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The effects of clonidine, cyproheptadine and baclofen on locomotor pattern in subjects with incomplete spinal cord injury

submitted by

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December 1996

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements of the degree of doctorate in Rehabilitation Science.

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Structure of the dissertation

According to the Guidelines for Thesis Preparation from McGill University's Faculty of Graduate Studies and Research, a dissertation may include the text of one or more papers that have already been published or that are intended for publication. Specifically, the guidelines state that

> Candidates have the option of including, as part of the thesis, the text of one or more paper submitted or to be submitted for publication, or the clearly-duplicated text of one or more published papers. These texts must be bound as an integral part of the thesis.
>
> If this option is chosen, CONNECTING TEXTS THAT PROVIDE LOGICAL BRIDGES BETWEEN THE DIFFERENT PAPERS ARE MANDATORY. The thesis must be written in such a way that is more than a mere collection of manuscripts; in other words, results of a series of papers must be integrated.
>
> The thesis must still conform to all other requirements of the "Guidelines for Thesis Preparation". THE THESIS MUST INCLUDE: A Table of Contents, an abstract in English and French, an Introduction which clearly states the rationale and objectives of the study, a comprehensive review of the literature, a final conclusion and summary, and a thorough bibliography or reference list.
>
> Additional material must be provided where appropriate (e.g. in appendices) and in sufficient detail to allow a clear and precise judgement to be made of the importance and originality of the research reported in the thesis.
>
> In the case of manuscripts co-authored by the candidate and others, THE CANDIDATE IS REQUIRED TO MAKE AN EXPLICIT STATEMENT IN THE THESIS AS TO WHO CONTRIBUTED TO SUCH WORK AND TO WHAT EXTENT. Supervisors must attest to the accuracy of such statements at the oral doctoral defense. Since the task of the examiners is made more difficult in these cases, it is in the candidate's interest to make perfectly clear the responsibilities of all the authors of the co-authored papers.

In keeping with these guidelines, I have chosen to include the text of a paper that has already been published (Manuscript #1) and the text of a paper that is intended for publication (Manuscript #2), among the sections of the dissertation. Although there is no thesis section between the Manuscript #1 and Manuscript #2 to provide "a connecting text that provides a logical bridge", I believe I have still fulfilled the intent of those requirements. Manuscript #1 is essentially a methods paper which logically precedes the experimental study reported in Manuscript #2. Furthermore, the thesis sections that precede and succeed it ensure that the thesis is "more than a mere collection of manuscripts".

Manuscript #1 was published in the Archives of Physical Medicine and Rehabilitation (August 1995; vol 76, pages 772-778) within their publication category of Prosthetics, Orthotics and Devices. As such, it is principally a description of the harness support and treadmill devices. Although it was not the objective of the thesis project to develop this apparatus, it is essential to understand the features of the harness support and treadmill in order to understand how the results were obtained in Manuscript #2, and the implications regarding the abilities of the participating subjects. In accordance with the instructions for authors in the Archives of Physical Medicine and Rehabilitation regarding the publication category of Prosthetics, Orthotics and Devices, the "Results" section of the paper is composed of case reports that illustrate the use of the device. Thus, it was appropriate for this manuscript to describe only harness-using subjects rather than all of the subjects who participated in this doctoral project. Furthermore, only two case reports were required to achieve the objective of demonstrating the utility of the device. The subjects of the case reports are also included in the results within Manuscript #2: the subjects of Case Reports 1 and 2 are subjects H4 and H1, respectively, in Manuscript #2. In keeping with copyright regulations, the content of this manuscript is not different from the published version (see below: "The text and authorship of Manuscript #1").

Manuscript #2 is a detailed report of the rationale, methods, results and discussion regarding the thesis project and it will be submitted for publication in a shortened form. The other sections of the dissertation have been included to support this paper and to

follow the Guidelines for Thesis Preparation. Manuscript #1 provides a detailed description of the apparatus used for the thesis project and thus may be considered as part of a description of methods for the dissertation. The Introduction and Review of Literature sections of the dissertation provide the rationale, objectives and background for the development and design of the project. Thus, there is some overlap between these sections of the dissertation and the Introduction and Discussion sections of Manuscript #2, although the information is less detailed in Manuscript #2. Similarly, there is some overlap between the Discussion section of Manuscript #2 and the Summary and Conclusions section of the dissertation.

The reference lists for Manuscripts #1 and #2 have been removed from those sections and the lists of references merged, along with the references from other sections of the dissertation. There is thus a common References section with all references in alphabetical order at the end of the dissertation.

