasma might be compromised. It may be noted that the mean half-life of levodopa (1.7 hours) in these patients is similar to that of 2.1 hours found in the study of Robertson *et al* (1989).

3-O-methyldopa, the product of O-methylation of levodopa, accumulates in the plasma of patients on chronic levodopa therapy due to its long half-life (Kuruma *et al*, 1971; Sharpless *et al*, 1972). Since it has a much higher affinity for the active transport system than levodopa, it may interfere with levodopa uptake into the striatum (Wade and Katzman, 1975b). Moreover, it could be suggested that the enhanced response to levodopa after a drug holiday might be explained by the elimination of 3OMD. There is evidence that 3OMD is converted back to levodopa (Bartholini *et al*, 1971; Kuruma *et al*, 1971; Tyce *et al*, 1976) and thus may act as a reservoir of the drug, playing a part in the sustained response to therapy in some patients. The half-life of 3OMD has been reported as 15 hours (Kuruma *et al*, 1971), but was more like 24 hours in the elderly and aged patients in the present study. One might therefore expect any adverse effect of 3OMD to be more pronounced in this age group. A significant correlation ($p < 0.05$) was found between the mean [3OMD] and the duration of levodopa treatment, the mean [3OMD] increasing with length of therapy. It has already been observed that the AUC decreases with increased duration of therapy and as a consequence of these concomitant changes the ratio of mean [3OMD] to

the AUC would be expected to be more sensitive to the duration of treatment. This is supported by the value of the correlation coefficient in table 36 (p<0.01).

The patients in this study showed no overt fluctuations in clinical state in response to treatment. Very small but often clinically useful changes in such patients might easily be missed using subjective observation alone. The development of objective measures of response is therefore important for monitoring the effectiveness of therapy. Objective assessment using gait analysis has been shown to be of value in this context in the present study. The differences in the magnitude of the treatment effect in individual subjects was neither explained by the concentrations of levodopa or 3OMD present nor their ratio, nor by any change in blood pressure. No difference was found in response at 2, 4 and 6 hours post-treatment despite the average half-life of levodopa being only 1.7 hours, a finding compatible with some preservation of storage capacity. Further analysis confirmed that there was no significant correlation between performance and plasma concentrations of levodopa or 3OMD during the active treatment. It remains to be seen whether clinical outcome is proportional to the retention of dopamine in the basal ganglia. Modern, relatively non-invasive, but expensive, techniques such as Positron Emission Tomography might give a better indication of the likely pattern of clinical responsiveness.

CHAPTER NINE

PROPOSALS FOR FUTURE WORK

The bed movement monitors described in this thesis measured lateral movements of the patient's centre of gravity only. However, it was not possible to discriminate between movements of the extremities and limbs, and those of the trunk. It may be that the ability to roll over is more significant from the viewpoint of the Parkinsonian patient and a device that continuously monitors axial rotation in the recumbent subject might therefore be appropriate. Such a device is in the course of development.

A night-time dose of Sinemet-Plus improved sleep in elderly Parkinsonian patients as judged subjectively by the patients, and objectively by the reduction in movement in bed. The measurement of EEGs would be useful in assessing whether this improvement was due to a dopaminergic sleep inducing effect of levodopa or was simply secondary to better control of the Parkinson's disease. Conventional EEG technology requires the use of sleep laboratory facilities for successful results and is expensive and labour intensive. Elderly patients may be particularly disturbed by being "tethered" to leads, especially if they need to get up frequently in the night. A method of monitoring the EEG without the use of leads to a recording device using infra-red telemetry is in existence. This could be used in the normal clinical environment, and even at home, and would be particularly useful for monitoring elderly patients.

The traces produced by the gait assessment trolley were laborious to analyse by hand. Computerisation of the system would permit almost instantaneous analysis of the gait parameters, and a more precise determination of double support time and the other gait parameters.

Despite the fact that double support time was significantly improved on active treatment, it was not possible to detect a difference between the 2, 4 and 6 hour time points. A longer period of withdrawal from medication prior to study might improve the detection of any response to therapy. It could be that storage of dopamine allowed the patients to compensate for missing one or two doses of levodopa thus masking treatment effects. Controlled withdrawal of therapy with performance tests to monitor any deterioration might therefore be informative in future studies.

Although no relationship between plasma concentrations of levodopa and the metabolite 3OMD and mobility could be detected, the effects of age and duration of therapy on the pharmacokinetics of levodopa were interesting. It was not ideal to carry out blood sampling and tests of performance on different days. However, elderly patients are easily tired, especially those that are frail and disabled, and it was considered necessary to limit the number of tests carried out in one day. Now that this study has indicated tests likely to be of most use, a repeat study could be carried out using one or two pertinent

tests only, and taking blood samples on the same day. Tests could also be carried out more frequently during the immediate post-dose period at which time the plasma levels of levodopa would be changing most rapidly.

In conclusion, a number of novel devices for assessing mobility have been tested in the course of this work. It would clearly be desirable to evaluate the more promising tests in a larger and possibly less variable group of Parkinsonian patients.

APPENDICES

Appendix 1

The Webster Scale

Directions
Apply a gross clinical rating to each of the 10 listed
items, assigning value ratings of 0-3 for each item,
where (0) = no involvement and (1), (2) and (3) are
equated to early, moderate and severe disease
respectively.

Bradykinesia of hands (including handwriting)
(0) No involvement
(1) Detectable lowering of the pronation-supination
    rate, evidenced by beginning of difficulty in
    handling tools, buttoning clothes, and with
    handwriting.
(2) Moderate slowing of supination-pronation rate, one
    or both sides, evidenced by moderate impairment of
    hand function. Handwriting is greatly impaired,
    micrographia is present.
(3) Severe slowing of supination-pronation rate.
    Unable to write or button clothes. Marked
    difficulty in handling utensils.

Rigidity
(0) None detectable
(1) Detectable rigidity in neck and shoulders.
    Activation* phenomenon is present. One or both
    arms show mild, negative**, resting rigidity.
(2) Moderate rigidity in neck and shoulders. Resting
    rigidity is positive when patient not on
    medication.
(3) Severe rigidity in neck and shoulders. Resting
    rigidity cannot be reversed by medication.

Posture
(0) Normal posture. Head flexed forward less than 4
    inches.
(1) Beginning 'poker' spine. Head flexed forward up to
    5 inches.
(2) Beginning arm flexion. Head flexed forward up to 6
    inches. One or both arms raised but still below
    waist.
(3) Onset of simian posture. Head flexed forward more
    than 6 inches. One or both hands elevated above
    waist. Sharp flexion of hand, beginning
    interphalangeal extension. Beginning flexion of
    knees.

Upper extremity swing
(0) Swings both arms well.
(1) One arm definitely decreased in amount of swing.
(2) One arm fails to swing.
(3) Both arms fail to swing.

Gait
(0) Steps out well with 18-30 inch stride. Turns about effortlessly.
(1) Gait shortened to 12-18 inch stride. Beginning to strike one heel. Turn around time slowing. Requires several steps.
(2) Stride moderately shortened - now 6-12 inches. Both heels beginning to strike floor forcefully.
(3) Onset of shuffling gait, steps less than 3 inches. Occasional stuttering type of blocking gait. Walks on toes - turns around very slowly.

Tremor
(0) None detectable.
(1) Less than 1 inch of peak-to-peak tremor movement observed in limbs or head at rest or in either hand while walking or during finger to nose testing.
(2) Maximum tremor envelope fails to exceed 4 inches. Tremor is severe but not constant and patient retains some control of hands.
(3) Tremor envelope exceeds 4 inches. Tremor is constant and severe. Patient cannot get free of tremor while awake. Writing and feeding are impossible.

Facies
(0) Normal. Full animation. No stare.
(1) Detectable immobility. Mouth remains closed. Beginning features of anxiety and depression.
(2) Moderate immobility. Emotion breaks through at markedly increased threshold. Lips parted some of the time. Moderate appearance of anxiety and depression. Drooling may be present.
(3) Frozen facies. Mouth open inch or more. Drooling may be severe.

Seborrhoea
(0) None
(1) Increased perspiration, secretion remaining thin.
(2) Obvious oiliness present. Secretion much thicker.
(3) Marked seborrhoea, entire face and head covered by thick secretion.

Speech
(0) Loud, clear, resonant, easily understood.
(1) Beginning of hoarseness with loss of inflection and resonance. Good volume and still easily understood.
(2) Moderate hoarseness and weakness. Constant monotone, unvaried pitch. Beginning of dysarthria, hesitancy, stuttering, difficult to understand.
(3) Marked harshness and weakness. Very difficult to hear and understand.

Self-care

(0) No impairment.
(1) Still provides full self-care but rate of dressing definitely impaired.
(2) Requires help in certain critical areas, such as turning in bed, rising from chairs etc. Very slow in performing most activities, but manages by taking more time.
(3) Continuously disabled. Unable to dress, feed or walk alone.

  * - Activation phenomenon is an increase in rigidity in involved limb evoked by voluntary movement of contralateral limb.
** - Negative rigidity indicates that the patient aids passive movements performed by the observer, to a greater or lesser extent. Positive rigidity implies involuntary resistance associated with increased tone.

Appendix 2

The North-Western University Disability Scale

Scale A: Walking
Never walks alone
   0 Cannot walk at all, even with maximum assistance.
   1 Needs considerable help, even for short
      distances; cannot walk outdoors with help.
   2 Requires moderate help indoors; walks outdoors
      with considerable help.
   3 Requires potential help indoors and active help
      outdoors.
Sometimes walks alone
   4 Walks from room to room without assistance, but
      moves slowly and uses external support; never
      walks alone outdoors.
   5 Walks from room to room with only moderate
      difficulty; may occasionally walk outdoors without
      assistance.
   6 Walks short distances with ease; walking outdoors
      is difficult but often accomplished without help.
Always walks alone
   7 Gait is extremely abnormal; very slow and
      shuffling; posture grossly affected; there may be
      propulsion.
   8 Quality of gait is poor and rate is slow; posture
      moderately affected; there may be a tendency
      towards mild propulsion; turning is difficult.
   9 Gait only slightly deviant from normal in quality
      and speed; turning is the most difficult task;
      posture essentially normal.
   10 Normal

Scale B: Dressing
Requires complete assistance
   0 Patient is a hindrance rather than a help to
      assistant.
   1 Movements of patient neither help nor hinder
      assistant.
   2 Can give some help through bodily movements.
   3 Gives considerable help through bodily movements.
Requires partial assistance
   4 Performs only gross dressing activities alone
      (hat, coat).
   5 Performs about half of dressing activities
      independently.
   6 Performs more than half of dressing activities
      alone, with considerable effort and slowness.
   7 Handles all dressing alone with the exception of
      fine activities (tie, buttons).
Complete self-help
   8 Dresses self completely with slowness and great
      effort.
   9 Dresses self completely with only slightly more
      time and effort than normal.
   10 Normal

Scale C: Hygiene
Requires complete assistance.
    0 Unable to maintain proper hygiene even with maximum help.
    1 Reasonably good hygiene with assistance, but does not provide assistant with significant help.
    2 Hygiene maintained well; gives aid to assistant.
Requires partial assistance.
    3 Performs a few tasks alone with assistant nearby.
    4 Requires assistance for half of toilet needs.
    5 Requires assistance for some tasks not difficult in terms of co-ordination.
    6 Manages most of personal needs alone; has substituted methods for accomplishing difficult tasks.
Complete self-help
    7 Hygiene maintained independently, but with effort and slowness; accidents are not infrequent; may employ substitute methods.
    8 Hygiene activities are moderately time-consuming; no substitute methods; few accidents.
    9 Hygiene maintained normally, with exception of slight slowness.
   10 Normal.

Scale D: Eating and feeding (scored separately)
Eating
    0 Eating is so impaired that a hospital·setting is required to get adequate nutrition.
    1 Eats only soft foods and liquids; these are consumed very slowly.
    2 Liquids and soft foods handled with ease; hard foods occasionally eaten, but require great effort and much time.
    3 Eats some hard foods routinely, but these require time and effort.
    4 Follows a normal diet, but chewing and swallowing are laboured.
    5 Normal.
Feeding
    0 Requires complete assistance.
    1 Performs only a few feeding tasks independently.
    2 Performs most feeding activities alone, slowly and with effort; requires help with feeding.
    3 Handles all feeding alone with moderate slowness; still may get assistance in specific situations (e.g. cutting meat in restaurant); accidents not infrequent.
    4 Fully feeds self with rare accidents; slower than normal.
    5 Normal

Scale E: Speech

  0 Does not vocalise at all.

  1 Vocalises, but rarely for communicative purposes.

  2 Vocalises to call attention to self.

  3 Attempts to use speech for communication, but has difficulty in initiating vocalisation; may stop speaking in middle of phrase and be unable to continue.

  4 Uses speech in most communication, but articulation is highly unintelligible; may have occasional difficulty in initiating speech; usually speaks in single words or short phrases.

  5 Speech always employed for communication, but articulation is still very poor; usually uses complete sentences.

  6 Speech can always be understood if listener pays close attention; both articulation and voice may be defective.

  7 Communication accomplished with ease, although speech impairment detracts from content.

  8 Speech easily understood, but voice or speech rhythm may be disturbed.

  9 Speech entirely adequate; minor voice disturbances present.

10 Normal

Appendix 3

The Hoehn & Yahr Staging System

Stage I

Unilateral involvement, usually minimal or no functional impairment.

Stage II

Bilateral or mid-line involvement, without impairment of balance.

Stage III

First signs of impaired righting reflexes: evident in unsteadiness as the patient turns or demonstrated when he is pushed from standing equilibrium with feet together and eyes closed. Functionally somewhat restricted, but may be able to work, depending on nature of employment. Capable of independent living, with mild to moderate overall disability.

Stage IV

Fully developed, severely disabling disease. Can stand and walk unaided, but is markedly incapacitated.

Stage V

Confined to wheel-chair or bed without assistance.

Appendix 4

Examples of objective tests for assessing Parkinson's disease

Type of Test	Author	Test
Timed manual dexterity tests	Brumlik and Boshes, 1966	Timed tasks: pick up a series of coins, put on a standard laboratory coat, button and unbutton it
	Mawdsley, 1970	Timed tasks: place 24 pegs into a pegboard, take a match from a box and strike it, thread 12 washers onto a rod, fold a piece of paper, place it in an envelope and seal the envelope, open the envelope, take 3 coins from a purse, stick 12 pins into a pin cushion, open and close a safety pin
	Anden et al, 1970	Time to put on a pair of socks
	Calne et al, 1971	Timed tasks: fold a piece of paper and place inside an envelope, insert 6 pegs into a cribbage board
	Walker et al, 1972	Timed tasks: put on a shirt, do up a 1 inch diameter button, do up a 0.5 inch diameter button, open and close a zipper, tie a bow, cut with a knife, use a fork, pour water into a glass, squeeze tooth-paste from a tube, dial a telephone, open and close a door, open an envelope, wash hands, put on gloves
	Cassell et al, 1973	Time to move 24 pegs from the top two rows of a pegboard to the bottom two rows
	Broe and Caird, 1973	Timed tasks: put on a sock, do up 3 buttons

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	Fahn and Isgreen, 1975	Timed tasks: pick up pins and coins (numbers not specified), place 10 pegs in pegboard, string 10 beads, put on and remove a shirt, do a button up, tie a bow, eat with a spoon, bring a glass to the mouth, cut food, dial telephone numbers, open and close a safety pin, carry a tray
	Mindham, 1976	Time to place 25 grooved pegs into matching holes
Writing tests	Mawdsley 1970	Time to copy a sentence, and to trace a circle
	Gilligan et al, 1970	Time to write a set phrase
	Timberlake, 1970	Length of standard sentence measured
	Calne et al, 1971	Time to write a standard sentence
	Broe and Caird, 1973	Time to write a sentence of 5 monosyllabic words, and to draw a circle
	Mindham, 1976	Time to write name and address, changes in form, size and area of paper covered also noted
Strength tests	Timberlake, 1970	Bulb ergograph and work adder used to measure the total distance moved by a pen during 30 seconds when the bulb is squeezed in time with a bell ringing once a second
	Mindham, 1976	Sphymomanometer cuff blown up to 60mmHg and squeezed as hard as possible with each hand in turn
Tapping tests		These usually use electronic circuitry to record the number of successful movements in a given time
	Perret et al, 1970	Number of buttons pushed in a) any order, and b) a fixed order, in 10 seconds measured using 4 push buttons

	Bowen *et al*, 1972	Number of taps in 10 seconds recorded for the right and left index fingers separately
	Mawdsley *et al*, 1972	Total number of keys of a laboratory digital counter depressed from left to right in 30 seconds recorded
	Cassell *et al*, 1973	Number of taps in 10 seconds recorded
	Pilling *et al*, 1975	Nine tests involving tapping metal discs in specified sequences, recording the number of successful movements in 10 seconds
	Mindham, 1976	Number of taps in a fixed period of time recorded
	Nutt *et al*, 1984	Number of times 2 keys 20cm apart alternately tapped in 60 seconds recorded
Movement and times tests		Electronic equipment is usually used to record the time taken to react to a given stimulus and that taken to complete a given movement
	Brumlik and Boshes, 1966	Reaction and movement times recorded when a button 6 inches away is depressed in response to a light going on using electromyography and accelerometry respectively
	Anden *et al*, 1970	Movement and reaction times measured using the pursuit of a spot of light on an oscilloscope with a second spot of light controlled by a joystick
	Bowen *et al*, 1972	Reaction time measured by following a light moving at random over a screen with a photocell on the index finger
	Cassell *et al*, 1973	Tracking task using a line on a screen operated by the assessor and followed with a dot by the subject

	Laitinen, 1973	Reaction and movement times measured using 2 buttons 23cm apart which operate an electrical circuit when pressed
	Flowers, 1975	Tracking task using joystick control and an oscilloscope display to measure movement and reaction times
	Heilman *et al*, 1976	Reaction time with and without a warning signal measured using a timer which starts when a light comes on and is stopped when a key is depressed
Walking and sitting tests	Brumlik and Boshes, 1966	Time to walk 20 feet
	Anden *et al*, 1970	Time and number of steps to walk 10 metres, time to rise from and return to a chair
	Timberlake, 1970	Time to walk 10 feet and return .
	Gilligan *et al*, 1970	Time to walk 25 yards with one turn
	Calne *et al*, 1971	Time to rise from a chair, walk 6 metres, turn, return to chair and sit down
	Broe and Caird, 1973	Time to walk 10 yards with one turn and time to rise from a chair
	Mindham, 1976	Time to walk 25 yards with one turn
	Nutt *et al*, 1984	Time to rise from an armless chair, walk 6 metres, turn, return to chair and sit down, 30 seconds allowed to complete task
Gait analysis	Knutsson and Martensson, 1971	Distance/time parameters of gait measured using interrupted light photography
	Gopinathan *et al*, 1981	Distance/time parameters of gait measured using a mat with sensors

Appendix 5

The Modified Tooting Bec Questionnaire

"Some people as they get older often tend to forget things. I should like to ask you some questions to see how well you remember things which have happened recently and in the past."

a) What is your name?

b) How old are you?

c) Are you married?

d) What was your work? (ask women about their work before marriage)

e) What year is it?

f) What is the name of this hospital? (If not known – inform)

g) I am going to tell you an address, and I want you to remember it: 74 Columbia Road   .

h) What year did the Second World War start? and finish?

i) Who was the Prime Minister at the end of the war?
                              The beginning of the war?

j) Who is the Prime Minister now?

k) What is the name of the queen?

l) What is the name of her eldest son?

m) Where is Belfast?

n) What is happening there now?

o) Now tell me the name of the hospital again?

p) Tell me the address that I told you?

Score 1 for each correct answer

Appendix 6

The Norton Score

A	Physical condition		
		Good	4
		Fair	3
		Poor	2
		Bad	1
B	Mental condition		
		Alert	4
		Apathetic	3
		Confused	2
		Stuporous	1
C	Activity		
		Ambulant	4
		Walk with aid	3
		Chairbound	2
		Bedfast	1
D	Mobility		
		Full	4
		Slightly limited	3
		Very limited	2
		Immobile	1
E	Incontinent		
		Not	4
		Occasional	3
		Usually	2
		Doubly	1

A total score of 14 or below is classified "at risk of pressure sore development"

Preliminary bed movement study: Frequency and size of movements in bed.

Patient Number *	Number of movements per hour									Total distance moved per hour (mm)			Mean move size (mm)		
	greater than 4mm			greater than 10mm			greater than 20mm								
	Night 1	Night 2	Night 3	Night 1	Night 2	Night 3	Night 1	Night 2	Night 3	Night 1	Night 2	Night 3	Night 1	Night 2	Night 3
1	1.8	1.7	1.4	0.8	1.3	1.3	0.3	0.8	0.8	27.2	47.7	42.8	15.1	28.7	30.5
2	10.3	10.2	12.3	2.1	2.6	3.7	0.1	0.0	0.0	85.3	89.1	115.3	8.3	8.8	9.4
3	19.3	13.6	13.2	6.1	6.1	4.8	0.9	3.4	1.9	170.8	198.1	137.7	8.9	14.6	10.5
4	4.3	3.0	3.5	0.3	0.5	1.2	0.0	0.2	0.3	25.0	23.0	31.3	5.8	7.7	8.8
5	2.8	2.9	4.7	1.3	1.3	0.6	0.6	0.5	0.0	38.3	41.9	35.0	13.6	14.3	7.4
6	0.6	0.9	1.3	0.0	0.5	0.6	0.0	0.2	0.0	4.2	11.6	11.6	7.2	12.7	8.9
7	12.0	15.4	16.1	5.3	8.6	5.4	2.1	4.3	0.8	149.6	216.7	150.9	12.5	14.1	9.4
8	1.3	4.7	6.3	0.4	2.1	3.1	0.3	0.6	1.6	18.8	59.4	108.9	14.1	12.7	17.3
9	9.7	10.7	2.9	2.0	4.5	0.8	0.3	0.3	0.0	71.4	98.1	22.0	7.3	9.2	7.7
10	2.3	3.6	4.3	0.3	0.9	1.0	0.0	0.3	0.6	15.2	31.1	42.0	6.8	8.6	9.7
11	4.8	4.5	6.4	3.4	2.1	3.0	2.0	1.2	1.4	135.9	91.6	102.6	28.6	20.6	16.0
12	5.6	2.3	7.8	2.0	0.7	2.5	1.3	0.2	1.3	78.1	23.3	116.9	14.0	9.9	15.0
13	10.1	9.4	8.4	3.7	5.5	3.3	0.4	2.8	2.1	92.4	180.7	103.5	9.1	19.3	12.3
14	17.8	28.1	16.5	11.7	21.4	11.3	2.0	8.6	4.1	218.5	494.5	296.5	12.3	17.6	18.0
15	2.8	1.7	2.0	2.2	1.2	0.9	0.2	0.3	0.3	34.3	20.8	24.5	12.4	12.5	12.3
16	28.7	9.6	19.8	14.3	1.0	6.6	5.2	0.0	0.9	387.5	66.5	192.6	13.5	6.9	9.8
17	10.7	9.9	8.0	6.7	4.4	3.9	1.6	1.4	0.5	48.7	136.9	92.5	13.9	13.8	11.6
18	6.1	2.8	2.5	3.2	1.8	1.2	2.0	0.8	0.4	130.3	59.5	33.6	21.4	21.3	13.7
19	0.7	0.4	0.7	0.0	0.0	0.0	0.0	0.0	0.0	3.9	1.6	3.2	5.3	4.7	4.7
20	7.0	3.7	5.0	3.3	2.5	3.3	2.0	1.2	1.4	153.1	67.4	97.8	21.9	18.2	19.5
21	1.2	1.4	0.6	0.4	0.6	0.3	0.3	0.4	0.3	19.7	22.3	13.1	15.9	16.2	20.8
22	3.9	5.6	3.8	2.3	2.7	1.7	0.4	1.4	0.5	47.7	88.1	49.3	12.4	15.8	13.2
23	9.3	12.9	13.8	4.5	10.3	10.4	1.1	5.4	6.9	106.2	279.3	373.3	11.5	21.6	27.2
24+	10.2	7.5	6.3	9.2	6.2	4.5	7.2	4.5	3.8	1159.2	683.3	333.9	114.2	90.6	53.0
25	4.0	4.1	3.1	2.1	1.2	0.9	1.0	0.0	0.0	79.2	37.6	26.9	19.8	9.1	8.8
26	2.6	2.3	0.6	2.0	1.4	0.3	1.0	0.9	0.0	58.4	61.7	5.7	22.2	27.4	9.1
27	13.8	9.1	6.0	9.8	5.1	5.2	6.3	3.4	3.6	253.9	148.3	161.7	18.4	17.5	27.0
28	6.5	4.7	5.2	3.0	1.0	1.8	0.4	0.2	1.6	63.7	38.9	72.7	9.9	8.3	13.9
29	7.0	0.7	2.7	2.7	0.0	0.5	1.2	0.0	0.0	148.9	4.6	20.9	21.2	6.8	7.8
30	3.4	3.0	7.7	2.5	2.1	5.4	2.4	1.4	3.4	130.7	103.7	289.0	39.0	34.2	37.7

* - patients 1 to 12 had idiopathic Parkinson's disease

+ - extremely obese patient hence axial rotation of the same degree would result in a larger lateral movement of the centre of gravity than a thinner patient

Quality of sleep visual analogue scale

How well did you sleep last night?

please put a cross on the black line below

The worst
night's sleep
I have
ever had

The best
night's sleep
I have
ever had
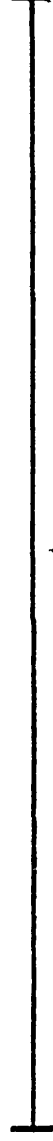
Appendix 9

Night-time Sinemet-Plus study: Patients' assessments of quality of sleep. (Values measured in mm on the visual analogue scale.)

Patient Number	Order of treatment	Treatment A (PP.P)				Treatment B (AA.P)				Treatment C (AP.A)			
		Night 1	Night 2	Night 3	Night 4	Night 1	Night 2	Night 3	Night 4	Night 1	Night 2	Night 3	Night 4
1	C,A,B	122	12	130	74	102	134	118	125c	123	92	72	80
2	A,B,C	17c	77c	49	48	93	92d	93de	80d	43cd	83cd	121cd	90
3	A,C	144	145	78	137	a	a	a	a	37	15	134	124
4	A,C	123	72	b	112	a	a	a	a	98	87	28	g
5	A,B,C	20	22	7	b	b	133	138	138	b	145	145	147
6	C,B,A	52	34	44	87	125	h	27	37	34	92	115	74
7	A,C,B	69	82	49	71	h	92d	76d	88	38	88	h	67
8	A,B,C	73	34	100	h*	h	27	108	23	74	51	2	57
9	C,A,B	69	67	62	32	146	106	145	144	141	140	139	71
10	C,A,B	75	h	73	55	75	77	76d	97	70	60	57	120
11	B,A,C	20	68	36	40	145	5f	5f	146	26	13	113	117

a - final treatment not completed due to intercurrent illness
b - middle of night tablet not given
c - leg cramp
d - "burning" pain in heels and/or legs
e - paraesthesia in legs
f - pain "like a current running through legs"
g - patient confused
h - failure of monitoring equipment (* - in second half of night only)

Night-time Sinemet-Plus study: Number of interventions (patients rising from bed or attendances by nursing staff) per hour during the night.

Patient Number	Order of treatment	Treatment A (PP.P)				Treatment B (AA.P)				Treatment C (AP.A)			
		Night 1	Night 2	Night 3	Night 4	Night 1	Night 2	Night 3	Night 4	Night 1	Night 2	Night 3	Night 4
1	C,A,B	0.25	0.25	0.13	0.25	0.13	0.13	0.13	0.38	0.25	0.38	0.38	0.25
2	A,B,C	0.38	0.38	0.50	0.25	0.25	0.25	0.25	0.25	0.25	0.38	0.38	0.38
3	A,C	0.13	0.25	0.13	0.25	a	a	a	a	0.38	0.38	0.25	0.38
4	A,C	0.14	0.29	b	0.14	a	a	a	a	0.14	0.29	0.14	0.29
5	A,B,C	0.71	0.71	0.43	b	b	0.29	0.29	0.29	b	0.14	0.29	0.14
6	C,B,A	0.25	0.25	0.25	0.25	0.25	c	0.25	0.25	0.25	0.25	0.25	0.25
7	A,C,B	0.38	0.13	0.25	0.25	c	0.25	0.25	0.25	0.38	0.25	c	0.13
8	A,B,C	0.25	0.25	0.25	0.25*	c	0.25	0.25	0.38	0.25	0.25	0.38	0.25
9	C,A,B	0.33	0.29	0.43	0.29	0.29	0.43	0.29	0.43	0.14	0.29	0.29	0.43
10	C,A,B	0.38	c	0.38	0.25	0.13	0.25	0.13	0.25	0.25	0.25	0.38	0.25
11	B,A,C	0.38	0.50	0.50	0.38	0.25	0.38	0.25	0.25	0.38	0.13	0.25	0.25

a - final treatment not completed due to intercurrent illness
b - middle of night tablet not given
c - failure of monitoring equipment
* - value for first half of night only - monitoring equipment failed during second half of night

Appendix 11

Night-time Sinemet-Plus study: Number of movements in bed greater than 4mm per hour during the whole night.

Patient Number	Order of treatment	Treatment A (PP.P) Night 1	Night 2	Night 3	Night 4	Treatment B (AA.P) Night 1	Night 2	Night 3	Night 4	Treatment C (AP.A) Night 1	Night 2	Night 3	Night 4
1	C,A,B	1.5	2.9	1.0	2.3	1.8	1.8	2.5	2.0	1.3	2.0	2.6	1.1
2	A,B,C	10.1	3.8	6.2	5.9	1.9	3.2	2.4	2.3	4.7	4.8	1.6	2.6
3	A,C	2.1	2.2	3.1	0.7	a	a	a	a	0.8	2.1	1.8	5.7
4	A,C	5.3	2.4	b	1.7	a	a	a	a	4.8	5.8	8.6	8.6
5	A,B,C	10.8	9.6	13.3	b	b	1.7	1.9	2.1	b	3.0	3.0	2.8
6	C,B,A	2.3	2.7	4.1	1.6	0.8	c	2.0	5.9	1.8	2.9	1.3	0.9
7	A,C,B	1.5	3.7	1.3	2.1	c	1.2	1.2	1.2	2.8	0.1	c	1.2
8	A,B,C	4.7	2.2	4.5	c*	c	4.7	3.7	5.4	6.8	4.7	7.8	2.7
9	C,A,B	4.5	4.0	2.8	3.9	1.5	2.5	2.9	3.9	2.0	1.0	1.9	1.7
10	C,A,B	3.9	c	4.4	4.0	4.6	2.9	4.0	4.1	3.5	7.5	4.0	5.7
11	B,A,C	2.0	1.4	1.0	2.0	1.8	1.7	1.8	1.9	1.1	1.3	0.8	1.3

a - final treatment not completed due to intercurrent illness

b - middle of night tablet not given

c - failure of monitoring equipment (* - in second half of night only)

Appendix 12

Night-time Sinemet-Plus study: Number of movements in bed greater than 10mm per hour during the whole night.

Patient Number	Order of treatment	Treatment A (PP.P)				Treatment B (AA.P)				Treatment C (AP.A)			
		Night 1	Night 2	Night 3	Night 4	Night 1	Night 2	Night 3	Night 4	Night 1	Night 2	Night 3	Night 4
1	C,A,B	0.8	1.5	0.4	0.7	0.4	0.1	1.0	0.4	0.4	1.3	1.4	0.4
2	A,B,C	3.6	1.5	3.0	3.5	0.9	2.1	1.3	1.3	3.1	2.1	1.0	1.4
3	A,C	1.2	1.1	1.2	0.3	a	a	a	a	0.6	0.8	0.8	3.4
4	A,C	2.1	0.9	b	0.5	a	a	a	a	2.6	3.8	5.1	4.0
5	A,B,C	6.4	6.4	10.8	b	b	0.8	0.5	1.7	b	1.3	1.9	1.5
6	C,B,A	1.4	0.6	1.4	0.4	0.5	c	0.8	2.7	0.5	0.9	0.8	0.3
7	A,C,B	0.5	2.9	0.9	0.7	c	0.5	0.7	0.8	2.0	0.0	c	0.4
8	A,B,C	2.4	1.0	2.0	c*	c	2.9	2.3	2.9	4.0	1.8	2.3	2.1
9	C,A,B	3.3	2.8	1.7	2.6	0.5	1.7	1.6	3.1	0.6	0.5	1.1	0.8
10	C,A,B	1.9	c	2.5	1.6	3.2	1.4	1.8	2.0	1.7	5.2	2.9	3.7
11	B,A,C	1.6	1.1	0.4	1.2	1.3	0.9	1.4	1.2	0.5	0.9	0.5	1.0

a – final treatment not completed due to intercurrent illness

b – middle of night tablet not given

c – failure of monitoring equipment (* – in second half of night only)

Appendix 13

Night-time Sinemet-Plus study: Number of movements in bed greater than 20mm per hour during the whole night.

Patient Number	Order of treatment	Treatment A (PP.P) Night 1	Night 2	Night 3	Night 4	Treatment B (AA.P) Night 1	Night 2	Night 3	Night 4	Treatment C (AP.A) Night 1	Night 2	Night 3	Night 4
1	C,A,B	0.3	0.5	0.3	0.6	0.1	0.0	0.4	0.3	0.1	0.4	0.5	0.1
2	A,B,C	1.2	1.0	1.7	1.4	0.3	1.2	1.2	0.6	1.9	0.8	0.5	0.8
3	A,C	0.7	0.7	0.5	0.1	a	a	a	a	0.2	0.1	0.3	1.3
4	A,C	0.7	0.1	b	0.3	a	a	a	a	1.4	1.6	1.8	1.7
5	A,B,C	3.7	3.3	5.2	b	b	0.2	0.2	0.8	b	0.1	0.8	0.6
6	C,B,A	0.4	0.0	0.1	0.0	0.0	c	0.1	0.4	0.1	0.1	0.1	0.1
7	A,C,B	0.0	0.0	0.3	0.0	c	0.1	0.1	0.0	0.1	0.0	c	0.3
8	A,B,C	0.5	0.6	1.0	c*	c	1.3	1.3	2.1	2.2	1.0	1.0	1.1
9	C,A,B	2.3	1.9	1.0	1.5	0.3	0.9	1.3	2.2	0.4	0.2	0.6	0.3
10	C,A,B	0.6	c	0.7	0.5	0.8	0.5	0.4	0.4	0.8	2.1	1.0	1.5
11	B,A,C	1.4	0.7	0.4	1.1	1.0	0.7	1.4	0.8	0.4	0.9	0.4	0.5

a - final treatment not completed due to intercurrent illness

b - middle of night tablet not given

c - failure of monitoring equipment (* - in second half of night only)

Appendix 14

Night-time Sinemet-Plus study: Total distance moved in bed (mm) per hour during the whole night.

Patient Number	Order of treatment	Treatment A (PP.P)				Treatment B (AA.P)				Treatment C (AP.A)			
		Night 1	Night 2	Night 3	Night 4	Night 1	Night 2	Night 3	Night 4	Night 1	Night 2	Night 3	Night 4
1	C,A,B	18.8	34.4	16.3	36.3	16.0	11.9	32.0	18.8	16.3	29.9	33.2	12.3
2	A,B,C	108.0	62.0	169.0	123.8	43.5	68.4	53.4	45.4	139.2	82.9	31.7	49.0
3	A,C	39.9	38.3	45.8	7.1	a	a	a	a	15.3	20.3	18.1	93.6
4	A,C	66.6	21.0	b	25.1	a	a	a	a	112.4	115.5	125.6	113.5
5	A,B,C	203.5	160.7	330.4	b	b	21.1	17.8	38.1	b	29.7	50.6	37.9
6	C,B,A	31.2	20.2	35.4	10.9	8.6	c	20.6	58.1	14.9	25.0	19.1	8.7
7	A,C,B	16.1	48.1	22.0	22.0	c	15.5	13.8	13.4	37.7	0.7	c	14.8
8	A,B,C	55.5	31.9	73.6	c*	c	116.2	188.4	178.8	162.9	68.8	93.3	59.2
9	C,A,B	110.7	101.7	49.3	84.9	14.9	52.3	81.9	100.7	24.8	12.2	41.0	22.9
10	C,A,B	58.1	c	57.4	44.2	66.2	37.5	41.2	47.7	52.3	124.1	66.0	94.1
11	B,A,C	107.1	69.0	27.2	50.7	54.0	51.7	85.7	48.4	35.8	55.0	24.6	30.0

a - final treatment not completed due to intercurrent illness

b - middle of night tablet not given

c - failure of monitoring equipment (* - in second half of night only)

Appendix 15

Night-time Sinemet-Plus study: Mean move size in bed (mm) during the whole night.

Patient Number	Order of treatment	Treatment A (PP.P)				Treatment B (AA.P)				Treatment C (AP.A)			
		Night 1	Night 2	Night 3	Night 4	Night 1	Night 2	Night 3	Night 4	Night 1	Night 2	Night 3	Night 4
1	C,A,B	12.3	11.9	15.6	15.5	8.7	6.5	12.8	9.4	12.2	14.8	12.7	10.9
2	A,B,C	10.7	16.5	27.2	21.1	23.3	21.6	22.0	19.9	29.8	17.2	19.4	18.7
3	A,C	18.7	17.6	14.8	10.1	a	a	a	a	20.2	9.6	10.2	16.4
4	A,C	12.6	8.9	b	15.0	a	a	a	a	23.6	20.0	14.5	13.1
5	A,B,C	18.9	16.7	24.8	b	b	12.3	9.5	18.2	b	10.0	16.9	13.5
6	C,B,A	13.3	7.5	8.7	6.9	11.1	c	10.2	9.8	8.5	8.5	15.3	9.7
7	A,C,B	11.0	13.0	16.8	10.4	c	13.2	11.8	11.4	13.6	5.0	c	12.9
8	A,B,C	11.7	14.7	16.5	c*	c	24.9	50.5	33.1	24.0	14.7	11.9	22.2
9	C,A,B	24.5	25.7	17.4	21.8	9.9	20.7	28.1	25.5	12.2	12.5	21.3	13.8
10	C,A,B	15.0	c	13.0	11.2	14.3	13.1	10.4	11.7	15.0	16.6	16.3	16.6
11	B,A,C	52.9	51.2	28.1	25.3	29.9	30.2	48.0	25.0	33.5	43.1	31.0	23.0

a – final treatment not completed due to intercurrent illness

b – middle of night tablet not given

c – failure of monitoring equipment (* – in second half of night only)

Appendix 16

Night-time Sinemet-Plus study: Number of movements in bed greater than 4mm per hour before the 03.00h. tablet administration time.

Patient Number	Order of treatment	Treatment A (PP.P)				Treatment B (AA.P)				Treatment C (AP.A)			
		Night 1	Night 2	Night 3	Night 4	Night 1	Night 2	Night 3	Night 4	Night 1	Night 2	Night 3	Night 4
1	C,A,B	1.0	4.5	1.0	2.8	1.4	1.6	1.2	1.8	1.2	0.5	2.1	1.3
2	A,B,C	10.5	5.3	6.0	5.4	1.7	3.7	2.3	2.8	6.2	5.4	1.2	3.4
3	A,C	2.5	1.2	1.8	0.4	a	a	a	a	0.4	1.1	1.9	5.8
4	A,C	5.0	1.3	b	2.1	a	a	a	a	6.0	5.8	8.3	5.7
5	A,B,C	1.0	10.4	8.2	b	b	2.1	1.5	3.7	b	4.0	3.2	3.5
6	C,B,A	1.1	1.8	3.5	1.0	0.5	c	2.0	6.3	1.0	2.0	1.2	1.2
7	A,C,B	0.6	1.0	0.6	3.0	c	1.3	1.8	1.3	0.8	0.2	c	0.0
8	A,B,C	5.4	1.2	3.8	10.2	c	4.9	4.2	4.4	8.1	4.3	9.8	0.2
9	C,A,B	2.0	3.9	2.1	5.5	0.0	0.0	2.1	2.6	1.0	1.8	2.8	2.1
10	C,A,B	4.1	c	5.2	4.3	6.1	1.7	4.1	4.1	3.7	8.4	4.1	4.2
11	B,A,C	1.8	1.5	1.3	1.4	1.0	1.7	1.7	2.0	1.1	1.4	0.7	1.4

a - final treatment not completed due to intercurrent illness

b - middle of night tablet not given

c - failure of monitoring equipment

Appendix 17

Night-time Sinemet-Plus study: Number of movements in bed greater than 10mm per hour before the 03.00h. tablet administration time.

Patient Number	Order of treatment	Treatment A (PP.P)				Treatment B (AA.P)				Treatment C (AP.A)			
		Night 1	Night 2	Night 3	Night 4	Night 1	Night 2	Night 3	Night 4	Night 1	Night 2	Night 3	Night 4
1	C,A,B	0.0	2.2	0.2	0.9	0.4	0.0	0.2	0.2	0.5	0.2	1.2	0.7
2	A,B,C	3.5	2.3	2.6	3.0	1.1	2.4	1.1	1.3	3.9	2.8	0.6	1.9
3	A,C	1.2	0.8	0.9	0.0	a	a	a	a	0.4	0.2	1.2	3.1
4	A,C	1.8	0.5	b	0.6	a	a	a	a	3.3	3.8	4.2	2.1
5	A,B,C	0.5	7.1	6.5	b	b	0.9	0.2	2.9	b	1.7	2.3	1.8
6	C,B,A	0.2	0.4	1.1	0.2	0.2	c	0.7	2.6	0.7	0.3	0.8	0.3
7	A,C,B	0.0	0.5	0.3	0.5	c	0.3	1.0	0.8	0.5	0.0	c	0.0
8	A,B,C	2.5	0.7	1.9	6.8	c	3.2	2.5	2.0	5.0	2.2	2.9	0.2
9	C,A,B	1.3	2.6	1.0	3.8	0.0	0.0	1.6	2.0	0.3	0.7	1.5	0.7
10	C,A,B	2.5	c	2.8	1.7	4.6	0.7	1.9	2.2	1.7	5.7	2.8	2.7
11	B,A,C	1.6	1.3	0.6	1.1	0.7	1.0	1.4	0.9	0.5	0.9	0.5	1.0

a - final treatment not completed due to intercurrent illness
b - middle of night tablet not given
c - failure of monitoring equipment

Night-time Sinemet-Plus study: Number of movements in bed greater than 20mm per hour before the 03.00h. tablet administration time.