The text and authorship of Manuscript #1

The text of Manuscript #1 has been reproduced here exactly as it was published except for altered formatting of references and correction of a spelling error that passed undetected in the galley proofs. The references have been re-formatted such that the author's(s') name(s) and the year of publication appear in the text instead of suprascript numerals, and the list of references has been merged with references from other sections, as described above. In addition, several peripheral elements necessary for publication (e.g. list of equipment suppliers, acknowledgements, etc.) have been omitted from the text reproduced in this dissertation.

All of the data presented in the case reports of the manuscript were gathered, analyzed and prepared for presentation by myself, the candidate. Furthermore, every draft of the manuscript text and figures prior to and including the published version were created by myself. The co-authorship of A. Pépin, M. Ladouceur and H. Barbeau reflects their contribution to the work. The construction of the treadmill and harness proceeded principally under the direction of H. Barbeau, with participation from A. Pépin, M.

Ladouceur and myself, among others. All three of the co-authors, but especially A. Pépin, assisted in the evaluation of the subjects described in the case reports of the manuscript. All three of the co-authors provided constructive criticism and useful suggestions during the development of the manuscript prior to submission. The manuscript was accepted by the journal without any revisions; the note on the published text regarding revision reflects that the editorial staff of the journal made minor grammar and style changes prior to publication. All of those minor changes have been incorporated into the text reproduced in this dissertation.

Acknowledgements

I gratefully acknowledge funding support from several sources over my years of graduate work. I was the recipient of three consecutive studentship awards from the Rick Hansen Man in Motion Legacy Fund. From this fund, I received salary and support for travel expenses. During my final year of support from the latter fund, I received supplementary support from the (Canadian) Network for Centers of Excellence in Neuronal Regeneration and Functional Recovery (organization later renamed the Neuroscience Network). I subsequently received 1½ years of salary and support for travel expenses in the form of a studentship award from the Network. In addition, I acknowledge the support provided by the Network to the laboratory in the form of funds granted to my supervisor, Dr. Hugues Barbeau, to carry out this project and others. Finally, I gratefully acknowledge financial support from my parents, Marilyn and Dan Norman, throughout my graduate work.

I gratefully acknowledge the guidance provided by committee members at the presentation of my M.Sc. research proposal and at the presentation of my Ph.D. progress report (in alphabetical order): Dr. Charles Rice, Dr. Denis Gravel, Dr. Lynette Jones, and Dr. Simon Tinawi. I also gratefully acknowledge the guidance provided by Dr. Serge Rossignol on several occasions, particularly in the critique of a previous version of part of the dissertation.

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Two graduate students in particular have helped me more than I can remember or express. Michel Ladouceur solved many technical problems, assisted at many of the laboratory evaluations for the project and is an indefatigable pursuer of better ways of knowing and doing things. To André Pépin I am especially grateful, for assisting at almost every laboratory evaluation for every subject and for his thoughtful and generous contributions to many other aspects of my time in graduate school. I hope I have helped him as much as he has helped me.

Finally, I gratefully acknowledge the supervision of Dr. Hugues Barbeau. His vision, leadership, support, praise, criticism, kindness and enthusiasm have guided me through my years of graduate work, and I continue to be glad that I chose to pursue a doctorate in his laboratory.

Abstract

Most new cases of spinal-cord-injured (SCI) persons in Canada have incomplete loss of sensory and/or motor function, but only a minority are able to walk. The study of animal models of spinal cord injury, especially the chronic spinal cat, has shown that monoaminergic drugs can modulate locomotion and spinal reflexes. Clonidine, a noradrenergic agonist, and cyproheptadine, a serotonergic antagonist, have each been associated with improved walking in SCI subjects. Baclofen, a GABA agonist, is frequently prescribed for spasticity in SCI patients, but its effects on walking have not been quantified. The objective of this doctoral project was to compare the effects of clonidine, cyproheptadine and baclofen on walking in incomplete SCI subjects. Subjects were evaluated on a motorized treadmill. Severely disabled subjects required harness support for their evaluations. The treadmill and harness system are described in detail, and their potential uses in the evaluation and rehabilitation of gait are discussed. A repeated single-subject design was employed for the twelve subjects. The greatest effects were found in the the subjects with greater severity of disability. Cyproheptadine was associated with greatly reduced need for assistance, increases in maximum treadmill speed (MTS) and reduced clonus, among other improvements in walking patterns. Clonidine was associated with increases in MTS, and a generally more upright posture, among other improvements in walking patterns. Baclofen was not associated with changes in walking, although two subjects showed small improvements following washout of baclofen. Among subjects with less severe motor disability, drug effects were less marked. Following washout of cyproheptadine or clonidine, subjects frequently retained walking improvements such as increases in MTS and reduced need for assistance that had first been evident in the drug periods. The significance and implications of the drug effects and the retention of effects during washout periods are discussed. It is concluded that clonidine and cyproheptadine have different effects but both appear useful for severely disabled SCI subjects. The effects of baclofen on walking after spinal cord injury remain unclear.