Patient Number	Order of treatment	Treatment A (PP.P)				Treatment B (AA.P)				Treatment C (AP.A)			
		Night 1	Night 2	Night 3	Night 4	Night 1	Night 2	Night 3	Night 4	Night 1	Night 2	Night 3	Night 4
1	C,A,B	0.0	0.8	0.2	0.7	0.2	0.0	0.2	0.2	0.2	0.2	0.2	0.2
2	A,B,C	1.8	1.5	1.5	1.7	0.2	1.3	1.1	0.7	2.5	1.3	0.2	1.3
3	A,C	0.8	0.6	0.7	0.0	a	a	a	a	0.2	0.0	0.2	1.1
4	A,C	0.5	0.0	b	0.4	a	a	a	a	1.6	1.2	0.9	1.0
5	A,B,C	0.5	3.8	2.7	b	b	0.3	0.0	1.3	b	0.0	0.8	0.6
6	C,B,A	0.2	0.0	0.2	0.0	0.0	c	0.0	0.5	0.2	0.0	0.2	0.2
7	A,C,B	0.0	0.0	0.3	0.0	c	0.3	0.3	0.0	0.0	0.0	c	0.0
8	A,B,C	0.2	0.5	1.0	4.3	c	1.1	1.4	1.3	2.9	1.2	1.4	0.2
9	C,A,B	1.3	1.3	0.5	2.2	0.0	0.0	1.3	0.7	0.3	0.0	0.8	0.7
10	C,A,B	0.6	c	0.7	0.5	1.1	0.2	0.2	0.5	0.7	2.3	0.8	1.3
11	B,A,C	1.3	0.9	0.6	0.9	0.5	0.7	1.4	0.9	0.4	0.9	0.4	0.7

a - final treatment not completed due to intercurrent illness

b - middle of night tablet not given

c - failure of monitoring equipment

Appendix 19
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Night-time Sinemet-Plus study: Total distance moved in bed (mm) per hour before the 03.00h. tablet administration time.

Patient Number	Order of treatment	Treatment A (PP.P)				Treatment B (AA.P)				Treatment C (AP.A)			
		Night 1	Night 2	Night 3	Night 4	Night 1	Night 2	Night 3	Night 4	Night 1	Night 2	Night 3	Night 4
1	C,A,B	5.2	52.3	15.1	45.2	13.6	8.6	11.2	15.4	19.1	7.7	29.4	16.2
2	A,B,C	116.6	91.2	168.0	139.6	40.5	78.4	48.9	55.0	191.0	112.8	20.6	68.2
3	A,C	46.1	35.6	34.7	2.9	a	a	a	a	13.3	8.5	19.8	100.7
4	A,C	58.0	10.2	b	33.1	a	a	a	a	149.8	97.0	110.1	78.6
5	A,B,C	14.4	178.9	171.4	b	b	24.2	12.6	66.4	b	35.6	56.8	45.4
6	C,B,A	11.4	13.2	32.8	6.7	3.9	c	17.5	60.9	11.6	13.6	21.5	11.7
7	A,C,B	5.7	11.6	8.3	29.2	c	18.6	22.0	14.2	9.3	1.1	c	0.0
8	A,B,C	63.1	18.2	71.6	263.2	c	98.4	208.5	117.6	207.5	72.9	117.5	4.8
9	C,A,B	72.5	86.5	27.5	132.0	0.0	0.0	65.2	37.4	17.1	18.6	58.4	34.9
10	C,A,B	63.7	c	66.4	47.9	91.0	18.8	40.5	49.4	47.9	134.3	61.4	74.1
11	B,A,C	95.0	91.3	36.9	39.7	32.6	55.6	89.1	55.0	39.9	57.4	25.4	34.8

a – final treatment not completed due to intercurrent illness
b – middle of night tablet not given
c – failure of monitoring equipment

Appendix 20

Night-time Sinemet-Plus study: Mean move size in bed (mm) before the 03.00h. tablet administration time.

Patient Number	Order of treatment	Treatment A (PP.P)				Treatment B (AA.P)				Treatment C (AP.A)			
		Night 1	Night 2	Night 3	Night 4	Night 1	Night 2	Night 3	Night 4	Night 1	Night 2	Night 3	Night 4
1	C,A,B	5.5	11.7	15.1	16.3	10.1	5.4	9.3	8.5	16.2	16.3	14.2	12.4
2	A,B,C	11.1	17.3	28.0	26.1	23.7	21.1	21.1	19.4	30.8	21.1	16.6	20.2
3	A,C	18.6	29.2	19.9	6.7	a	a	a	a	30.5	8.0	10.6	17.4
4	A,C	11.7	7.8	b	15.7	a	a	a	a	25.0	16.7	13.2	13.7
5	A,B,C	14.4	17.3	20.9	b	b	11.8	8.4	18.2	b	8.9	18.0	13.1
6	C,B,A	10.5	7.5	9.5	6.5	7.4	c	8.6	9.7	11.6	6.8	18.5	9.7
7	A,C,B	9.9	11.6	14.9	9.8	c	14.5	12.0	10.9	11.6	5.0	c	0.0
8	A,B,C	11.6	15.6	19.0	25.9	c	19.9	49.4	26.6	25.7	16.8	12.0	26.4
9	C,A,B	36.3	22.4	13.2	24.2	0.0	0.0	31.2	14.4	17.1	10.2	21.2	16.5
10	C,A,B	15.7	c	12.9	11.2	15.0	11.0	10.0	12.0	13.1	16.1	15.1	17.8
11	B,A,C	52.2	60.9	28.1	28.1	31.3	32.4	51.9	27.5	37.7	41.9	36.1	25.4

a - final treatment not completed due to intercurrent illness

b - middle of night tablet not given

c - failure of monitoring equipment

Appendix 21

Night-time Sinemet-Plus study: Number of movements in bed greater than 4mm per hour following the 03.00h. tablet administration time.

Patient Number	Order of treatment	Treatment A (PP.P)				Treatment B (AA.P)				Treatment C (AP.A)			
		Night 1	Night 2	Night 3	Night 4	Night 1	Night 2	Night 3	Night 4	Night 1	Night 2	Night 3	Night 4
1	C,A,B	2.3	1.0	1.1	1.6	2.9	2.3	4.7	2.3	1.6	4.5	3.7	0.8
2	A,B,C	9.4	0.8	6.6	6.8	2.1	2.3	2.6	1.2	1.9	3.9	2.4	1.2
3	A,C	1.5	4.1	5.3	1.2	a	a	a	a	1.5	4.1	2.0	5.6
4	A,C	5.7	3.8	b	0.6	a	a	a	a	2.5	5.7	9.2	17.1
5	A,B,C	16.0	5.2	18.2	b	b	1.3	2.9	0.0	b	1.2	2.5	1.1
6	C,B,A	5.5	5.1	5.6	3.3	1.5	c	2.0	5.0	4.0	6.0	1.5	0.0
7	A,C,B	2.3	6.5	2.0	1.3	c	1.1	0.5	1.0	4.4	0.0	c	2.5
8	A,B,C	3.1	5.5	6.5	c*	c	3.8	1.9	7.8	2.7	5.7	1.6	9.5
9	C,A,B	5.4	5.1	3.2	3.2	2.3	3.5	4.3	5.5	3.3	0.3	0.4	1.5
10	C,A,B	3.4	c	2.2	2.9	1.3	6.6	3.7	4.0	3.0	4.6	4.0	10.9
11	B,A,C	2.6	1.0	0.0	3.8	4.0	1.7	2.0	1.8	1.1	1.0	1.0	1.1

a - final treatment not completed due to intercurrent illness
b - middle of night tablet not given
c - failure of monitoring equipment (* - in second half of night only)

Appendix 22

Night-time Sinemet-Plus study: Number of movements in bed greater than 10mm per hour following the 03.00h. tablet administration time.

Patient Number	Order of treatment	Treatment A (PP.P)				Treatment B (AA.P)				Treatment C (AP.A)			
		Night 1	Night 2	Night 3	Night 4	Night 1	Night 2	Night 3	Night 4	Night 1	Night 2	Night 3	Night 4
1	C,A,B	2.0	0.7	0.8	0.4	0.4	0.4	2.3	0.8	0.4	3.0	1.8	0.0
2	A,B,C	3.8	0.0	3.9	4.4	0.7	1.5	1.9	0.4	1.5	0.8	1.6	0.4
3	A,C	1.1	1.7	1.8	0.8	a	a	a	a	1.0	2.1	0.4	3.9
4	A,C	2.3	1.4	b	0.0	a	a	a	a	1.2	3.7	6.8	9.2
5	A,B,C	9.6	1.7	14.9	b	b	0.7	1.1	0.0	b	0.8	1.0	0.6
6	C,B,A	4.6	1.4	2.2	1.1	1.5	c	1.0	3.0	0.0	2.7	0.5	0.0
7	A,C,B	1.0	5.5	1.5	0.8	c	0.8	0.3	0.8	3.1	0.0	c	0.8
8	A,B,C	2.1	2.2	2.5	c*	c	2.2	1.3	5.1	1.1	0.5	0.6	7.5
9	C,A,B	4.0	3.7	2.0	2.1	0.7	2.4	1.7	4.4	0.8	0.3	0.4	0.9
10	C,A,B	0.5	c	1.6	1.1	0.0	3.8	1.7	1.5	1.5	3.4	3.4	7.4
11	B,A,C	1.6	0.5	0.0	1.6	3.0	0.6	1.5	1.8	0.6	1.0	0.5	1.1

a - final treatment not completed due to intercurrent illness
b - middle of night tablet not given
c - failure of monitoring equipment (* - in second half of night only)

Night-time Sinemet-Plus study: Number of movements in bed greater than 20mm per hour following the 03.00h. tablet administration time.

Patient Number	Order of treatment	Treatment A (PP.P)				Treatment B (AA.P)				Treatment C (AP.A)			
		Night 1	Night 2	Night 3	Night 4	Night 1	Night 2	Night 3	Night 4	Night 1	Night 2	Night 3	Night 4
1	C,A,B	0.7	0.0	0.4	0.4	0.0	0.0	0.7	0.4	0.0	0.8	0.9	0.0
2	A,B,C	0.4	0.0	1.9	0.8	0.4	1.1	1.5	0.4	0.8	0.0	1.2	0.0
3	A,C	0.4	0.8	0.4	0.4	a	a	a	a	0.0	0.4	0.4	1.7
4	A,C	1.0	0.3	b	0.0	a	a	a	a	1.2	2.6	3.2	3.2
5	A,B,C	5.3	0.0	7.5	b	b	0.0	0.6	0.0	b	0.4	0.5	0.6
6	C,B,A	0.9	0.0	0.0	0.0	0.0	c	0.5	0.0	0.0	0.6	0.0	0.0
7	A,C,B	0.0	0.0	0.3	0.0	c	0.0	0.0	0.0	0.0	0.0	c	0.6
8	A,B,C	0.5	1.1	1.0	c*	c	2.2	1.3	4.2	0.0	0.5	0.0	3.5
9	C,A,B	2.6	2.1	1.2	1.2	0.5	1.3	1.3	4.0	0.4	0.3	0.4	0.2
10	C,A,B	0.5	c	0.6	0.6	0.0	1.6	0.8	0.0	1.0	1.7	1.1	2.3
11	B,A,C	1.6	0.0	0.0	1.6	2.5	0.6	1.5	0.4	0.6	1.0	0.5	0.0

a - final treatment not completed due to intercurrent illness

b - middle of night tablet not given

c - failure of monitoring equipment (* - in second half of night only)

Appendix 24

Night-time Sinemet-Plus study: Total distance moved in bed (mm) per hour following the 03.00h. tablet administration time.

Patient Number	Order of treatment	Treatment A (PP.P) Night 1	Night 2	Night 3	Night 4	Treatment B (AA.P) Night 1	Night 2	Night 3	Night 4	Treatment C (AP.A) Night 1	Night 2	Night 3	Night 4
1	C,A,B	37.7	13.1	18.5	20.9	21.2	18.0	66.7	24.0	11.5	65.2	40.7	5.2
2	A,B,C	93.3	4.7	170.9	94.2	48.2	51.9	61.4	27.4	45.3	28.8	53.0	12.5
3	A,C	28.8	43.8	63.7	14.8	a	a	a	a	19.9	42.7	19.1	79.7
4	A,C	77.6	35.2	b	4.3	a	a	a	a	43.0	163.9	152.4	221.5
5	A,B,C	304.3	45.5	481.2	b	b	17.6	31.5	0.0	b	19.7	33.6	17.7
6	C,B,A	81.2	38.4	41.6	24.2	22.1	c	29.8	50.2	24.7	62.2	11.9	0.0
7	A,C,B	25.2	86.2	34.0	15.2	c	12.3	5.6	12.5	58.2	0.0	c	32.3
8	A,B,C	37.8	76.7	79.2	c*	c	171.3	112.9	330.8	21.6	55.9	16.3	208.8
9	C,A,B	124.2	138.2	59.6	65.0	22.9	72.3	109.9	171.6	34.4	7.0	10.0	19.2
10	C,A,B	44.1	c	30.5	31.9	8.5	97.4	42.4	43.2	64.8	90.5	80.2	162.5
11	B,A,C	141.3	11.9	0.0	84.7	115.5	39.0	76.0	32.4	22.9	48.1	21.8	14.4

a – final treatment not completed due to intercurrent illness
b – middle of night tablet not given
c – failure of monitoring equipment (* – in second half of night only)

Appendix 25

Night-time Sinemet-Plus study: Mean move size in bed (mm) following the 03.00h. tablet administration time.

Patient Number	Order of treatment	Treatment A (PP.P)				Treatment B (AA.P)				Treatment C (AP.A)			
		Night 1	Night 2	Night 3	Night 4	Night 1	Night 2	Night 3	Night 4	Night 1	Night 2	Night 3	Night 4
1	C,A,B	16.2	13.1	16.4	13.1	7.3	8.0	14.3	10.7	7.2	14.5	11.1	6.5
2	A,B,C	10.0	5.7	25.9	13.9	22.8	23.1	23.4	22.1	24.2	7.4	22.1	10.4
3	A,C	19.2	10.6	12.0	12.4	a	a	a	a	13.3	10.3	9.5	14.3
4	A,C	13.7	9.3	b	7.8	a	a	a	a	17.4	28.6	16.6	13.0
5	A,B,C	19.0	8.8	26.5	b	b	13.2	11.0	0.0	b	16.4	13.4	16.2
6	C,B,A	14.7	7.6	7.5	7.4	14.7	c	14.9	10.0	6.2	10.4	7.9	0.0
7	A,C,B	11.2	13.2	17.3	11.9	c	11.6	10.8	12.0	13.1	0.0	c	12.8
8	A,B,C	12.1	14.0	12.2	c*	c	44.8	59.4	42.2	7.9	9.8	9.9	22.0
9	C,A,B	23.0	27.3	18.7	20.1	9.9	20.7	25.6	31.5	10.4	24.0	22.4	12.6
10	C,A,B	13.1	c	14.0	11.2	6.6	14.9	11.4	10.8	21.6	19.8	20.1	15.0
11	B,A,C	54.3	12.4	0.0	22.1	28.9	22.7	38.0	18.2	21.0	48.1	21.0	13.2

a – final treatment not completed due to intercurrent illness
b – middle of night tablet not given
c – failure of monitoring equipment (* – in second half of night only)

Appendix 26

Night-time Sinemet-Plus study: Time (seconds) to walk an individually set distance ("timed walking" test).

Patient Number	Order of treatment	Treatment A (PP.P)				Treatment B (AA.P)				Treatment C (AP.A)			
		Morning 1	Morning 2	Morning 3	Morning 4	Morning 1	Morning 2	Morning 3	Morning 4	Morning 1	Morning 2	Morning 3	Morning 4
1	C,A,B	75	53	60	50	44	32	35	29	44	43	58	35
2	A,B,C	42	50	62	53	60	55	49	38	42	39	36	38
3	A,C	32	30	26	29	a	a	a	a	33	40	40	42
4	A,C	735	856	b	800	a	a	a	a	212	568	1166	d
5	A,B,C	25	22	20	b	b	20	19	15	b	23	20	15
6	C,B,A	259	403	270	235	372	216	207	280	270	c	405	225
7	A,C,B	192	155	169	156	48	140	133	144	134	145	170	160
8	A,B,C	230	183	364	473	215	328	440	209	254	285	138	132
9	C,A,B	88	88	95	65	62	85	70	59	65	80	72	63
10	C,A,B	140	138	132	157	153	c	158	135	84	114	153	125
11	B,A,C	240	220	223	239	253	265	265	172	220	185	135	165

a – final treatment not completed due to intercurrent illness
b – middle of night tablet not given
c – patient declined to walk
d – patient unable to walk

Appendix 27

Night-time Sinemet-Plus study: Time (seconds) for ten blinks. (In the initial protocol values for four consecutive occasions one minute apart were specified. However, the test usually had to be terminated after three observations due to either the patient becoming aware of the test or distractions on the ward.)

Patient Number	Order of treatment	Treatment A (PP.P)				Treatment B (AA.P)				Treatment C (AP.A)			
		Morning 1	Morning 2	Morning 3	Morning 4	Morning 1	Morning 2	Morning 3	Morning 4	Morning 1	Morning 2	Morning 3	Morning 4
1	C,A,B	31,33, 25	34,37, 47	30,35, 39	32,20, 34	35,35, 44	41,37, 36	31,31, 30	25,42, 39	30	26	30	29
2	A,B,C	50	46	50	67	65	31,35, 45	46,40, 40	60,50, 55	75,43, 45	45,63, 55	67,52, 56	60,31, 40
3	A,C	47	39	14,27, 19	23,24	a	a	a	a	43,50, 29	c	18,17, 24	19,22, 36
4	A,C	225,150	150,113, 900	b	300,225, 300	a	a	a	a	450,225, 180	180,225, 113	113,100, 225	225,150, 180
5	A,B,C	60,54, 44	55,83, 71	72,45, 70	b	b	58,47, 54	46,59, 57	56,49, 47	b	39,40, 50	54,54, 38	35,57, 56
6	C,B,A	33,33, 46,52	69,26, 30,26	40,26, 30,34	105,101, 70,105	35,35, 42	79,94, 85,35	75,67, 45,45	65,55, 35,62	29,23, 30	32,30, 45	37,35, 33	27,27, 35
7	A,C,B	41,40, 35	35,41, 35	42,35, 37	33,30, 32	36,37, 38	34,35, 35	34,30, 30	40,31, 28,30	38,43, 33	30,33, 28	33,31, 35	37,38, 36
8	A,B,C	33,24, 29	36,40, 34	26,30, 33	28,30, 29	25,25, 23	24,23, 28	28,27, 32	25,23, 21	24,25, 30	23,21, 28	25,28, 24	28,29, 23
9	C,A,B	80,71, 73	60,51, 67	49,47, 53	65,74, 73	45,58, 66	54,84, 51	48,55, 69	52	48,48, 40	43,39	44,47, 49	35,43, 38
10	C,A,B	21,22, 25	27	22,30, 30	30,18, 18	17,20, 25	15	17,11, 22	10,16, 15	17,29, 36	11,12	20,15, 24	10,24
11	B,A,C	65,53	55,56	50,65, 62	53,55	57,55, 75	65,65, 70	68,58, 70	68,58, 59	46,63, 60	73,76, 80	60,73, 63	78,71, 85

a – final treatment not completed due to intercurrent illness
b – middle of night tablet not given
c – patient aware of the assessment being made

Appendix 28

Normal control gait data

Subject Number	Age (years)	Height (cm)	Number of swings	Mean (sd) double support time (seconds)	Mean (sd) swing time (seconds)	Mean (sd) swing length (mm)	Reaction time (seconds)	First step length (mm)	First step time (seconds)	Velocity (cm/second)
1	72	154	10	0.148 (0.053)	0.518 (0.049)	877.3 (172.4)	0.825	279.0	0.450	76.3
2	77	151	9	0.128 (0.034)	0.525 (0.043)	944.8 (98.1)	0.350	302.5	0.525	88.6
3	71	174	9	0.094 (0.054)	0.481 (0.030)	1003.4 (96.5)	0.350	401.5	0.375	90.3
4	74	155	6	0.117 (0.022)	0.513 (0.038)	979.9 (74.7)	0.375	451.0	0.650	78.4
5	74	157	6	0.154 (0.029)	0.580 (0.045)	988.9 (58.4)	0.875	478.5	0.500	71.7
6	65	172	10	0.163 (0.043)	0.611 (0.060)	926.1 (112.6)	0.600	335.5	0.400	62.7
7	66	156	8	0.106 (0.022)	0.553 (0.071)	1059.4 (84.8)	0.450	495.0	0.600	83.1
8	66	173	8	0.103 (0.034)	0.456 (0.029)	1188.7 (139.3)	0.500	495.0	0.450	111.9
9	78	158	11	0.177 (0.044)	0.564 (0.048)	916.0 (115.5)	0.650	253.0	0.500	76.4
10	72	178	8	0.128 (0.028)	0.663 (0.091)	1064.9 (87.7)	0.600	528.0	0.450	69.3
11	81	151	11	0.148 (0.071)	0.520 (0.086)	867.9 (101.9)	0.500	346.5	0.450	64.6
12	70	156	8	0.163 (0.090)	0.500 (0.094)	754.2 (93.6)	0.600	390.5	0.450	61.3
13	69	163	9	0.217 (0.071)	0.541 (0.088)	922.6 (47.6)	0.650	438.9	0.550	63.1
14	74	155	6	0.117 (0.013)	0.505 (0.037)	1003.2 (54.0)	0.375	451.0	0.650	66.9
Mean (sd)	72 (5)	161 (9)	9 (2)	.0.140 (0.034)	0.538 (0.054)	964.1 (103.9)	0.550 (0.168)	403.3 (87.7)	0.500 (0.086)	76.0 (14.0)

Appendix 29

Daytime Sinemet-Plus study: Gait analysis data for the
entire walk

    To avoid the errors that would be inherent in re-
typing the large amount of data generated this Appendix
is based on relevant computer printouts. Data for
successive swings of a particular gait analysis are
printed across the page, carrying on to the next line
if necessary. The far left hand column of figures
refers to the times during one day upon which gait
analysis was carried out. Time 1 refers to the zero
hour measurements, 2 to the two hour measurements, 3 to
the four hour measurements and 4 to the six hour
measurements. The first group of times 1 to 4
correspond to day 1, the second group to day 2, the
third group to day 3 and the fourth group to day 4.
The order of treatment for each patient is given in
Appendix 30. The data has been quoted in mm as
measured directly from the gait trace. To convert into
absolute values (cm) for swing length the given values
must be multiplied by a factor of 1.12, and to convert
into absolute values (seconds) for double support time
the given values must be divided by a factor of 20.
Times when gait analysis was not possible owing to
equipment failure (patient 1) or intercurrent illness
(patients 4 and 5) have been left blank.

Patient Number 1

Swing length

```
       9.0  15.0  11.0  11.5  12.0  12.0  12.0   9.5  11.0   6.0   6.0  11.0  10.0   8.0   6.0   7.0   5.5   7.0   6.0   7.0   4.0   3.5
 3.5                                                                                                     7.0   8.0  10.0   7.5   7.5   7.0   6.0  14.0  11.0   7.0
 4.0                                                                                                     8.0  10.0  12.0   8.0   8.0   7.5   9.0  15.5  11.0   7.5
 7.0                          7.0  10.0   9.5  12.0  10.0   7.5   6.5   8.0  13.0   9.0  12.0
 6.0                          9.0  10.0  10.0  11.0   9.5   7.0   9.0   7.5  12.5  10.5   7.5
 7.0                         10.0   7.0   8.5  12.0   8.5   6.5   6.5   8.0  12.5  12.5   5.5
 5.5                          8.0  13.5  10.0  12.5  10.0   6.5   6.5   9.0  13.0  14.0   9.5
 6.0      8.0   8.5  12.0   9.5  10.0  10.5   6.5   5.0  12.0  15.0  12.5   7.0
 8.0      5.0  11.0  10.0   7.0  11.5   6.0   4.0   6.0  15.5  17.5  14.0   4.0
10.0      7.0  15.0  12.5  10.0  13.0  10.0   5.5   6.0  14.5  14.0  17.0   7.0
11.0     10.0  14.0  12.0  13.0  15.0  12.0   8.0   3.0  21.5  16.5  16.0   9.0
 6.0     10.0  17.0  10.0  12.0  14.0  12.5   8.5   7.0  16.0  18.0  19.0   8.0   8.5
 6.0     14.0  15.0  12.0  10.0  16.5  14.0   4.5   7.0  20.5  18.0  17.5   6.5   7.0
11.0     14.5  15.0  15.0  11.0  13.0  13.5   5.0   7.5  21.0  20.0  16.5  11.0   6.0
 9.5      6.0  11.0  13.0  15.0  11.0  17.5  12.5   9.0   8.0  23.0  17.0  17.5  10.0   6.0
12.0      6.0  12.0  12.0  12.0   9.0   7.0  14.0  13.0  10.0   9.0   8.0  25.0  20.0  20.0   8.0   9.0
12.0      5.0  15.0  17.0  14.0  10.0   7.5  13.0  15.5   9.0   7.5   8.0  24.0  19.0  16.5   9.0   6.0
11.5      7.0  15.0  15.0  18.0  17.0  13.5   7.0  16.5  11.5  11.0   6.5   6.0  23.0  13.5  18.0  16.5   3.0  11.5   6.0
11.0      5.0  15.0  19.0  21.0  14.0  13.0   8.0  16.0  10.0  11.0   9.0   6.0
 9.0      7.0  14.0  21.5
```

1 2 3 4   1 2 3 3 4   1 2 3 4   1 2 3 4

Patient Number 1

```
Double support time

       30.0  24.0 19.0 30.0 16.0 10.0 11.5 16.5 23.0 21.0 10.0
       31.0  36.0 20.0 29.0 28.0 30.5 32.0 22.0 20.0 15.0 36.0
       14.0  30.0 26.0 16.0 26.5  9.0 10.5 12.5 21.0 23.0 18.0  7.0
       38.0  31.0 32.0 21.0 23.0 29.0 29.0 30.0 25.5 21.0 20.5 30.5
       19.0  29.0 27.0 20.0 31.5  9.0 19.0 12.0 25.0 30.0 19.0  8.0
       39.0  29.5 39.0 23.0 19.0 33.0 32.0 30.5 44.5 26.0 16.0 32.5
       16.0   8.0 24.0 31.0 14.0 37.5  8.5 18.0 10.5 51.5 25.0 22.0  8.0
       42.0  19.0 26.0 39.0 26.0 21.0 38.0 45.0 45.5 21.5 16.0 16.0 44.0
       13.0   9.0 21.5 26.0 21.0 21.5  8.0 25.0 13.5 35.0 23.5 19.0  8.5
       33.0   7.0 22.0 34.0 31.0 16.5 38.0 56.0 54.5 17.5 22.0 17.0 39.5
       13.0  27.5 21.5 24.0 32.0 20.0  6.0 13.0 14.0 19.0 20.5 20.0 10.5 26.0
       31.0   8.0 29.5 32.0 23.0 20.0 26.0 39.0 35.0 18.0 19.5 20.0 34.0  9.0
       15.0  28.0 26.0 29.0 22.5 25.0  5.5 17.5 14.5 24.0 27.5 22.0 11.0 26.0
       31.0   9.0 28.0 27.0 30.0 20.0 33.0 30.0 31.5 16.0 30.0 23.0 41.0  6.0
       15.0  24.0      30.0 25.0 18.0 26.0 22.0  6.0 14.0 16.0 22.5 21.5 19.0 24.0 12.0 29.5
       40.0  16.0 10.0 33.0 25.0 26.0 23.0 27.0 38.0 35.0 10.0 19.0 23.5 23.5 42.0 10.0
       14.0  20.0 34.0 28.0 23.0 39.0 24.0 22.0 11.0 11.0 19.0 25.5 18.0 26.0 21.5 22.0 26.0 24.5 30.0 13.5 25.5
       37.0  15.0 12.0 22.0 30.0 29.0 28.0 21.0 41.0 22.5 37.0 10.0 36.5 15.0 20.5 16.0 24.5 24.0 25.0 39.0  8.0
       16.0  26.0 32.0 30.0 25.0 22.0 22.5 18.0  9.0 51.0 12.5 31.0 19.0 26.5 26.5 21.5 15.5 25.0 29.5 15.0 12.0 29.0
       38.0  18.0 10.0 34.0 24.0 22.5 29.0 27.5 39.0 19.5 28.0 13.5 59.5  9.0 27.5 18.0 21.0 22.0 25.0 24.0 31.0  9.0
       21.0  21.0 24.0 39.0 32.0 34.0 20.0 39.0 27.5 18.5 16.5 29.0 17.0 41.5 14.0 26.5 14.5 19.5 21.0 21.5 22.5 11.0 22.5 15.0 27.0

              1    2    3    4    1    2    3    4    1    2    3    4    1    2    3    4
```

Patient Number 2

Swing length

Trial	Values
1	17.0 37.0 46.0 47.0 50.0 53.0 55.0 46.0 45.0 47.0 45.0 42.0 41.0 39.0 36.0 33.0 32.0 26.0 14.0
2	7.0 17.5 28.0 41.0 54.0 59.0 57.0 54.5 55.0 50.5 48.0 44.5 45.0 47.0 43.5 31.0
3	24.0 34.5 44.0 49.0 51.0 46.5 46.0 49.5 51.0 46.0 42.0 39.0 33.0 33.0 31.0 24.0 26.0
4	26.5 48.0 58.5 65.0 62.0 60.5 62.0 63.5 61.0 57.0 52.0 46.0 36.0
1	34.0 46.5 58.5 62.5 55.0 47.5 47.0 48.5 46.0 47.0 42.5 40.0 37.5 28.0
2	15.5 23.0 36.0 45.5 46.0 42.0 45.5 41.0 43.5 51.5 52.0 52.5 49.5 45.5 30.0
3	33.0 42.0 52.0 52.0 51.5 51.5 54.5 53.0 45.5 47.0 42.5 39.0 38.5 37.0
4	33.0 53.5 66.0 65.0 58.5 58.0 53.0 51.0 56.0 51.0 46.5 45.5 34.0
1	47.0 52.0 76.0 68.0 75.0 77.0 74.0 68.0 64.0 57.0 50.0 39.0
2	54.5 67.0 76.0 76.0 78.0 78.5 79.5 77.0 65.5 59.0 57.5 53.0
3	58.0 68.0 71.0 78.0 75.5 76.0 73.5 70.0 61.5 57.5 48.0 41.5 32.0
4	36.5 45.0 53.5 54.5 53.5 60.0 62.0 58.5 53.0 50.0 48.0 51.0 53.0 54.5 49.0
1	52.5 63.5 66.0 63.5 64.0 61.5 60.0 59.5 48.0 51.0 53.0
2	58.0 56.0 71.5 77.5 72.0 76.5 62.5 59.0 59.5 48.0 37.5
3	73.5 78.0 85.0 67.0 86.0 80.0 80.0 61.5 48.0 44.0 42.0
4	55.0 69.5 80.0 85.0 83.5 84.0 82.5 80.0 77.5 62.0 52.0 41.0

Double support time

Trial	Values
1	6.0 6.5 3.0 3.0 2.0 2.0 2.0 2.0 2.0 2.5 2.0 2.0 3.0 2.0 3.0 3.5
2	5.0 4.5 3.0 3.0 2.0 1.0 1.0 2.0 1.0 0.5 1.5 0.5 1.0 1.5 1.5
3	10.0 6.0 3.5 2.0 1.5 2.0 2.0 3.0 2.0 3.0 3.0 3.0 2.0 3.0 4.0
4	4.5 2.5 1.0 2.0 1.0 1.5 1.5 1.0 1.5 2.0 2.0 2.0 3.5 3.0
1	7.0 4.5 2.5 1.5 3.0 4.0 2.0 1.5 2.0 2.0 2.0 1.0 1.5 1.0
2	4.5 6.0 3.0 2.0 2.5 2.5 2.0 1.0 1.0 1.0 1.0 1.0 1.0 1.5 2.0
3	5.0 3.0 2.0 1.5 1.5 1.0 1.0 1.0 1.5 1.5 1.0 1.5 1.0 2.0
4	3.0 3.0 1.5 1.0 1.0 1.0 0.5 0.5 0.5 1.0 1.5 1.0 1.0 1.5 2.0
1	3.0 2.5 1.5 1.5 1.5 1.0 1.0 1.0 0.5 1.0 1.5 2.0
2	2.5 1.5 2.0 1.0 1.0 1.5 1.0 1.5 1.0 1.0 0.5 1.0 2.0
3	2.5 2.0 1.5 1.5 1.0 1.0 1.0 1.5 1.0 1.0 1.5 1.5
4	4.0 2.0 1.5 1.5 1.0 0.5 1.0 1.0 0.5 1.0 2.0 2.0 2.0
1	2.5 1.5 2.0 1.5 1.0 1.0 1.5 1.0 1.0 0.5 1.0 2.0 3.0 3.0 3.5
2	2.5 1.5 1.5 2.0 1.0 1.5 1.5 1.5 1.0 1.5 1.5 1.5 4.0 2.5
3	6.0 2.5 2.0 1.0 1.0 0.5 1.5 1.0 1.5 2.5 2.5 1.5
4	6.5 2.0 1.5 1.0 1.0 1.0 1.5 1.0 3.0

Patient Number 3

Swing length

1	49.0	63.5	66.0	69.0	70.0	72.0	73.0	72.0	71.0	71.0	71.0	69.0		
2	46.5	62.0	65.0	67.0	68.0	69.0	65.0	67.0	69.0	70.0	68.0	63.5		
3	72.0	77.5	79.0	80.0	80.0	81.0	77.0	70.0	66.0					
4	45.5	48.0	56.0	67.5	68.0	71.0	72.0	75.0	79.0	78.0	78.0	67.0	59.0	
1	49.0	62.0	61.5	62.0	64.0	67.0	66.5	66.0	69.0	57.5	50.0	40.0	59.0	
2	40.5	52.0	57.5	63.0	61.5	58.0	55.0	58.0	57.5	60.0	60.0	52.5		
3	57.0	62.0	62.0	65.0	63.0	60.5	65.0	68.0	62.0	68.0	55.0	40.0		
4	52.0	60.0	60.0	59.0	64.0	65.0	65.0	65.0	64.0	62.0	54.0	40.0		
1	40.0	47.5	54.5	58.5	63.5	66.5	68.5	71.0	71.5	72.0	74.0	69.0	61.5	59.0
2	37.0	53.0	59.0	59.5	57.5	57.5	60.0	62.5	63.0	65.5	68.0	67.0	64.5	59.5
3	56.5	66.0	71.0	73.5	74.5	80.5	80.5	81.0	80.0	77.0	74.5	68.0		
4	55.0	62.0	66.0	72.5	78.0	77.0	78.0	78.0	76.5	76.5	75.0	70.0		
1	61.5	62.5	69.5	71.5	74.5	76.0	73.5	74.0	75.5	71.5	67.5	63.5	52.0	
2	58.0	56.5	61.0	64.5	68.5	69.0	69.0	71.0	72.5	67.5	62.5	55.5	55.0	
3	56.5	60.5	63.0	65.5	68.0	71.5	71.0	68.5	68.0	67.0	68.5	68.0	65.0	60.0
4	68.5	71.0	74.0	76.0	76.5	77.0	77.0	76.5	75.0	68.5	64.0	48.0		

Double support time

1	6.0	3.0	4.0	3.0	3.0	2.0	2.0	2.0	3.0	2.0	2.0	3.0		
2	8.0	3.0	2.5	2.5	2.5	3.0	2.0	2.5	2.0	3.0	2.5	3.0		
3	3.0	1.0	2.0	2.0	2.0	1.0	1.0	2.0	2.0	2.0	2.0			
4	8.0	5.0	3.5	2.0	3.0	2.0	3.0	2.0	2.0	7.0				
1	6.0	4.0	4.0	3.0	3.0	3.0	5.0	4.0	4.0	5.0	7.0			
2	6.0	6.0	5.0	3.5	5.0	5.0	6.0	4.0	5.0	3.0				
3	6.0	3.5	3.5	3.0	3.5	3.0	4.0	3.0	3.5	3.5				
4	5.0	2.0	3.0	2.5	3.0	3.0	3.0	3.0	3.0					
1	6.0	3.5	3.0	2.0	2.5	1.5	1.5	2.0	1.5	1.5	2.0	1.2	2.0	
2	5.0	2.0	2.0	2.5	2.5	2.5	2.0	1.5	2.5	2.0	2.0	2.0	2.0	2.5
3	3.0	2.0	2.0	2.0	2.0	1.5	2.0	1.5	2.0	2.0	1.5	1.0		
4	3.5	2.5	2.5	2.5	2.5	2.5	2.0	2.0	2.0	1.0				
1	2.5	4.0	3.0	3.0	3.0	3.0	2.5	3.0	3.5	2.5	2.5	3.0		
2	3.0	4.0	3.5	2.5	2.5	2.0	2.5	3.0	3.5	3.0	3.0	3.0	2.0	
3	4.0	3.5	2.0	2.5	2.0	2.5	3.0	2.5	3.5	3.5	3.5	3.0	3.0	
4	2.5	3.0	2.5	1.5	2.5	2.5	3.0	2.0	2.5	3.0				

Patient Number 4

```
1   15.0 11.5  7.0 13.0 10.5 16.0 16.5 18.0 18.5 15.0 13.0 14.5 14.0 15.0 14.5 11.0 13.0  7.0  7.0  8.0 11.5
    12.0 11.5 11.5 12.5 15.0 12.5 11.5 11.5 13.0 11.5  9.0 11.5 16.0 16.5 18.5 18.0 19.5 17.0 16.5 16.5 24.0
2    7.5  7.0 14.5 18.0 15.5 15.5 16.5 16.0 18.0 20.5 18.5 19.0 20.0 21.5 20.5 18.5 19.5 18.5 16.5 19.0 22.0
    31.0 25.0 18.5 18.0 18.0 18.0 20.5 21.0 20.5 22.0 20.5 19.5 18.5 18.0 19.0 22.0 22.5 19.0 17.0 18.0 18.5
3   12.5 15.0 17.0 16.0 22.0 23.0 17.5 18.5  7.0 16.5 19.5 18.5 16.5 15.5 17.0 18.5 18.5 16.5 12.5 13.5 13.5
    22.0 23.0 21.0 20.5 21.0 20.0 18.5 10.0 22.5 12.0 13.5  6.5 12.0 13.5  7.0  8.5 11.0  6.0  4.5  6.5  9.0
4   11.0 12.5 10.0 19.0 19.5 18.5 21.5 21.5  8.5 21.5 12.0 16.0 14.5  6.0 13.0 12.5 13.0 15.5 14.5 18.0 19.0
    18.0 19.0 21.0 16.5 16.5 17.5 16.0 17.0 15.5 18.5 17.0 16.0 16.0 19.0 22.5 16.5 16.0 16.0 16.0 12.5 11.0

1   11.0 12.0 12.5 13.0 11.5 12.5 11.5 16.0  9.0
    16.0 11.0 11.0 11.5 15.0 19.0 19.0 18.0 19.0
2    4.0  5.0  4.0  5.0  9.0 11.5 13.5  6.5  7.0
    10.5 20.0 21.0 18.0 15.0 19.0 12.0 18.0
3   11.5 10.0 11.0 11.5 17.0 16.5 16.0 14.5 13.0
    18.0
4    7.0  5.0  6.5 11.5 12.0 14.0 16.0 16.0 22.5
    12.5 15.0 18.0 16.5
```

Swing length

Patient Number 4.

```
1   6.0   2.0  15.0   1.5   1.5  20.5   2.0  19.0   2.0  18.0   2.5  16.0   2.5  15.0   2.5  16.5   2.5  15.0   2.5   4.0  22.0  21.5   4.0
    2.0  17.0   2.5  16.0   2.0  15.5
2   1.5   3.0  15.0   3.0  19.0   6.0  16.0   3.0  16.0   5.0  39.5   4.0  17.5   3.0  16.0   3.0  15.5   3.0  16.0   3.0  15.0
    2.0  16.0   1.5  16.0   1.5  17.5
3   1.5   1.5  15.0   3.0  17.5   2.0  13.5   3.0  14.5   2.0  16.0   2.0  11.5   1.5  12.5   1.5  14.0   2.0  14.0   1.5  14.0
    2.5  14.5   3.0  14.5   2.5   2.0
4   5.5   2.0   5.0  19.5   3.0  16.0   2.0  14.0   3.0  17.0  16.0   2.5  15.0   3.0  15.0   3.0   3.0  15.0
   15.0   2.5  15.0   2.5  13.5   2.0  14.5  14.5

1  19.0   4.0  18.0   2.5   4.5  18.0   2.5   2.5  17.5   3.0  17.0   2.5  17.5   2.5  15.0   2.5  17.0
    2.0   1.0  15.5  17.0  15.5
2   2.0   4.0  14.0   4.0   2.0  17.0   4.0  16.0   2.0  16.0   2.0  15.5   3.0   1.5  15.0   1.5
    2.0  19.0   3.0  16.5  18.0   1.5
3   2.5   3.5  16.5   4.5  19.0   3.0  16.0   2.0  15.0   2.5   1.0  17.0   2.0   1.5   2.0  14.5
    2.5
4   6.5   2.5  18.5   2.0  17.0   2.0  14.5   2.5  16.0   1.5  14.5   1.5  14.5   2.0  14.5  36.5   4.5
   12.0   3.0  14.0
```

1
2
3
4
1
2
3
4

Double support time

Patient Number 5

```
1  25.5 19.0 22.0 21.0 26.5 23.0 20.5 22.0 23.0 24.0 23.5 25.0 22.0 22.0 23.5 25.0 23.5 25.0 21.0 17.0 15.0
1  22.0 26.0 23.0 22.0 17.0 21.0 20.5 21.0 23.0 23.0 22.0 25.0 20.5 21.0 21.0 25.6 22.0 16.0 10.0
2  25.0 30.0 30.5 26.0 29.0 34.0 34.0 35.5 32.0 29.0 32.0 30.0 32.0 40.5 33.5 32.0 33.0 34.0 33.0 32.0
2  30.0 30.5
3  32.0 35.0 41.0 40.0 39.0 37.5 35.0 35.0 37.0 41.5 38.0 38.5 29.5 25.0 33.0 33.5 35.0 36.5 39.0 35.0 30.0
4  42.0 41.0 43.0 43.5 44.0 45.0 42.0 46.0 49.0 53.0 55.0 53.0 62.0 50.0 37.0 43.0 35.0
1  18.0 16.0 19.5 22.0 23.0 26.0 24.0 25.0 28.0 28.0 29.5 28.5 22.0 26.0 26.0 22.5 23.0 22.0 20.0 21.0 23.5
2  25.0 20.0 18.0 21.0 23.0 24.0 24.0 24.0 24.0 21.5 26.0 19.0
   17.5 21.5 23.5 24.0 22.5 20.0 22.0 27.0 25.0 25.0 26.0 27.0 27.0 26.0 25.0 21.0 22.0 21.0 19.5
3  25.0 24.0 22.0 18.0 17.5 18.0 20.0 24.0 24.0 27.0 34.0 30.0 30.0 24.0 20.0
   26.0 23.0 25.0 21.0 24.0 25.0 22.0 22.0 23.0 22.0 22.0 20.0 21.0 25.0 23.0 24.0 19.0 18.0 20.0
   22.0 23.0 22.0 21.5 21.0 19.0 22.0 22.0 22.0 23.0 22.5 24.0 22.0 16.0 22.0 17.0 24.0 21.0 20.0
4  33.0 37.0 40.0 42.0 36.0 32.0 34.5 35.0 33.0 33.5 37.0 31.0 31.0 34.0 31.5 32.0 33.5 29.0 32.0 31.5 34.5
   35.0
```

1 2 3 4 1 2 3 4

Swing length

Patient Number 5

1	8.0	9.0	10.0	9.0	6.0	11.0	8.0	9.0	7.0	8.0	7.0	6.0	12.0	9.0	7.0	5.0	7.0	6.0	7.0	7.0
	9.0	6.5	6.0	13.0	9.0	7.0	6.0	12.0	6.5	6.0	6.0	6.0	6.0	5.0	4.5	5.0	10.0	4.0	4.5	4.0
2	8.0	5.5	8.0	5.5	8.0	6.0	4.5	6.0	5.5	6.0	5.0	5.0	5.5	3.0	6.0	6.0	5.0	5.0	4.0	5.0
	6.0	11.0																		
3	10.0	6.0	6.0	4.5	6.0	4.5	6.0	4.0	7.0	7.0	8.0	6.0	6.0	8.0	5.0	6.0	5.0	6.0	3.0	5.0
4	7.0	4.0	5.0	4.0	4.5	5.0	2.5	6.0	3.0	4.0	2.5	3.0	4.0	8.0	8.0	4.0				
1	10.0	6.0	11.0	5.0	10.0	5.0	8.0	8.0	5.0	5.0	6.0	6.0	8.0	6.0	7.0	9.0				
2	4.0	8.0	8.0	4.0	9.0	6.0	7.0	6.0	6.0	11.0	8.5	9.0	10.0	10.0	7.0	8.0	13.0			
3	10.0	9.0	9.0	8.0	7.0	10.0	7.0	7.0	9.0	6.0	2.0	7.0	6.0	6.0	9.0					
4	12.0	8.0	7.0	5.0	7.0	11.0	7.0	7.0	4.0	5.0	6.0	9.0	14.0	8.0	6.0	11.5	10.0	5.0		
1	10.0	7.5	10.0	7.0	9.0	9.0	8.0	7.0	13.0	8.0	3.0	9.0	8.0	6.0	8.0	9.0	8.0			
2	5.0	8.0	8.0	6.0	6.0	5.0	8.0	8.0	5.0	5.0	5.0	8.0	7.0	5.0	5.0	8.0	7.0			
3	5.0	7.0	5.0	3.0	6.0	7.0	6.0	3.5	7.0	6.0	4.0	7.0	5.0	6.0	7.0					
4	7.0																			

1 2 3 4 1 2 3 4

Double support time

Patient Number 6

Swing length

1	50.5	67.5	72.0	73.5	76.5	79.0	72.0	68.5	66.0	61.0	56.0				
2	52.0	65.5	65.0	68.0	75.5	73.0	67.0	67.5	67.5	62.5	56.5				
3	53.5	64.0	67.5	72.0	72.0	68.5	68.5	72.5	70.5	67.0	60.5				
4	57.5	72.0	67.5	64.5	65.5	68.0	70.5	69.0	65.0	63.0	58.0				
1	52.5	62.5	63.0	68.0	73.0	73.0	72.0	73.0	68.5	65.5	60.0	51.5			
2	72.5	79.5	82.5	87.5	86.0	82.5	79.5	74.0	58.0						
3	70.5	80.0	84.0	81.0	80.0	84.5	85.5	78.0	67.5						
4	61.5	71.0	79.5	83.0	85.0	81.0	79.5	79.0	74.0	59.0					
1	59.5	62.0	66.5	69.0	73.5	74.5	74.0	74.5	74.0	71.0	64.5	57.5	51.0		
2	51.5	60.5	68.0	71.0	74.0	75.5	80.0	79.0	75.0	70.0	66.0	65.5	57.0	44.5	
3	52.0	62.0	66.5	65.5	67.0	70.0	73.0	68.5	65.5	68.5	67.5	62.5	59.0	55.5	
4	53.0	57.5	62.0	63.5	63.5	68.0	70.0	68.0	66.0	68.0	65.5	60.5	60.0	55.0	46.0
1	63.0	66.0	72.0	75.0	79.5	80.5	81.0	80.0	75.5	73.5	71.5	65.0	53.0		
2	65.0	74.0	82.0	85.5	92.0	92.0	88.5	87.5	82.5	71.0	66.0	52.5			
3	59.0	64.5	63.0	62.5	73.0	79.5	82.5	81.5	77.5	72.0	70.5	62.5	57.0		
4	64.0	71.5	77.0	77.5	80.0	82.0	79.5	76.0	77.0	78.0	72.0	63.5	57.0		

Double support time

1	6.0	2.5	2.0	2.0	2.0	2.0	2.0	1.5	2.0	2.0	2.0				
2	7.0	2.5	2.5	3.0	1.5	2.5	2.5	1.0	2.0	2.0	3.0				
3	7.0	3.5	2.0	2.0	2.0	2.0	2.5	1.5	2.5	2.5	2.0				
4	4.5	2.0	2.0	2.5	3.0	2.0	2.0	2.0	2.0	3.0	3.0				
1	6.5	2.0	1.5	2.0	2.0	1.5	2.0	1.5	1.5	1.5	2.0	3.5			
2	2.0	2.0	1.5	1.0	1.0	1.0	2.0	2.0	2.5						
3	3.0	3.0	3.0	2.0	1.5	1.0	2.0	1.5	2.0						
4	4.0	3.0	2.5	2.0	1.5	1.5	1.5	1.0	1.5	2.0					
1	3.0	3.0	1.5	2.0	1.5	1.5	2.0	2.0	1.0	1.5	2.0	3.0	3.5		
2	5.5	3.0	3.0	2.0	1.0	1.0	1.5	1.0	1.0	1.5	2.0	2.0	2.0	3.5	
3	5.0	2.5	2.5	1.5	2.5	2.0	2.0	1.5	2.0	1.5	2.5	2.0	2.5	3.0	
4	4.5	4.0	2.0	2.5	2.5	2.0	1.5	1.5	1.0	2.0	2.0	2.5	2.0	2.5	
1	4.0	3.0	1.5	2.5	1.5	2.0	2.0	1.0	1.0	2.0	1.5	2.0	2.0		
2	3.0	3.0	1.5	1.5	2.0	2.0	2.0	2.0	1.0	2.0	2.0	3.5	2.0		
3	3.0	3.0	1.5	2.0	1.5	1.0	2.0	1.0	1.0	1.5	1.5	1.0	1.5		
4	2.0	1.5	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.5	1.5	1.5		

Patient Number 7

Swing length

	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	C14	C15	C16	C17
1	26.5	31.5	43.5	53.0	54.0	57.0	57.0	56.0	59.0	56.0	56.0	60.0	58.0	49.0	33.0		
2	30.0	51.0	63.0	69.0	72.5	72.0	74.5	75.0	70.0	66.0	61.5	44.0					
3	33.0	51.0	64.0	74.0	71.0	68.0	63.5	62.0	62.0	63.0	59.0	40.5					
4	50.0	64.0	72.0	73.5	69.0	67.0	68.0	62.0	68.0	69.5	60.5	44.0					
1	41.5	52.0	58.0	61.0	58.0	57.0	60.0	62.5	56.0	50.0	62.5	50.0	53.0	44.0			
2	44.0	52.0	58.5	62.0	62.5	61.0	63.0	60.0	58.5	56.0	54.0	52.0	47.0	44.0			
3	34.0	47.5	52.0	54.0	55.0	54.0	55.5	55.0	56.0	55.0	55.5	54.0	52.0	45.0	27.0		
4	44.0	62.0	61.0	61.0	59.5	65.0	62.0	58.0	62.0	59.0	55.0	61.0	51.0	22.5			
1	38.0	56.0	64.0	65.5	72.0	67.0	69.0	76.0	68.0	63.0	59.5	63.0	53.5	55.5	52.0	34.5	
2	38.0	50.5	59.5	55.5	63.0	74.0	76.0	73.5	68.0	72.5	69.0	55.0	58.5	48.0	44.5	37.0	22.0
3	34.0	42.0	51.0	61.0	63.0	63.5	63.5	64.5	73.5	72.0	66.5	62.0	63.0	50.5	38.5	29.5	
4	25.5	41.5	46.0	54.5	64.5	61.5	66.0	64.5	64.0	63.5	62.0	61.0	50.5	42.0	39.5	34.5	38.0
1	34.0	42.0	45.0	47.0	51.5	46.5	51.0	58.0	66.0	54.0	52.0	48.0	51.0				
2	21.0	39.0	42.5	48.0	52.0	55.0	50.0	51.0	58.0	48.0	49.5	46.0	54.5				
3	32.5	49.0	53.0	55.5	51.0	54.5	57.0	59.0	51.5	58.0	55.5	52.5	54.0				
4	14.0	21.0	37.5	41.5	46.0	48.5	51.5	53.0	52.0	53.0	51.5	47.5	44.0				
	23.5																

Double support time

	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	C14	C15	C16	C17
1	6.0	5.5	4.0	3.0	2.0	2.0	2.0	3.0	1.0	2.0	2.0	2.0	3.0	2.0	3.0	4.5	
2	5.0	1.5	3.0	2.0	2.0	1.0	1.5	1.0	1.0	2.0	1.0	3.0	2.0				
3	6.0	2.0	3.0	1.5	1.0	1.5	2.0	2.0	2.5	2.0	2.5	3.0					
4	4.0	3.0	2.0	1.0	2.0	2.0	2.0	2.0	2.0	2.0	4.0	2.0					
1	4.0	3.0	2.0	2.0	2.0	3.0	2.0	3.0	3.0	3.0	3.5	3.0					
2	6.0	3.0	2.5	2.0	3.0	3.0	3.0	4.0	3.0	3.0	4.0	5.0	6.0				
3	5.5	3.0	3.0	3.0	3.0	4.0	3.0	3.0	3.5								
4	6.0	2.5	2.0	3.0	3.0	3.0	2.5	3.0	2.5	2.0	3.0	3.0					
1	5.0	3.5	2.0	1.5	2.5	1.5	2.0	2.5	1.5	1.5	2.5	2.0	2.5				
2	4.0	4.0	2.5	1.5	1.0	2.0	1.5	1.5	1.5	1.5	1.5	2.0	2.5				
3	4.0	3.0	3.0	2.0	2.0	2.0	2.0	2.0	2.0	1.5	2.0	2.0	2.0	3.0	3.5		
4	4.0	3.0	3.5	2.5	1.5	1.5	2.0	2.5	2.0	1.5	2.0	2.5	2.5	2.0	2.5	4.5	
1	5.0	3.0	3.0	3.0	2.0	2.0	2.5	1.5	2.0	2.0	2.0	3.0	3.0	3.5			
2	7.5	3.0	3.5	3.0	2.0	2.5	2.0	2.0	2.0	2.5	2.0	3.0	2.5	4.5			
3	6.0	3.5	3.0	3.5	3.0	3.0	2.5	2.5	3.0	3.0	2.5	3.0	3.5	5.0			
4	9.0	5.5	3.5	4.5	3.0	3.5	3.5	3.0	2.5	4.5	3.5	2.5	4.0	4.5	4.0	5.0	3.0
	4.0																

Patient Number 8

Swing length

#											
1	17.5	17.0	15.0	15.5	16.0	10.0	8.5	12.5	8.0	8.5	4.5
2	15.0	12.5	14.0	12.0	13.0	11.0	11.5	4.0	3.0	4.0	
3	5.0	7.0	4.5	7.0	15.5	14.0	5.0	2.0	6.5		
4	5.5	4.0	14.5	12.0	6.5	4.0	1.5	5.0			
1	4.5	3.5	3.0	3.0	4.0	2.0	7.0	10.0			
2	11.0	10.0	12.0	8.5	8.5	6.5	11.5	5.5			
3	8.0	12.5	13.5	11.0	12.0	8.0	5.5	7.5			
4	5.0	8.5	4.5	5.0	6.0	4.0	11.0				
1	13.0	16.0	13.5	12.5	14.5	14.0	15.0				
2	11.5	15.0	15.0	13.5	12.0	15.5					
3	6.0	6.0	6.5	5.0	5.5	4.5					
4	8.0	5.0	4.0	6.0	6.0	5.0					
1	7.0	7.0	12.0	9.0	9.5	9.5					
2	49.5	49.5	52.0	54.0	50.0	50.5	50.5	49.0			
3	8.5	10.0	9.5	8.5	7.5	8.0	9.5	10.0			
4	21.0	11.0	7.0	8.5	6.0	8.0	5.0				

Double support time

#									
1	10.0	6.0	6.0	4.0	6.0	4.0	3.5	2.5	1.5
2	10.0	9.0	10.0	6.0	7.0	4.0	2.0	7.0	8.0
3	8.5	3.5	5.0	4.5	4.0	3.0	16.0	3.0	8.0
4	10.0	7.0	3.0	2.5	5.5	5.0	3.5		
1	13.5	10.5	9.5	6.0	7.5	6.5	3.5		
2	6.0	4.5	5.0	2.0	3.5	2.5	8.0		
3	3.0	3.0	3.0	5.5	3.5	3.5	7.0		
4	22.5	15.0	11.0	5.0	8.5	8.5			
1	6.5	6.0	4.0	5.5	4.5	4.5			
2	15.0	6.5	6.5	3.0	5.0	2.5			
3	15.0	10.0	11.0	10.5	7.0	8.0			
4	19.0	11.0	14.0	5.0	9.0	5.5			
1	12.0	17.0	6.0	10.0	7.0	7.5			
2	1.0	1.5	2.5	1.5	2.0	2.0	1.5		
3	7.0	6.0	5.5	7.0	4.5	7.0	5.0		
4	3.0	2.5	5.0	4.0	5.0	5.0			

Patient Number 9

```
       24.0 24.0 24.0 23.5 20.0 18.5 22.5 22.5 23.0 23.5 26.0 25.0 26.0 28.0 26.0 24.0 22.5 22.5 23.5 16.5 10.5
 1     24.0 24.0 22.0 24.0 26.5 20.5 18.0 18.0 18.5 17.5 18.0 18.5 18.0 21.0 18.0 16.5 21.5 22.0 21.0 25.0 24.5
       26.0 22.0 30.0 28.0 26.0 25.0 27.0 28.5 26.5 29.0 28.0 29.0 26.0 21.5 19.0 16.0 13.0 13.0 12.0  9.0 11.0
 2     27.0 26.0 23.0 29.0 30.5 30.0 29.0 30.5 33.5 35.0 33.5 36.0 33.0 34.5 36.0 35.0 33.5 31.0 26.0 27.0 24.0
       22.0 21.0 20.0 20.5 24.0 24.5 28.0 28.0 31.0 32.0 33.0 35.0 34.0 32.5 34.0 32.5 32.0 31.5 31.0 25.0 22.5
 3     15.0 25.5 31.0 33.5 38.0 36.0 33.0 32.0 34.0 43.0 40.5 42.5 39.5 41.0 42.0 40.0 39.5 36.0 28.5 24.5 18.0
       29.5 30.0 33.0 37.0 36.0 36.0 32.0 34.0 38.0 38.0 38.0 37.0 40.0 39.5 36.0 36.0 35.0 33.5 23.0 19.0 22.0
 4     31.0 28.0 29.5 36.0 27.0 27.5 28.0 28.5 31.0 38.0 33.5 36.5 34.0 38.5 37.5 34.5 30.5 31.0 23.5 36.0 35.0
 1     20.5 19.0 20.5 21.0 21.5 19.0 28.5 26.0 26.0 20.5 25.0 19.0 27.5 26.5 28.0 27.5 26.0 23.5 24.5 28.0 24.5
       18.0 20.0 21.0 24.0 22.5 21.0 19.5 16.5 18.0 14.0 13.0 12.0 13.5 13.5 18.0 19.5 22.0 19.5 22.5 23.0 22.5
 2     26.0 26.0 25.0 24.0 23.0 24.0 28.0 25.0 27.5 29.0 24.5 33.5 29.0 32.0 24.0 23.5 24.0 27.0 27.0 25.0 22.0
 3     20.5 18.0 13.0 10.0 19.0 18.0 22.0 15.5 16.0 20.0 15.0 16.0 16.0 20.0 20.5 25.0 20.0 22.0 21.5 24.0 20.0
       20.5 20.0 24.0 24.0 22.0 25.0 23.0 21.5 21.5 22.0 18.0 17.0 25.0 26.0 18.0 20.0 21.5 22.5 21.0 22.0 20.0
 4     21.5 24.5 26.0 17.0 25.0 22.0 24.0 23.0 22.0 24.5 26.5 27.5 28.5 24.5 26.5 28.0 27.5 29.0 29.0 29.5 22.0
 1     20.5 16.0 17.0 21.5 20.5 16.0 18.0 17.0 18.5 19.0 18.0 18.0 17.0 16.5 18.0 21.0 16.5 24.0 24.0 28.0 25.0
       26.0 28.0 28.0 26.0 27.0 28.0 29.0 30.0 28.0 28.0 27.0 28.0 25.0 24.0 25.5 25.0 24.0 24.5 24.5 21.0 15.0
 2     25.5 26.5 28.0 29.0 16.5 20.5 21.5 22.5 22.0 20.5 22.0 24.0 24.0 24.0 24.0 24.5 25.0 24.5 22.5 26.5 22.0
       20.5 18.0 13.0 15.0 17.5 20.0 19.0 17.5 17.5 20.0 16.0 19.0 19.0 22.0 21.0 18.5 32.5 32.0 30.5 30.0 16.0
 3     23.0 24.0 23.0 22.0 26.5 29.0 29.0 30.0 29.0 30.0 32.0 33.0 32.0 32.5 32.5 33.0 37.0 28.0 29.0 32.0 27.5
       21.5 24.5 26.0 23.0 23.5 20.0 23.5 21.0 23.0 23.0 21.0 16.0 21.0 19.0 24.0 25.5 24.0 25.0 24.0 26.5 24.0
 4     22.5 19.5 15.5 18.0 26.0 14.0 16.0 20.0 18.0 21.5 20.0 18.0 16.5 17.5 27.5 27.0 27.5 28.0 27.0 20.0 12.0
       14.0 10.5 15.5 20.0 13.5 22.5 19.0 21.5 22.5 22.0 22.5 22.0 20.5 21.5 21.0 16.0 16.5 17.5 16.0 16.5 16.5
                                                                                                           17.5
```

Swing length

Patient Number 9

Double support time

5.0	5.0	4.0	3.5	3.5	4.0	3.5	3.5	3.5	5.0	5.0	3.0	3.5	5.0	3.5	4.5	3.5	5.0	3.0	4.0	3.5
3.0	5.0	3.0	4.0	5.0	3.0	5.0	6.0	5.0	5.0	3.5	6.0	5.5	5.0	3.0	3.0	4.0	4.0	3.0	3.0	2.0
7.0	5.5	8.0	5.5	5.0	3.0	5.0	3.5	3.0	3.5	2.0	3.0	3.5	2.0	2.5	2.0	3.0	3.0	3.0	3.0	2.5
1.5	1.0	3.0	2.0	3.0	1.0	2.0	2.5	2.0	2.5	2.0	2.0	2.5	2.0	2.5	3.5	1.5	2.0	1.0	2.0	2.0
7.5	6.0	2.0	2.0	2.5	2.0	3.5	2.5	2.5	2.0	2.0	2.0	2.0	2.0	3.0	3.5	2.0	3.5	4.5	3.0	4.0
3.0	2.0	3.5	3.0	3.0	1.5	3.0	3.0	3.0	2.5	3.0	2.5	2.5	3.0	3.0	3.0	4.5	3.5	4.0	3.0	5.5
3.5	4.5	4.5	2.0	4.0	2.0	6.0	6.5	6.0	2.0	2.5	2.0	11.5	2.5	2.5	3.0	3.5	3.0	3.0	4.0	3.0
2.0	2.5	3.0	4.0	3.0	2.5	2.0	1.5	1.5	2.5	2.0	2.0	2.0	2.0	2.0	2.5	2.0	2.0	2.5	2.0	2.5
6.5	4.0	3.0	2.0	3.0	3.0	2.5	4.5	5.0	5.0	5.0	5.5	5.0	5.0	4.5	4.5	4.5	4.5	5.0	5.0	3.5
3.5	3.5	3.0	4.5	6.0	5.0	4.0	5.0	6.0	6.0	6.5	3.5	5.5	4.0	3.5	3.5	3.5	4.0	4.0	3.5	4.0
4.0	3.5	5.0	5.0	2.5	4.5	4.0	4.0	4.5	2.5	3.5	3.5	3.0	3.5	4.5	4.0	2.5	3.0	3.5	2.5	4.0
6.0	5.5	4.0	3.0	5.0	4.0	3.5	3.0	4.0	2.5	5.0	3.0	4.5	5.0	4.0	5.0	2.5	4.5	4.0	4.5	3.5
3.0	3.0	3.0	3.5	4.0	4.0	3.0	3.5	4.5	3.5	3.5	5.5	3.5	3.5	2.5	3.0	3.5	2.5	4.0	4.0	4.0
3.0	3.0	3.5	3.5	3.0	3.0	3.0	3.0	2.5	5.0	5.5	4.0	3.0	2.5	4.0	4.5	4.5	4.0	5.5	3.5	4.0
2.0	2.5	2.5	4.0	2.5	3.0	3.0	3.0	3.0	4.0	5.0	3.5	3.5	4.5	2.5	2.0	1.5	2.5	3.5	2.0	2.0
5.0	3.0	3.5	4.0	5.5	5.0	4.0	4.0	4.0	5.0	5.5	3.0	5.0	2.5	4.0	5.0	4.5	5.5	4.5	5.5	5.0
5.5	5.5	4.0	4.0	3.0	3.0	3.0	3.5	4.0	2.5	2.5	2.5	3.5	5.0	2.5	3.5	4.5	2.5	2.5	3.0	3.0
7.0	6.0	2.5	2.0	3.0	3.5	3.0	3.0	3.0	3.0	5.5	7.5	4.0	5.0	5.0	4.5	4.5	5.5	4.0	4.0	4.0
8.0	5.5	3.5	3.0	4.0	3.0	3.0	3.0	3.0	3.5	3.0	3.5	3.5	3.0	3.0	3.5	1.5	3.5	3.0	3.0	4.5
3.0	3.5	3.5	4.0	4.0	3.5	3.0	4.0	3.0	4.0	4.0	4.0	3.5	4.0	4.0	3.0	4.5	4.0	4.0	4.0	4.5
5.5	5.5	4.0	4.0	4.0	4.0	4.0	4.0	4.0	5.0	5.0	4.0	5.0	5.0	5.5	5.5	4.5	5.0	5.0	5.0	6.5
6.0	2.0	2.0	2.0	2.0	2.0	2.0	5.5	5.0	2.5	2.5	2.5	2.5	2.5	2.5	3.0	4.5	2.0	4.0	3.5	3.5
2.5	7.5	4.5	4.5	4.0	4.0	4.0	2.5	2.5	5.0	5.0	5.5	5.5	5.5	5.0	5.5	4.5	5.5	4.0	4.0	3.5
7.5	3.0	6.5	6.0	5.0	5.5	4.5	5.5	5.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	6.0	2.5	5.0	4.0	3.5
3.0	2.5	2.0	3.5	2.5	3.0	3.0	3.0	3.0	5.5	5.5	5.5	5.5	5.5	5.5	5.5	3.5	5.5	5.5	3.5	4.5
2.5	2.5	3.5	4.5	4.0	4.0	3.5	4.0	4.0	4.5	4.5	4.5	4.0	4.5	4.0	4.0	4.5	3.5	5.0	4.0	4.5
7.5	8.0	3.0	3.0	3.0	9.5	4.0	4.0	3.0	5.5	6.0	3.0	5.5	6.0	3.5	3.5	6.0	2.5	5.5	3.0	6.5
5.5	4.5	4.5	4.5	4.0	4.0	5.0	4.5	4.5	4.5	4.5	5.0	4.5	4.0	4.0	4.0	4.0	6.0	4.5	5.0	4.5
7.0	8.5	4.0	4.0	5.0	5.5	7.5	4.0	4.0	4.0	4.0	5.5	4.0	5.0	4.0	9.0	5.5	4.0	4.0	5.0	4.5

| 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |

Patient Number 10

```
  34.0  40.0        43.0         48.0  26.5  45.5  40.0        37.0  45.0  40.0  41.0  46.0
  27.5  42.0        42.0         44.5  27.0  47.5  40.5        39.5  36.0  42.0  48.0  43.0
  36.5  47.0  40.5  42.0   23.0  50.5  29.0  36.0  37.0  47.5  39.0  24.5  39.5  53.0  41.0
  32.5  52.0  51.0  38.0   38.0  40.5  41.0  35.5  36.5  43.5  38.0  26.0  42.5  46.0  44.0
  33.0  49.0  49.5  37.0   52.0  30.5  27.0  41.0  43.0  38.0  41.0  36.0  40.0  42.0  48.0
  44.5  42.5  50.0  38.0   52.0  51.0  13.0  38.5  48.5  40.5  45.5  40.0  35.0  42.5  46.5  51.0
  43.0  43.0  52.0  35.0   40.5  50.5  28.5  43.5  46.0  46.0  50.0  39.5  29.0  49.0  43.5  40.5
  41.0  47.5  50.0  37.0   43.0  57.5  43.5  59.0  42.0  40.0  41.5  41.0  29.5  48.5  39.5  30.5
  45.0  49.0  51.0  42.5   32.0  49.0  42.0  49.0  44.0  37.0  43.0  42.0  37.0  38.5  42.0  30.5
  46.5  50.5  51.0  38.5   39.0  50.0  41.0  49.0  48.5  46.0  48.5  40.5  46.0  33.0  41.0  35.0
  43.0  47.0  54.5  37.5   50.0  49.5  34.0  48.5  46.5  52.5  47.5  43.0  48.0  32.0  46.5  40.0
  45.0  44.0  57.5  32.0   53.0  47.0  41.0  50.5  42.0  52.0  47.0  46.0  52.0  35.5  57.0  42.0
  40.0  48.0  59.0  25.0   55.0  53.5  52.5  39.0  46.5  50.0  46.5  53.0  50.5  39.5  50.5  45.0
  38.5  49.5  58.0  23.5   52.5  55.5  55.5  35.5  47.5  44.0  50.0  49.0  44.0  46.5  48.5  43.0
  43.5  47.0  49.0  26.5   33.0  51.0  57.5  53.5  45.5  44.0  42.5  49.0  46.0  42.0  44.0  35.5
  39.5  44.5  47.5  27.0   23.0  53.0  61.0  44.0  50.0  49.0  38.0  41.0  45.0  36.0  31.5  46.5  23.0
  38.5  39.5  50.0  30.5   31.0  49.0  56.5  39.0  47.0  50.5  39.5  44.0  43.0  24.0  45.5  37.5  29.5
  25.0  35.0  46.0  32.5   46.0  46.0  55.5  48.0  35.5  45.0  41.5  49.5  43.5  23.5  39.0  36.5  36.5
   7.0  35.0  39.0  16.0   47.0  50.0  58.5  49.5  39.0  39.0  32.0  40.0  37.0  22.5  33.5  37.5  33.0
  33.5  39.0                                                   50.0  39.5
  50.5  43.5  31.5  32.5   29.0  41.5  51.0  42.0  46.5  39.0  27.0  41.0        45.5  37.0  23.5  26.0
        35.5  29.0        38.5  33.0  37.5  39.5  41.5  27.0              45.5  50.0  37.0  39.5  33.0
  50.5  36.0  24.5
```

1   2   3   4   1   2   3   4   1   2   3   4   1   2   3   4

Swing length

Patient Number 10

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1	8.0	3.0	4.5	3.5	3.5	3.0	2.0	2.5	3.0	1.5	2.5	1.0	2.0	2.5	4.0	2.0	3.0	3.0
2	3.0	1.0	4.0	3.5	3.5	2.5	2.0	2.0	2.0	2.0	1.5	1.0	3.0	1.5	2.0	2.0	1.0	2.5
3	5.5	2.5	3.0	2.0	2.5	2.0	2.0	2.0	2.5	1.5	2.0	2.0	2.0	2.0	2.5	2.0	2.0	
4	2.5	2.0																
1	5.0	3.5	2.5	5.0	2.0	2.0	1.5	1.0	3.5	3.5	3.0	3.5	4.0	1.0	2.0	2.5	3.0	2.0
2	5.0	5.0	5.0	3.5	7.0	3.5	3.0	4.0	6.5	3.0	2.0	3.5	4.0	2.0	3.0	4.0	3.5	2.5
3	3.5	2.0	1.0	4.5	1.5	3.0	4.5	3.0	1.5	3.5	3.0	3.5	3.5	2.5	4.0	3.5	3.0	3.5
4	3.0	2.0	3.5	2.5	2.0	3.5	3.0	3.0	2.5	3.5	3.0	2.5	2.5	2.0	3.5	3.0	3.0	3.0
1	2.5	2.5	1.5	1.5	2.0	2.5	2.0	3.0	2.5	2.5	3.0	2.0	2.0	2.5	2.5	2.0	3.5	3.5
2	4.5	4.0	2.0	2.0	3.0	2.5	2.5	2.0	2.5	3.5	2.5	3.0	3.0	3.0	3.0	3.5	3.0	3.0
3	3.5	2.5	4.0	4.0	3.0	2.5	1.5	3.5	2.5	3.5	2.0	2.0	3.5	3.5	3.0	2.5	3.0	3.0
1	11.0	5.5	4.5	4.0	4.5	3.0	3.0	4.5	3.5	3.5	3.5	3.0	3.0	3.0	2.5	3.5	3.5	2.5
2	6.5	7.0	3.0	3.0	3.0	4.5	4.0	3.0	3.0	4.0	2.0	2.5	3.5	3.0	2.5	2.0	2.5	3.0
2	2.5																	
3	5.0	3.5	3.0	3.5	3.0	3.5	2.5	2.5	2.5	2.5	2.0	2.0	2.0	3.0	3.0	3.5	3.0	3.5
4	6.0	3.5	3.5	2.0	2.0	3.5	4.0	3.5	4.0	3.5	2.5	3.5	4.0	4.0	3.5	3.0	3.5	3.0
1	7.5	3.5	5.5	4.5	2.0	2.0	2.5	2.0	3.5	1.0	2.0	4.0	2.5	2.5	4.0	3.0		
2	2.0	1.5	4.5	3.5														
2	6.5	2.0	3.0	3.5	2.5	2.5	3.5	2.5	3.0	4.0	3.0	2.0	3.0	2.5	2.5	3.0	3.0	3.0
2	2.0	2.5																
3	9.5	4.5	3.0	3.5	2.0	2.5	2.0	2.0	2.0	2.5	3.5	3.0	3.0	2.0	3.0	2.0	3.0	2.0
4	4.5	4.0	4.0	3.5	4.0	2.0	1.5	2.0	2.2	1.5	3.0	3.0	2.0	3.5	2.0	5.0	3.5	2.5
4	3.5	5.0	4.5															

Double support time

Patient Number 11

Swing length

#											
1	69.0	79.0	82.0	80.5	81.0	82.5	76.0	70.0	71.0	76.0	76.0
2	71.0	78.0	84.0	91.0	89.0	94.0	90.0	82.0	75.0	63.5	
3	79.0	87.0	94.0	101.0	95.0	95.0	93.5	100.0			
4	85.0	91.5	96.0	102.5	101.5	96.0	95.0	87.0	61.0		
1	87.0	90.5	95.0	103.0	96.5	97.5	96.0	92.0	76.0		
2	83.5	84.0	92.0	97.5	96.5	97.5	94.0	94.0			
3	87.0	80.0	92.0	85.0	94.0	95.0	88.0	88.5	89.5		
4	79.0	77.5	88.0	90.5	90.5	92.5	88.0	90.0	91.0		
1	75.0	74.5	82.0	85.0	81.5	82.5	85.5	82.0	75.0	62.5	
2	87.5	92.0	93.0	98.0	95.0	92.0	94.5	92.0			
3	86.0	95.0	91.0	94.0	92.5	88.0	84.5	83.0	74.0		
4	78.5	89.5	94.0	93.5	82.0	82.5	87.0	87.5	78.0		
1	87.0	93.0	92.0	91.5	84.5	88.5	91.5	90.5	81.5		
2	90.0	98.5	102.0	109.0	105.0	102.5	93.5	86.5			
3	87.0	93.5	96.0	102.5	100.5	102.0	90.0	85.0			
4	90.0	100.5	107.0	109.0	106.0	100.5	108.0				

Double support time

#											
1	5.0	3.0	2.5	2.0	1.5	2.0	1.5	3.0	3.0	2.5	1.5
2	3.0	2.0	1.5	1.5	1.0	1.5	1.0	1.5	2.0	2.5	
3	2.5	2.5	2.0	1.5	1.5	1.5	1.5	3.0			
4	2.5	2.0	1.0	1.5	1.0	1.5	1.5	2.0	1.5		
1	5.0	2.5	2.0	1.0	2.0	1.0	1.0	1.5	2.0		
2	3.5	1.0	1.5	1.0	2.0	0.5	0.5	1.5			
3	2.0	1.5	1.0	2.0	1.0	1.0	1.0	1.5	1.0		
4	3.0	1.5	2.0	1.5	1.0	1.0	1.0	1.0	0.5		
1	3.0	2.0	1.5	1.5	1.5	2.0	1.5	1.0	1.0	1.5	
2	3.5	1.5	2.0	2.0	1.0	1.5	1.0	1.0			
3	3.0	1.5	2.0	1.5	1.0	1.0	1.5	2.0	1.5		
4	3.0	2.5	1.5	2.5	2.0	1.5	1.5	1.5	1.5		
1	3.0	1.5	1.0	1.0	1.0	1.0	1.5	1.5	1.5		
2	1.5	1.0	1.0	2.0	1.0	1.5	1.5	1.5			
3	3.0	1.0	1.0	0.5	0.5	1.0	1.0	1.5			
4	2.0	1.0	0.5	0.5	0.5	1.5	1.0	1.0			

Patient Number 12

1	8.5	13.5	13.5	11.0	11.5	10.5	11.5	13.5	12.5	13.5	14.5	16.0	13.5	12.5	12.5	13.5	12.0	9.5	12.0
	13.5	13.5	12.0	9.5	10.0	8.0	10.0	10.0	11.5	7.5	11.5	9.0	7.5	11.0	8.0	9.5	10.0	6.0	6.0
	10.0	9.0	10.0	7.0	12.0	10.0	13.0	9.5	9.0	10.0	7.5	9.0	11.0	12.0	6.0	7.0			9.0
2	10.0	10.0	9.0	8.0	12.0	11.0	13.0	12.0	9.5	6.5	10.0	7.5	9.0	6.5	8.0	6.0	7.0	9.5	9.0
	9.0	5.5	7.5	14.0	12.5	7.5	4.5	9.0	5.0	5.0	5.0	8.0	6.5	5.0	8.0	8.0	2.5	3.0	8.0
	7.0	8.5	5.5	4.5	3.0	8.5	3.5	3.0	3.0	7.0	3.5	6.0	9.5	6.0	6.0	9.5	6.0	9.0	5.0
	7.5	9.0																	
3	11.0	15.5	15.0	19.0	22.5	25.0	15.5	17.0	21.0	19.0	26.5	25.0	19.0	14.0	18.5	9.0	9.0	16.5	20.0
	13.0	12.0	12.5	17.0	12.0	5.0	2.5	6.0	1.0	6.0	7.0	6.0	6.5	4.0	5.5	2.0	2.0	8.0	16.0
	14.0	10.5	11.5	10.0	17.5	15.0	15.5	16.5	9.0	11.0	6.5	11.5	13.5	11.0	8.0	4.0	4.0	2.0	4.0
4	11.5	11.5	14.0	13.0	10.0	10.5	11.0	10.5	12.0	12.5	16.0	15.0	10.0	13.0	17.0	17.5	17.0	16.0	17.0
	18.0	17.0	10.0	14.0	24.0	17.0	12.5	10.5	10.5	9.5	9.0	12.5	11.0	6.0	6.0	12.5	12.5	12.0	8.0
	7.5	8.0	7.0	7.0	5.0	7.0	6.0	6.5	10.5	6.0	12.5	9.5	12.0	12.5	17.5	10.0	11.5		9.0
	6.5																		
1	20.0	31.0	34.5	35.0	36.5	29.0	26.5	28.0	30.5	26.5	23.5	20.5	34.0	29.5	22.0	21.5	20.5	23.0	25.0
	21.0	20.0	20.5	16.5	14.0	13.5	10.5	14.0	15.5	11.0	6.0	8.0	6.5	17.5	14.5	13.0	2.0	13.0	
2	15.0	13.5	14.0	11.0	9.0	6.5	10.0	17.0	16.5	12.5	10.5	12.5	11.0	19.5	19.5	16.2	17.0	24.0	9.0
	11.0	16.5	26.0	28.0	27.0	30.0	30.0	25.0	24.0	22.0	14.5	18.0	14.0	16.0	17.0	21.0	24.0	17.5	18.0
3	23.5	22.5	26.5	26.0	26.5	33.0	30.0	31.0	28.0	22.5	23.0	24.5	22.5	20.0	24.0	12.0	21.0	24.0	15.5
	17.0	18.5	22.5	36.0	19.5	15.0	17.0	18.0	22.0	30.5	22.0	24.5	20.5	13.5	12.0	31.5	35.0	12.0	26.5
4	23.5	28.0	22.0	36.0	23.5	25.0	23.5	29.5	31.0	29.5	30.5	23.0	16.0	24.5	24.0	28.5	28.5	24.0	26.5
	25.0	19.0	23.5	22.0	17.0	14.5	20.0	20.0	19.5	20.0	20.0	13.5	12.0	15.0	8.5				
1	37.0	39.0	42.0	45.0	43.0	42.0	42.0	41.0	42.0	38.5	33.5	31.0	30.5	38.0	35.0	30.0	38.0	30.5	30.5
	22.0	19.0																	
2	28.0	30.0	34.0	35.0	28.0	31.5	41.5	40.5	41.5	39.0	34.5	33.0	33.0	37.0	35.5	34.0	33.0	29.5	30.5
	34.0	32.0	26.0	20.0	14.0	9.5	9.5			9.5					9.5				
3	18.5	28.0	30.0	32.0	27.0	28.5	33.0	33.5	28.5	29.5	28.0	30.0	29.5	30.0	31.5	29.5	32.0	23.0	28.5
	16.0	16.0	25.0	20.0	25.5	30.0	18.5	17.5	19.0	11.0	19.0	30.5	33.0	45.5	13.5	24.0	24.5	29.5	
4	24.0	28.0	40.0	36.0	30.5	35.0	36.5	33.5	35.5	42.0	35.5	42.0	39.0	40.5	28.0	12.0	27.0	29.5	28.0
	29.5	30.0	23.0	22.0		22.5										13.5			
1	27.0	30.0	35.0	35.0	34.0	37.0	37.5	36.0	38.0	39.5	38.0	38.0	40.5	38.0	36.0	38.5	38.0	30.5	32.0
	34.0	29.5	32.5	22.0															
2	19.5	28.0	31.0	32.5	36.0	41.0	40.0	40.0	43.0	40.0	41.0	42.0	42.0	40.5	39.5	35.0	33.0	33.5	38.0
	32.5	29.5	33.5	28.0															
3	27.5	36.0	33.0	42.5	41.5	42.0	43.0	41.5	42.0	42.0	35.0	43.0	34.5	40.5	42.0	35.0	37.5	32.5	30.5
	30.0	25.0	21.0	21.5															
4	25.5	34.0	39.0	40.0	37.5	37.0	34.0	38.0	38.0	39.0	33.0	35.0	33.0	34.5	39.0	36.0	34.5	31.0	32.0
	33.0	30.5	26.5	20.0															

Swing length

Patient Number 12

Double support time

Patient Number 13

Swing length

#															
1	73.5	90.0	95.0	97.0	96.0	92.5	89.0	87.0	80.5	57.5					
2	88.5	96.5	96.5	96.5	101.0	100.5	97.0	87.5	69.0	54.0		39.0			
3	81.5	96.0	96.0	92.0	93.0	90.5	84.0	82.0	75.5	59.5	45.5	38.0			
4	89.0	95.0	97.0	94.5	94.5	97.0	91.5	79.5	68.5	46.5		37.5			
1	75.0	75.5	82.5	86.5	92.5	92.5	89.0	82.0	74.5	65.5	54.5	46.0	36.0		
2	68.0	72.5	75.0	83.0	86.0	86.0	85.0	81.0	75.0	65.5	57.5	51.5	49.5	44.0	39.0
3	72.0	72.5	77.0	82.5	85.5	86.0	83.0	82.0	73.5	64.5	62.0	53.0	49.5	39.0	29.5
4	73.0	74.5	78.5	81.5	80.0	82.0	81.5	79.0	76.5	70.0	53.0	57.0	49.0	36.0	29.0
1	66.5	73.0	77.0	77.0	77.0	76.0	77.0	75.0	73.5	67.0	59.0	46.0	50.0		
2	43.5	52.5	63.0	71.0	70.0	72.0	74.5	70.5	68.5	63.5	54.5	51.5	43.0		
3	54.0	62.0	68.0	69.5	67.5	73.5	72.5	68.5	67.0	61.5	61.5	53.0	46.5		
4	54.5	55.0	58.5	67.0	70.0	70.0	72.5	68.5	67.5	68.0	65.5	57.5	51.5		
1	53.5	61.0	66.0	72.0	71.5	72.0	74.5	75.0	72.0	67.0	64.5	50.5	50.0		36.5
2	58.0	56.0	72.0	72.0	75.0	77.0	76.5	76.5	75.0	72.0	63.5	53.5	43.0		
3	58.5	65.5	67.0	68.0	73.0	76.5	73.0	73.5	76.5	71.0	64.0	53.5	46.5		
4	61.0	65.0	65.0	67.0	70.0	69.5	68.5	68.0	66.0	64.0	61.5	57.5	51.5	36.5	28.0

Double support time

#															
1	3.0	2.5	1.5	1.5	1.0	1.0	1.5	2.0	1.5	2.0					
2	2.5	2.0	1.0	2.0	1.5	1.5	1.0	2.0	1.5	3.5					
3	2.5	2.0	1.0	2.0	2.0	1.5	1.0	3.0	1.5	2.5					
4	2.5	2.0	1.5	1.0	1.5	1.5	1.5	2.0	2.0	3.0					
1	2.5	2.0	2.0	1.5	2.0	1.0	1.5	1.5	1.5	2.0	3.0	4.0	5.0		
2	2.5	3.0	2.5	2.0	1.5	1.0	1.5	1.5	2.0	2.5	3.0	3.0	3.5	4.5	5.0
3	2.0	3.0	2.0	2.0	2.0	1.5	2.0	2.5	2.0	2.0	2.5	5.0	4.5	5.0	5.5
4	3.0	2.0	2.5	1.5	1.5	2.0	2.0	2.0	2.0	1.5	2.0	3.0	3.5	4.0	5.5
1	3.5	2.5	2.0	2.5	3.0	2.0	2.0	1.5	2.0	2.5	2.5	3.0	3.5		
2	6.0	3.5	4.5	2.0	3.0	3.0	3.0	3.0	2.5	2.0	2.5	4.0	3.5		
3	5.0	3.5	2.5	2.0	2.5	2.5	2.5	3.5	2.5	3.0	3.0	3.5	4.5		
4	4.0	3.0	3.5	2.5	2.0	2.5	3.0	2.0	3.0	3.0	3.5	3.0	3.5		
1	4.0	3.0	2.0	3.5	3.0	3.0	3.0	3.0	1.5	4.0	3.0	2.5	5.0	5.0	5.5
2	4.0	2.0	2.5	2.5	2.5	3.0	3.0	2.0	2.0	3.0	3.0	3.0	4.0		
3	3.5	2.5	2.5	3.0	2.5	2.5	3.0	2.5	3.0	3.0	3.5	2.5	3.5		
4	3.5	2.5	3.0	3.0	2.5	2.5	2.5	2.5	2.0	2.5	2.5	3.5	3.0		

Patient Number 14

Swing length

1	95.5	110.0	115.0	116.5	116.5	113.0	110.0	103.0	
2	94.5	101.0	110.0	108.5	109.0	109.0	106.5	99.5	
3	90.0	105.5	114.0	109.5	109.5	111.0	108.5	103.0	
4	67.0	108.0	115.0	108.0	107.0	109.0	107.5	106.5	
1	86.0	104.0	106.0	105.0	109.0	108.0	101.0	98.0	79.0
2	71.0	110.0	118.0	124.0	119.0	111.0	112.0	97.5	
3	97.5	109.0	110.0	114.0	111.0	113.0	108.0	90.5	
4	88.5	99.5	115.0	110.5	110.0	114.5	110.0	103.5	
1	96.5	107.0	116.0	117.0	113.0	111.5	108.0	92.0	
2	67.0	113.0	113.0	114.5	118.0	112.5	105.0	74.5	
3	95.0	99.0	109.0	112.0	112.0	108.0	105.0	95.0	76.0
4	94.0	103.5	106.0	107.0	109.5	112.0	106.5	96.0	
1	91.0	101.5	103.0	121.0	104.0	103.5	101.0	97.5	85.0
2	94.0	107.0	113.5	111.0	109.5	108.0	108.0	96.5	
3	94.0	124.5	111.0	110.5	111.0	109.0	106.0	100.0	71.0
4	79.5	103.0	112.5	110.0	114.0	108.0	106.5	98.5	74.0

Double support time

1	2.0	1.0	1.5	0.5	1.0	1.0	1.0	1.0	
2	2.0	1.0	1.0	1.0	1.0	0.5	0.5	1.0	
3	2.0	1.0	0.5	1.0	1.0	1.0	1.0	0.5	
4	3.0	1.0	1.0	1.0	0.5	0.5	0.5	0.5	
1	3.0	1.5	1.0	1.0	1.0	0.5	0.5	1.5	1.0
2	2.0	0.5	1.0	0.5	1.0	0.5	0.5	1.0	
3	2.0	1.0	1.0	0.5	0.5	1.0	1.0	1.0	
4	2.0	1.0	0.5	1.0	1.0	0.5	0.5	0.5	
1	2.5	1.0	1.0	1.0	0.5	1.0	1.0	1.0	
2	1.5	1.0	1.0	1.0	1.0	0.5	0.5	0.5	
3	2.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	
4	2.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
1	2.5	1.0	1.0	1.0	1.0	0.5	1.0	1.0	1.0
2	2.5	1.0	0.5	1.0	1.0	1.0	1.0	1.0	1.0
3	2.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
4	2.0	1.0	1.0	1.0	0.5	1.0	1.0	1.0	1.0

Daytime Sinemet-Plus study: Values of speed of walking and cadence

Patient Number	Day	Treatment *	Speed of walking (cm/second)** at time (hours)				Cadence (number of swings/ minute) at time (hours)			
			0	2	4	6	0	2	4	6
1	1	Active	2.85	a	a	3.03	36.06	a	a	35.73
	2	Placebo	3.58	a	2.73	2.63	27.63	a	29.45	27.60
	3	Active	2.56	1.83	1.48	1.18	26.92	30.58	28.25	29.58
	4	Placebo	3.01	2.96	2.55	2.05	27.14	24.80	28.31	27.92
2	1	Placebo	34.03	42.88	34.33	50.77	93.06	101.69	91.48	100.00
	2	Active	36.13	38.29	43.40	56.05	82.57	97.14	97.83	106.12
	3	Placebo	55.31	64.42	59.41	49.78	89.14	91.92	93.41	102.00
	4	Active	48.40	56.87	68.44	67.83	90.00	88.34	93.22	95.65
3	1	Active	45.03	44.88	57.54	46.14	66.06	70.59	75.52	69.47
	2	Placebo	37.71	33.73	36.07	43.16	62.86	61.18	59.46	72.13
	3	Active	48.17	36.84	58.41	53.87	78.79	65.45	80.19	75.43
	4	Placebo	47.62	41.45	44.08	54.69	71.23	65.82	67.94	75.43
4	1	Active	9.85	8.94	13.85	14.03	79.17	66.18	77.82	79.44
	2	Placebo	10.81	9.92	10.50	12.25	71.08	102.04	79.72	86.36
	3	b								
	4	b								
5	1	Placebo	14.95	20.52	21.58	29.81	71.84	67.32	63.64	65.22
	2	Active	14.42	12.78	13.10	20.15	67.23	58.67	63.73	61.46
	3	b								
	4	b								

Appendix 30 continued

Patient Number	Day	Treatment *	Speed of walking (cm/second) at time (hours)**				Cadence (number of swings/minute) at time (hours)			
			0	2	4	6	0	2	4	6
6	1	Placebo	58.87	52.08	53.97	51.51	82.70	81.48	82.50	80.49
	2	Active	54.51	74.37	68.97	65.74	84.08	87.50	87.38	85.04
	3	Placebo	54.30	61.02	58.65	50.38	83.16	91.76	92.31	84.91
	4	Active	60.23	65.61	56.46	66.73	86.19	82.71	82.98	93.41
7	1	Active	38.77	52.06	50.45	51.80	81.97	84.08	84.08	80.00
	2	Placebo	43.01	39.50	37.70	44.52	78.39	74.78	76.73	81.68
	3	Active	44.24	53.75	48.93	45.41	78.60	84.32	87.98	88.08
	4	Placebo	36.99	39.20	42.06	32.96	79.28	88.03	82.73	81.55
8	1	Placebo	16.42	13.58	3.73	3.80	92.31	76.60	61.02	65.46
	2	Active	3.39	11.60	2.71	1.63	69.23	81.08	98.36	59.02
	3	Placebo	12.83	13.46	5.31	5.97	110.00	104.85	91.53	102.86
	4	Active	7.70	35.58	8.74	4.10	90.00	114.78	105.88	120.00
9	1	Active	19.77	19.26	24.48	27.21	98.01	94.64	100.00	108.14
	2	Placebo	21.75	30.81	30.51	32.26	88.78	94.88	97.53	105.63
	3	Active	17.51	19.63	18.05	20.49	92.21	90.00	91.96	97.34
	4	Placebo	22.50	21.36	25.68	18.72	107.09	96.89	105.04	98.66
10	1	Active	34.06	37.94	44.00	28.53	94.33	94.38	96.20	90.86
	2	Placebo	37.70	43.75	39.44	40.24	98.82	103.64	97.67	102.44
	3	Active	38.44	32.86	36.64	34.67	92.31	85.25	90.84	89.05
	4	Placebo	31.98	37.35	41.63	32.89	96.90	97.32	103.45	91.39

Appendix 30 continued

Patient Number	Day	Treatment*	Speed of walking (cm/second) at time (hours)**				Cadence (number of swings/minute) at time (hours)			
			0	2	4	6	0	2	4	6
11	1	Placebo	55.12	66.92	74.85	82.41	71.90	82.71	78.26	87.10
	2	Active	76.35	73.73	70.08	70.40	80.00	77.92	77.92	80.00
	3	Placebo	62.80	77.25	78.04	78.62	80.68	83.08	86.68	88.52
	4	Active	70.21	88.65	79.35	90.33	76.60	88.82	82.44	84.85
12	1	Placebo	11.78	8.23	13.54	13.63	110.64	106.48	100.96	116.59
	2	Active	21.12	11.63	19.88	20.53	99.29	83.06	92.09	93.18
	3	Placebo	27.05	35.11	29.37	34.29	70.59	110.70	111.11	110.29
	4	Active	33.65	37.02	36.10	37.75	99.61	114.07	104.94	122.73
13	1	Active	77.00	78.30	73.05	73.70	87.10	85.04	83.40	82.13
	2	Placebo	72.51	66.51	66.17	64.92	86.40	83.08	83.08	81.82
	3	Active	49.77	43.74	44.86	45.62	75.73	73.24	71.89	74.29
	4	Placebo	48.72	47.40	46.70	47.60	76.10	72.90	72.22	76.10
14	1	Placebo	105.65	103.82	105.50	102.63	92.31	94.38	95.45	98.82
	2	Active	87.82	105.00	109.87	110.92	89.26	95.45	96.55	100.00
	3	Placebo	106.56	101.42	98.55	104.00	93.85	94.92	97.74	95.45
	4	Active	93.00	103.32	92.70	97.30	94.32	92.82	92.31	98.18

* - treatment with one active Sinemet-Plus tablet or one placebo Sinemet-Plus tablet
** - time (hours) following the tablet administration time
a - failure of monitoring equipment
b - treatment not given due to intercurrent illness

Appendix 31

Daytime Sinemet-Plus study: Values of mean (sd) double support time for the first four swings of "steady state" gait

Patient Number	Day	Treatment*	Mean (sd) double support time (seconds) at time (hours)**			
			0	2	4	6
1	1	Active	1.338(0.682)	a	a	1.075(0.665)
	2	Placebo	1.200(0.173)	a	1.363(0.229)	1.219(0.213)
	3	Active	1.113(0.085)	0.894(0.711)	1.256(0.576)	1.213(0.525)
	4	Placebo	1.006(0.171)	1.375(0.143)	1.156(0.043)	1.356(0.831)
2	1	Placebo	0.119(0.024)	0.056(0.031)	0.094(0.013)	0.088(0.032)
	2	Active	0.106(0.038)	0.106(0.024)	0.069(0.024)	0.038(0.014)
	3	Placebo	0.075(0.020)	0.056(0.013)	0.063(0.014)	0.056(0.013)
	4	Active	0.069(0.031)	0.069(0.024)	0.050(0.000)	0.050(0.000)
3	1	Active	0.125(0.029)	0.119(0.013)	0.075(0.029)	0.113(0.025)
	2	Placebo	0.138(0.025)	0.238(0.025)	0.194(0.043)	0.150(0.000)
	3	Active	0.150(0.020)	0.125(0.020)	0.094(0.013)	0.119(0.013)
	4	Placebo	0.131(0.043)	0.138(0.032)	0.119(0.024)	0.106(0.024)
4	1	Active	0.513(0.477)	0.550(0.385)	0.413(0.333)	0.438(0.364)
	2	Placebo	0.506(0.426)	0.500(0.420)	0.450(0.376)	0.425(0.391)
	3	b				
	4	b				
5	1	Placebo	0.425(0.104)	0.275(0.035)	0.256(0.038)	0.219(0.024)
	2	Active	0.325(0.087)	0.400(0.071)	0.475(0.119)	0.275(0.087)
	3	b				
	4	b				

Appendix 31 continued

Mean (sd) double support time (seconds) at time (hours)**

Patient Number	Day	Treatment*	0	2	4	6
6	1	Placebo	0.094(0.013)	0.100(0.035)	0.106(0.013)	0.119(0.024)
	2	Active	0.075(0.000)	0.063(0.025)	0.069(0.024)	0.081(0.031)
	3	Placebo	0.088(0.014)	0.069(0.024)	0.094(0.024)	0.100(0.020)
	4	Active	0.094(0.013)	0.050(0.020)	0.050(0.000)	0.050(0.000)
7	1	Active	0.113(0.025)	0.081(0.024)	0.063(0.014)	0.088(0.025)
	2	Placebo	0.113(0.025)	0.100(0.020)	0.144(0.013)	0.119(0.031)
	3	Active	0.131(0.031)	0.056(0.013)	0.081(0.013)	0.088(0.014)
	4	Placebo	0.113(0.025)	0.100(0.000)	0.144(0.013)	0.156(0.052)
8	1	Placebo	0.325(0.126)	0.438(0.095)	0.163(0.032)	0.200(0.074)
	2	Active	0.519(0.116)	0.219(0.085)	0.188(0.060)	0.388(0.060)
	3	Placebo	0.225(0.035)	0.169(0.055)	0.425(0.090)	0.613(0.293)
	4	Active	0.408(0.080)	0.081(0.031)	0.300(0.061)	0.181(0.055)
9	1	Active	0.181(0.013)	0.138(0.025)	0.113(0.048)	0.106(0.038)
	2	Placebo	0.150(0.020)	0.106(0.024)	0.150(0.035)	0.106(0.024)
	3	Active	0.231(0.063)	0.175(0.041)	0.188(0.043)	0.156(0.024)
	4	Placebo	0.200(0.058)	0.188(0.032)	0.163(0.032)	0.206(0.031)
10	1	Active	0.113(0.032)	0.094(0.013)	0.063(0.025)	0.275(0.117)
	2	Placebo	0.150(0.046)	0.081(0.031)	0.106(0.013)	0.119(0.031)
	3	Active	0.144(0.024)	0.188(0.043)	0.131(0.024)	0.125(0.035)
	4	Placebo	0.106(0.013)	0.144(0.024)	0.106(0.013)	0.119(0.055)

Appendix 31 continued

Patient Number	Day	Treatment*	Mean (sd) double support time (seconds) at time (hours)**			
			0	2	4	6
11	1	Placebo	0.100(0.020)	0.063(0.014)	0.069(0.013)	0.063(0.014)
	2	Active	0.069(0.024)	0.069(0.031)	0.075(0.035)	0.056(0.013)
	3	Placebo	0.075(0.020)	0.088(0.014)	0.063(0.014)	0.056(0.013)
	4	Active	0.100(0.020)	0.044(0.013)	0.038(0.014)	0.044(0.013)
12	1	Placebo	0.225(0.054)	0.306(0.181)	0.263(0.025)	0.206(0.126)
	2	Active	0.175(0.029)	0.388(0.189)	0.194(0.055)	0.231(0.107)
	3	Placebo	0.281(0.080)	0.063(0.025)	0.119(0.013)	0.088(0.032)
	4	Active	0.125(0.035)	0.075(0.000)	0.100(0.020)	0.075(0.020)
13	1	Active	0.063(0.014)	0.075(0.020)	0.081(0.024)	0.069(0.013)
	2	Placebo	0.075(0.020)	0.088(0.032)	0.100(0.020)	0.088(0.014)
	3	Active	0.081(0.013)	0.138(0.014)	0.125(0.020)	0.113(0.014)
	4	Placebo	0.131(0.038)	0.125(0.020)	0.125(0.020)	0.113(0.014)
14	1	Placebo	0.050(0.020)	0.044(0.013)	0.050(0.000)	0.031(0.013)
	2	Active	0.044(0.013)	0.038(0.014)	0.031(0.013)	0.038(0.014)
	3	Placebo	0.038(0.014)	0.038(0.014)	0.044(0.013)	0.050(0.000)
	4	Active	0.044(0.013)	0.050(0.020)	0.038(0.014)	0.038(0.014)

* – treatment with one active Sinemet-Plus tablet or one placebo Sinemet-Plus tablet

** – time (hours) following the tablet administration time

a – failure of monitoring equipment

b – treatment not given due to intercurrent illness

Appendix 32

Daytime Sinemet-Plus study: Values of mean (sd) swing length for the first four swings of "steady state" gait

Patient Number	Day	Treatment *	Mean (sd) swing length (cm) at time (hours)**			
			0	2	4	6
1	1	Active	13.0(0.5)	a	a	16.8(0.0)
	2	Placebo	21.0(1.9)	a	16.5(2.5)	17.2(4.1)
	3	Active	17.1(2.4)	15.3(1.5)	8.0(3.1)	8.8(1.0)
	4	Placebo	26.0(1.9)	21.3(1.6)	20.3(1.7)	10.8(1.7)
2	1	Placebo	57.4(3.9)	63.1(2.3)	54.0(2.7)	68.9(3.1)
	2	Active	58.8(7.2)	50.3(2.2)	58.7(1.6)	70.7(4.7)
	3	Placebo	84.6(1.4)	87.9(0.8)	84.8(2.1)	64.4(4.6)
	4	Active	71.4(2.1)	86.1(1.2)	93.9(3.6)	93.8(1.2)
3	1	Active	79.5(2.0)	75.3(1.9)	89.0(1.9)	80.1(3.2)
	2	Placebo	75.2(1.5)	66.5(4.0)	70.1(2.1)	72.5(0.6)
	3	Active	72.0(4.9)	65.5(1.6)	86.5(4.2)	86.7(0.8)
	4	Placebo	82.5(1.9)	78.8(1.9)	78.1(2.0)	85.8(0.5)
4	1	Active	19.0(1.8)	17.8(0.5)	22.3(2.7)	22.7(1.7)
	2	Placebo	18.8(1.7)	20.2(2.7)	19.3(1.3)	18.9(1.3)
	3	b				
	4	b				
5	1	Placebo	25.5(3.1)	37.9(1.6)	42.4(2.4)	48.0(1.5)
	2	Active	29.4(2.3)	24.8(1.9)	25.8(1.6)	40.5(4.8)
	3	b				
	4	b				

Appendix 32 continued

Patient Number	Day	Treatment*	Mean (sd) swing length (cm) at time (hours)**			
			0	2	4	6
6	1	Placebo	82.9(5.2)	77.0(3.2)	78.7(2.3)	74.3(1.9)
	2	Active	80.2(2.4)	93.9(4.0)	92.7(3.0)	92.0(2.7)
	3	Placebo	83.2(0.3)	84.1(4.2)	77.1(3.7)	74.1(3.8)
	4	Active	89.9(0.7)	100.2(3.5)	89.9(2.5)	89.3(2.1)
7	1	Active	62.9(1.6)	80.6(2.5)	80.4(3.2)	78.5(3.1)
	2	Placebo	66.4(2.3)	68.7(2.2)	61.2(0.8)	67.3(4.6)
	3	Active	69.0(7.0)	82.7(1.9)	69.7(1.3)	73.9(1.2)
	4	Placebo	58.0(5.3)	60.2(4.6)	60.5(2.3)	52.5(4.7)
8	1	Placebo	18.2(1.3)	15.0(1.5)	15.0(2.0)	10.4(5.4)
	2	Active	3.9(0.8)	11.1(1.2)	13.7(1.2)	5.9(1.0)
	3	Placebo	15.3(1.0)	15.7(1.8)	5.6(0.6)	6.4(1.9)
	4	Active	10.5(0.3)	57.4(2.4)	9.4(1.0)	13.3(7.1)
9	1	Active	26.6(1.9)	28.7(1.5)	36.4(2.9)	36.0(3.8)
	2	Placebo	36.4(1.2)	43.5(4.5)	42.1(2.8)	39.2(2.6)
	3	Active	28.4(2.4)	31.4(4.7)	27.9(1.5)	31.1(1.2)
	4	Placebo	28.4(1.4)	34.7(0.9)	36.3(0.5)	29.7(4.3)
10	1	Active	46.8(3.4)	53.1(3.0)	62.2(4.0)	30.1(3.2)
	2	Placebo	55.0(2.6)	62.0(3.6)	51.7(6.9)	47.6(7.3)
	3	Active	52.4(2.4)	45.9(3.1)	51.5(4.8)	51.2(2.8)
	4	Placebo	51.2(7.1)	43.0(7.0)	54.6(7.5)	47.0(2.7)

Appendix 32 continued

Patient Number	Day	Treatment*	Mean (sd) swing length (cm) at time (hours)**			
			0	2	4	6
11	1	Placebo	91.3(1.0)	101.4(3.0)	109.5(3.6)	109.8(4.0)
	2	Active	112.0(3.9)	107.9(1.9)	100.7(6.0)	101.2(2.1)
	3	Placebo	93.7(2.2)	104.6(1.8)	97.4(4.7)	98.8(7.8)
	4	Active	101.2(4.5)	117.9(3.2)	111.7(3.1)	117.5(4.0)
12	1	Placebo	14.8(1.1)	9.9(3.5)	22.4(5.0)	12.3(1.5)
	2	Active	38.4(1.3)	15.1(0.8)	31.8(3.2)	22.8(9.1)
	3	Placebo	48.2(1.6)	44.2(2.2)	35.4(1.4)	38.6(3.1)
	4	Active	38.9(0.6)	45.4(0.6)	47.0(0.5)	43.0(1.7)
13	1	Active	106.5(2.2)	110.5(2.8)	104.0(2.6)	107.2(1.6)
	2	Placebo	99.7(5.5)	93.5(3.7)	94.2(2.2)	91.0(1.0)
	3	Active	86.0(0.6)	80.5(2.2)	79.2(3.1)	78.7(1.9)
	4	Placebo	81.2(1.5)	84.1(2.5)	83.9(2.1)	76.2(1.6)
14	1	Placebo	129.1(1.9)	122.2(0.7)	124.3(2.4)	122.9(4.0)
	2	Active	120.4(1.9)	132.2(6.0)	127.7(3.3)	126.0(2.9)
	3	Placebo	128.1(2.9)	128.2(2.8)	122.4(1.1)	121.7(3.0)
	4	Active	115.2(1.5)	123.8(2.6)	123.6(1.1)	124.5(3.0)

* – treatment with one active Sinemet-Plus tablet or one placebo Sinemet-Plus tablet

** – time (hours) following the tablet administration time

a – failure of monitoring equipment

b – treatment not given due to intercurrent illness

Appendix 33

Daytime Sinemet-Plus study: Values of mean (sd) swing time for the first four swings of "steady state" gait

Patient Number	Day	Treatment *	Mean (sd) swing time (seconds)** at time (hours)**			
			0	2	4	6
1	1	Active	0.475(0.087)	a	a	0.600(0.129)
	2	Placebo	1.063(0.317)	a	0.700(0.071)	0.838(0.155)
	3	Active	0.838(0.214)	0.731(0.191)	0.563(0.050)	0.469(0.125)
	4	Placebo	1.000(0.079)	0.963(0.085)	0.913(0.118)	0.619(0.189)
2	1	Placebo	0.588(0.025)	0.569(0.038)	0.513(0.025)	0.569(0.047)
	2	Active	0.650(0.074)	0.519(0.031)	0.550(0.046)	0.531(0.047)
	3	Placebo	0.581(0.013)	0.594(0.013)	0.613(0.025)	0.538(0.032)
	4	Active	0.606(0.024)	0.606(0.024)	0.581(0.013)	0.556(0.013)
3	1	Active	0.763(0.025)	0.713(0.025)	0.658(0.014)	0.713(0.048)
	2	Placebo	0.817(0.029)	0.775(0.104)	0.800(0.100)	0.633(0.029)
	3	Active	0.631(0.024)	0.800(0.087)	0.644(0.024)	0.656(0.013)
	4	Placebo	0.669(0.024)	0.769(0.024)	0.763(0.032)	0.688(0.014)
4	1	Active	0.344(0.013)	0.375(0.020)	0.381(0.043)	0.356(0.055)
	2	Placebo	0.363(0.043)	0.363(0.035)	0.331(0.024)	0.344(0.031)
	3	b				
	4	b				
5	1	Placebo	0.513(0.085)	0.675(0.194)	0.756(0.209)	0.788(0.085)
	2	Active	0.656(0.153)	0.613(0.075)	0.663(0.083)	0.713(0.095)
	3	b				
	4	b				

Mean (sd) swing time (seconds) at time (hours)**

Patient Number	Day	Treatment *	0	2	4	6
6	1	Placebo	0.619(0.024)	0.633(0.038)	0.631(0.031)	0.650(0.035)
	2	Active	0.644(0.038)	0.619(0.024)	0.613(0.014)	0.606(0.055)
	3	Placebo	0.606(0.013)	0.600(0.000)	0.594(0.038)	0.613(0.043)
	4	Active	0.581(0.013)	0.625(0.020)	0.631(0.013)	0.581(0.024)
7	1	Active	0.575(0.065)	0.619(0.090)	0.631(0.052)	0.638(0.111)
	2	Placebo	0.650(0.108)	0.681(0.069)	0.606(0.077)	0.563(0.075)
	3	Active	0.650(0.020)	0.575(0.046)	0.569(0.043)	0.581(0.052)
	4	Placebo	0.594(0.038)	0.556(0.072)	0.638(0.043)	0.613(0.066)
8	1	Placebo	0.431(0.055)	0.519(0.055)	0.419(0.066)	0.469(0.052)
	2	Active	0.163(0.014)	0.388(0.060)	0.400(0.035)	0.256(0.066)
	3	Placebo	0.363(0.032)	0.388(0.043)	0.250(0.020)	0.250(0.071)
	4	Active	0.294(0.031)	0.525(0.029)	0.319(0.038)	0.213(0.025)
9	1	Active	0.463(0.052)	0.513(0.060)	0.538(0.025)	0.488(0.066)
	2	Placebo	0.500(0.054)	0.494(0.052)	0.525(0.029)	0.506(0.031)
	3	Active	0.506(0.083)	0.488(0.043)	0.481(0.024)	0.500(0.079)
	4	Placebo	0.369(0.024)	0.481(0.031)	0.431(0.024)	0.375(0.054)
10	1	Active	0.506(0.055)	0.538(0.032)	0.506(0.013)	0.481(0.066)
	2	Placebo	0.550(0.041)	0.569(0.063)	0.525(0.029)	0.463(0.032)
	3	Active	0.519(0.024)	0.531(0.024)	0.494(0.055)	0.569(0.055)
	4	Placebo	0.494(0.105)	0.488(0.066)	0.481(0.024)	0.481(0.055)

Appendix 33 continued

Patient Number	Day	Treatment *	Mean (sd) swing time (seconds) at time (hours)**			
			0	2	4	6
11	1	Placebo	0.725(0.035)	0.650(0.025)	0.694(0.031)	0.650(0.020)
	2	Active	0.688(0.048)	0.700(0.043)	0.688(0.060)	0.681(0.038)
	3	Placebo	0.688(0.025)	0.663(0.048)	0.644(0.031)	0.613(0.032)
	4	Active	0.713(0.014)	0.638(0.032)	0.688(0.025)	0.663(0.025)
12	1	Placebo	0.313(0.043)	0.275(0.114)	0.481(0.197)	0.331(0.063)
	2	Active	0.463(0.085)	0.413(0.144)	0.469(0.103)	0.381(0.146)
	3	Placebo	0.669(0.038)	0.469(0.043)	0.413(0.025)	0.431(0.059)
	4	Active	0.506(0.069)	0.469(0.052)	0.481(0.024)	0.444(0.043)
13	1	Active	0.600(0.089)	0.619(0.094)	0.619(0.085)	0.631(0.097)
	2	Placebo	0.600(0.074)	0.638(0.088)	0.625(0.074)	0.625(0.058)
	3	Active	0.681(0.080)	0.675(0.087)	0.688(0.092)	0.675(0.074)
	4	Placebo	0.669(0.013)	0.681(0.043)	0.681(0.047)	0.694(0.031)
14	1	Placebo	0.594(0.013)	0.588(0.025)	0.588(0.088)	0.569(0.024)
	2	Active	0.625(0.020)	0.594(0.043)	0.600(0.020)	0.563(0.032)
	3	Placebo	0.588(0.088)	0.569(0.109)	0.563(0.103)	0.575(0.087)
	4	Active	0.581(0.097)	0.569(0.080)	0.581(0.097)	0.563(0.088)

* - treatment with one active Sinemet-Plus tablet or one placebo Sinemet-Plus tablet
** - time (hours) following the tablet administration time
a - failure of monitoring equipment
b - treatment not given due to intercurrent illness

Appendix 34

Daytime Sinemet-Plus study: Time taken to walk an
individually set distance ("timed walking" test)

Patient Number	Day	Treatment *	Distance walked (metres) +	Time (seconds) to walk set distance at time (hours)**			
				0	2	4	6
1	1	Active	6	413	285	130	335
	2	Placebo		225	182	195	165
	3	Active		343	332	691	512
	4	Placebo		244	266	299	310
2	1	Placebo	10	28	30	28	25
	2	Active		23	30	28	31
	3	Placebo		35	37	33	27
	4	Active		30	26	30	30
3	1	Active	10	26	25	29	29
	2	Placebo		26	32	30	30
	3	Active		30	30	30	27
	4	Placebo		29	27	30	25
4	1	Active	6	107	80	79	68
	2	Placebo		98	80	83	70
	3	b			.		
	4	b					
5	1	Placebo	10	83	60	70	44
	2	Active		65	67	64	65
	3	b					
	4	b					
6	1	Placebo	10	15	15	15	13
	2	Active		14	13	13	14
	3	Placebo		17	16	17	17
	4	Active		17	18	18	20
7	1	Active	8	29	29	48	32
	2	Placebo		40	45	43	43
	3	Active		51	38	46	40
	4	Placebo		45	37	51	40
8	1	Placebo	6	445	427	320	400
	2	Active		530	166	67	253
	3	Placebo		a			
	4	Active		a			
9	1	Active	10	74	64	52	41
	2	Placebo		51	40	41	37
	3	Active		80	75	63	66
	4	Placebo		50	60	54	50

Appendix 34 continued

Patient Number	Day	Treatment *	Distance walked (metres) +	Time (seconds) to walk set distance (hours)**			
				0	2	4	6
10	1	Active	10	50	43	43	42
	2	Placebo		36	31	33	39
	3	Active		46	36	36	43
	4	Placebo		42	35	30	36
11	1	Placebo	12	20	21	23	21
	2	Active		19	19	20	22
	3	Placebo		24	22	22	21
	4	Active		22	20	19	20
12	1	Placebo	a				
	2	Active					
	3	Placebo					
	4	Active					
13	1	Active	12	16	16	17	19
	2	Placebo		18	20	19	21
	3	Active		22	23	24	21
	4	Placebo		22	21	21	22
14	1	Placebo	12	11	11	11	11
	2	Active		11	12	12	12
	3	Placebo		11	12	11	12
	4	Active		11	11	12	12

* - treatment with one active Sinemet-Plus tablet or one placebo Sinemet-Plus tablet
** - time (hours) following the tablet administration time
+ - distance walked by patient measured from chair to turning point and back
a - complete battery of tests considered to be impractical
b - treatment not given due to intercurrent illness

Appendix 35

Daytime Sinemet-Plus study: Time taken to do up a given number of buttons

Patient Number	Day	Treatment *	Number of buttons consistently done up	Time (seconds) to do up given number of buttons at time (hours)**			
				0	2	4	6
1	1	Active	1+	84	60	a	75
	2	Placebo		30	54	41	30
	3	Active		85	a	a	a
	4	Placebo		120	a	55	a
2	1	Placebo	7	120	62	88	63
	2	Active		55	75	62	84
	3	Placebo		66	99	104	75
	4	Active		51	75	86	55
3	1	Active	7	64	85	90	49
	2	Placebo		40	54	34	35
	3	Active		67	74	70	72
	4	Placebo		114	90	69	62
4	1	Active	7	115	88	70	62
	2	Placebo		64	80	100	72
	3	b					
	4	b					
5	1	Placebo	4	68	54	113	79
	2	Active		49	115	95	118
	3	b					
	4	b					
6	1	Placebo	9	72	72	84	80
	2	Active		96	50	54	103
	3	Placebo		63	63	67	70
	4	Active		65	41	63	57
7	1	Active	1	73	40	19	24
	2	Placebo		14	29	15	20
	3	Active		31	13	10	21
	4	Placebo		42	45	10	23
8	1	Placebo	1+	29	a	a	a
	2	Active		14	32	40	105
	3	Placebo		64	78	80	10
	4	Active		70	10	35	20
9	1	Active	7	89	77	107	79
	2	Placebo		64	59	54	70
	3	Active		79	79	90	98
	4	Placebo		55	50	68	68

Appendix 35 continued

Patient Number	Day	Treatment *	Number of buttons consistently done up	Time (seconds) to do up given number of buttons at time (hours)**			
				0	2	4	6
10	1	Active	5	76	77	59	45
	2	Placebo		70	46	98	52
	3	Active		62	50	42	35
	4	Placebo		34	33	33	76
11	1	Placebo	8	97	85	103	62
	2	Active		71	72	102	73
	3	Placebo		107	75	105	58
	4	Active		73	65	63	90
12	1	Placebo	1	8	15	10	10
	2	Active		5	49	44	20
	3	Placebo		6	7	6	8
	4	Active		5	23	15	7
13	1	Active	8	115	109	54	110
	2	Placebo		77	78	110	65
	3	Active		77	113	108	90
	4	Placebo		78	80	87	57
14	1	Placebo	9	59	46	58	50
	2	Active		67	52	49	53
	3	Placebo		56	41	70	57
	4	Active		41	35	59	40

 * - treatment with one active Sinemet-Plus tablet or
     one placebo Sinemet-Plus tablet
** - time (hours) following the tablet administration
     time
 + - patient unable to do up even only one button
     consistently
 a - maximum time of 2 minutes exceeded
 b - treatment not given due to intercurrent illness

Appendix 36

Daytime Sinemet-Plus study: Cumulative time to do up each button

Patient Number	Treatment	Day	Time post-dose (hours)	Cumulative time to do up buttons (seconds) Button Number								
				1	2	3	4	5	6	7	8	9
1	Active	1	0	84	a							
			2	60	a							
			4	a								
			6	75	a							
	Placebo	2	0	30	84	a						
			2	54	a							
			4	41	112	a						
			6	30	a							
	Active	3	0	85	a							
			2	a								
			4	a								
			6	a								
	Placebo	4	0	120	a							
			2	a								
			4	55	a							
			6	a								
2	Placebo	1	0	5	13	30	40	55	75	120	a	
			2	8	14	22	28	42	50	62	70	85
			4	10	23	30	35	52	65	88	93	112
			6	5	15	20	30	40	50	63	80	100
	Active	2	0	8	13	19	26	36	47	55	95	a
			2	8	17	30	38	50	60	75	85	92
			4	6	15	30	40	46	55	62	72	104
			6	6	10	15	38	51	63	84	92	108
	Placebo	3	0	10	18	26	38	54	60	66	78	116
			2	8	19	25	44	60	70	99	107	a
			4	10	18	46	52	63	75	104	118	a
			6	9	22	33	38	48	54	75	97	110
	Active	4	0	7	13	24	28	34	40	51	64	74
			2	6	14	21	30	46	56	75	107	116
			4	6	28	44	48	57	70	86	103	109
			6	5	10	24	29	40	46	55	88	114

Appendix 36 continued

Patient Number	Treatment	Day	Time post-dose (hours)	Cumulative time to do up buttons (seconds) Button Number								
				1	2	3	4	5	6	7	8	9
3	Active	1	0	5	15	30	38	47	56	64	85	105
			2	5	25	40	50	65	70	85	94	118
			4	3	20	28	45	62	72	90	104	a
			6	4	8	14	25	34	42	49	58	67
	Placebo	2	0	3	7	12	17	26	32	40	45	55
			2	5	12	29	37	44	49	54	65	75
			4	5	10	15	19	22	28	34	40	55
			6	4	11	17	20	25	30	35	40	48
	Active	3	0	8	14	20	24	37	48	67	83	a
			2	4	11	17	22	48	53	74	85	a
			4	5	14	23	36	42	52	70	117	a
			6	8	16	23	33	50	57	72	85	95
	Placebo	4	0	10	21	38	52	87	98	114	a	
			2	5	11	22	54	66	80	90	a	
			4	5	12	16	27	34-	60	69	90	108
			6	6	16	23	36	45	53	62	75	90
4	Active	1	0	6	23	37	44	57	102	115	a	
			2	7	16	33	40	60	73	88	a	
			4	4	10	17	27	41	62	70	a	
			6	4	9	14	23	34	49	62	74	86
	Placebo	2	0	4	9	20	27	40	54	64	74	88
			2	5	12	22	32	40	60	80	90	97
			4	7	12	20	30	44	56	100	a	
			6	5	11	19	27	53	60	72	94	100
	b	3	0									
			2									
			4									
			6									
	b	4	0									
			2									
			4									
			6									

Appendix 36 continued

Patient Number	Treatment	Day	Time post-dose (hours)	Cumulative time to do up buttons (seconds) Button Number								
				1	2	3	4	5	6	7	8	9
5	Placebo	1	0	9	20	44	68	82	95	a		
			2	6	19	32	54	85	95	a		
			4	4	14	27	113	a				
			6	7	41	53	79	107	a			
	Active	2	0	7	22	31	49	60	82	120	a	
			2	8	53	88	115	a				
			4	7	30	80	95	105	a			
			6	12	32	80	118	a				
	b	3	0									
			2									
			4									
			6									
	b	4	0									
			2									
			4									
			6									
6	Placebo	1	0	3	8	15	27	34	45	52	65	72
			2	4	12	19	27	42	50	56	67	72
			4	3	7	14	19	27	32	56	64	84
			6	3	10	16	22	34	51	62	72	80
	Active	2	0	2	5	35	50	56	62	70	90	96
			2	2	5	8	14	18	26	34	40	50
			4	3	11	16	23	29	36	41	44	54
			6	4	14	33	40	48	54	85	93	103
	Placebo	3	0	4	7	14	20	25	37	46	56	63
			2	4	10	21	27	33	38	45	57	63
			4	4	9	14	20	25	44	55	62	67
			6	4	9	15	21	27	35	51	59	70
	Active	4	0	3	9	15	23	31	37	49	56	65
			2	4	7	11	14	18	24	29	33	41
			4	5	9	14	19	24	30	36	51	63
			6	4	8	13	19	24	33	43	52	57

Appendix 36 continued

Patient Number	Treatment	Day	Time post-dose (hours)	Cumulative time to do up buttons (seconds) Button Number								
				1	2	3	4	5	6	7	8	9
7	Active	1	0	73	95	a						
			2	40	a							
			4	19	31	a						
			6	24	80	a						
	Placebo	2	0	14	65	110	a					
			2	29	47	57	70	83	105	a		
			4	15	52	70	84	a				
			6	20	95	a						
	Active	3	0	31	70	120	a					
			2	13	47	69	89	119	a			
			4	10	31	a						
			6	21	43	72	a					
	Placebo	4	0	42	120	a						
			2	45	110	a						
			4	10	a							
			6	23	75	a						
8	Placebo	1	0	29	55	a						
			2	a								
			4	a								
			6	a								
	Active	2	0	14	26	a						
			2	32	a							
			4	40	80	85	91	a				
			6	105	a							
	Placebo	3	0	64	104	a						
			2	78	a							
			4	80	a							
			6	10	78	a						
	Active	4	0	70	95	120	a					
			2	10	25	35	53	65	a			
			4	35	85	117	a					
			6	20	45	120	a					

Patient Number	Treatment	Day	Time post-dose (hours)	Cumulative time to do up buttons (seconds) Button Number								
				1	2	3	4	5	6	7	8	9
9	Active	1	0	4	12	24	35	49	63	89	a	
			2	8	15	22	28	41	66	77	102	115
			4	10	20	37	47	58	79	107	110	a
			6	4	12	21	35	43	55	79	100	109
	Placebo	2	0	7	14	19	29	44	53	64	74	83
			2	7	12	18	27	35	45	59	68	101
			4	10	13	18	27	33	45	54	64	79
			6	6	10	23	37	51	58	70	81	104
	Active	3	0	4	10	21	40	49	59	79	90	103
			2	14	25	34	50	59	69	79	94	118
			4	6	14	23	31	44	57	90	a	
			6	5	15	21	34	48	58	98	109	a
	Placebo	4	0	4	18	24	31	39	45	55	68	81
			2	3	15	24	29	34	40	50	58	62
			4	4	14	20	35	49 .	60	68	74	81
			6	10	20	28	36	46	54	68	82	87
10	Active	1	0	4	21	45	57	76	104	a		
			2	8	17	37	60	77	101	115	a	
			4	5	11	22	37	59	90	100	106	115
			6	8	15	25	33	45	54	63	71	95
	Placebo	2	0	4	16	39	51	70	95	118	a	
			2	8	15	27	37	46	82	94	107	114
			4	5	19	38	80	98	106	a		
			6	8	15	24	37	52	71	85	97	107
	Active	3	0	5	11	25	44	62	80	92	115	a
			2	4	7	19	28	50	58	68	84	92
			4	5	16	23	34	42	53	120	a	
			6	3	9	16	25	35	51	a		
	Placebo	4	0	3	6	18	25	34	45	76	113	a
			2	3	10	18	24	33	53	76	101	120
			4	5	13	19	27	33	42	88	a	
			6	4	18	28	36	76	a			

Appendix 36 continued

Patient Number	Treatment	Day	Time post-dose (hours)	Button Number								
				1	2	3	4	5	6	7	8	9
11	Placebo	1	0	4	10	20	30	36	51	70	97	107
			2	3	10	18	37	52	60	70	85	95
			4	4	12	18	25	30	51	75	103	114
			6	4	9	15	25	35	44	54	62	80
	Active	2	0	4	8	15	26	34	47	61	71	81
			2	4	9	20	31	39	49	59	72	86
			4	5	11	24	31	42	49	88	102	114
			6	4	8	17	24	30	36	53	73	84
	Placebo	3	0	5	15	25	41	52	62	75	107	113
			2	6	10	17	24	36	45	61	75	85
			4	5	11	23	29	46	59	85	105	a
			6	4	9	14	22	30	38	44	58	65
	Active	4	0	6	8	18	25	35	42	65	73	77
			2	4	8	15	25	33	37	58	65	69
			4	4	8	16	23	32.	43	50	63	73
			6	3	7	16	24	37	49	78	90	100
12	Placebo	1	0	8	26	36	80	93	107	a		
			2	15	79	a						
			4	10	80	115	a					
			6	10	25	120	a					
	Active	2	0	5	19	28	90	a				
			2	49	a							
			4	44	a							
			6	20	35	49	63	100	a			
	Placebo	3	0	6	35	42	49	67	72	119	a	
			2	7	24	41	70	107	118	a		
			4	6	18	28	43	63	104	120	a	
			6	8	21	40	77	108	a			
	Active	4	0	5	10	17	71	83	105	120	a	
			2	23	60	76	100	a				
			4	15	112	a						
			6	7	17	27	41	58	a			

Appendix 36 continued

Patient Number	Treatment	Day	Time post-dose (hours)	Cumulative time to do up buttons (seconds) Button Number								
				1	2	3	4	5	6	7	8	9
13	Active	1	0	5	13	22	38	58	76	95	115	a
			2	3	12	24	35	41	74	100	109	a
			4	3	10	13	23	31	38	44	54	83
			6	3	17	26	45	60	74	85	110	a
	Placebo	2	0	3	11	25	32	40	51	70	77	87
			2	3	16	32	42	54	60	70	78	96
			4	2	8	16	22	60	78	100	110	120
			6	5	10	14	17	28	36	57	65	71
	Active	3	0	5	12	17	24	40	51	65	77	88
			2	4	15	23	33	44	64	92	113	a
			4	4	23	30	55	63	81	93	108	a
			6	8	15	22	31	40	67	80	90	99
	Placebo	4	0	3	12	17	27	37	44	55	78	85
			2	3	16	20	31	40	47	67	80	a
			4	5	17	25	31	42.	55	77	87	95
			6	5	14	19	25	30	40	49	57	63
14	Placebo	1	0	5	9	13	17	24	43	47	52	59
			2	2	10	14	18	23	29	35	40	46
			4	2	7	10	15	22	26	36	44	58
			6	4	7	11	16	20	30	40	43	50
	Active	2	0	2	6	15	24	30	40	50	60	67
			2	3	7	14	19	24	29	34	43	52
			4	2	7	12	16	20	25	30	44	49
			6	3	9	15	20	29	33	40	45	53
	Placebo	3	0	2	8	11	19	24	29	36	44	56
			2	2	5	8	12	19	23	30	36	41
			4	2	6	11	19	27	33	41	55	70
			6	3	9	14	17	23	32	39	45	57
	Active	4	0	3	7	12	16	20	25	31	34	41
			2	2	5	9	13	16	20	24	29	35
			4	3	5	15	19	29	36	43	53	59
			6	2	6	10	14	18	23	30	34	40

a - maximum time of 2 minutes exceeded
b - treatment not given due to intercurrent illness

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