Abrégé

La plupart des nouveaux cas de patients ayant une lésion de la moëlle épinière (LMÉ) au Canada présente une perte partielle des fonctions sensorielles et/ou motrices. Cependant, seule une minorité de cette population est en mesure de marcher. L'étude chez le chat spinal ayant une LMÉ a montré que les drogues monoaminergiques sont importantes dans la modulation de la locomotion et des réflexes spinaux. La clonidine, un agoniste de la noradrénaline, et la cyproheptadine, un antagoniste de la sérotonine, ont déjà été associées à une amélioration de la marche chez certains sujets ayant une LMÉ. Le baclofen, un agoniste du GABA, est souvent prescrit aux patients ayant une LMÉ pour réduire la spasticité, mais les effets de cette drogue sur la marche n'ont pas été quantifiés. L'objectif de ce projet doctoral était de comparer les effets de la cyproheptadine, de la clonidine et du baclofen sur la marche chez les sujets présentant une LMÉ. L'importance de la perte de la fonction motrice variait entre les sujets. Les sujets étaient évalués sur un tapis roulant motorisé et ceux présentant des déficits sévères avaient besoin d'un harnais de support durant leurs évaluations. Le tapis roulant et le harnais sont présentés de façon détaillée, et l'utilité de ces appareils pour l'évaluation et la réadaptation de la marche est discutée. Un protocole expérimental de mesures répétées a été utilisé pour les douze sujets. Les sujets présentant des déficits plus sévères ont présenté des changements plus importants. La cyproheptadine est associée à une diminution du besoin d'assistance à la marche, à l'augmentation de la vitesse maximale sur le tapis roulant (VMTR), et à une réduction du clonus, parmi d'autres améliorations du patron de marche. La clonidine est associée à l'augmentation de la VMTR, et à une posture plus verticale, parmi d'autres améliorations du patron de marche. Le baclofen n'est associé à aucun changement important de la marche. Cependant, deux sujets ont montré une légère amélioration de la marche après le retrait du baclofen. Les effets des drogues sont moins importants chez les sujets présentant des déficits moins sévères. L'amélioration observée avec les drogues, telle que l'augmentation de la VMTR, est encore présente chez certains sujets après le retrait de la clonidine ou de la cyproheptadine. L'importance et les implications des effets des drogues et de la rétention de ces effets durant les périodes de retrait sont discutées. En conclusion,

la cyproheptadine et la clonidine ont des effets différents, mais les deux semblent être utiles pour les sujets dont les déficits sont plus sévères. Les effets du baclofen sur la marche après une LMÉ demeurent incertains.

Introduction

Spinal cord injury often leads to profound disability including a limited ability to walk. Most spinal-cord-injured (SCI) individuals rely on a wheelchair for locomotion at least part of the time and many are entirely unable to walk, even some who have partial preservation of voluntary motor function caudal to the spinal cord lesion. This relatively poor prognosis for walking in many SCI individuals exists despite the importance accorded to walking by many of the SCI individuals themselves as well as by clinicians in their measurement of functional status.

In recent decades, there has been a great deal of understanding gained regarding the spinal cord circuitry involved in the control of walking. Specifically in regards to the pharmacology of locomotion, there is evidence from experiments in several animal species that monoaminergic systems play roles in the modulation of walking. From experiments in chronic spinal cats, it was suggested that clonidine, a noradrenergic agonist, and cyproheptadine, a serotonergic antagonist, may enhance recovery of walking in SCI human subjects. Preliminary trials have borne out these suggestions. Each of clonidine and cyproheptadine have been compared to placebo for their effects on walking pattern in spastic paretic subjects. In these studies, several subjects have shown improvement in walking with the active drug that was not seen with the placebo.

Clinical management of spinal cord injury has not incorporated many of the strategies developed in animal models for the recovery of walking. The use of drug therapy to assist in the restoration of movement is generally in the form of antispastic drugs, one of the most common being baclofen. In some cases, the reason for using drugs to reduce spasms and other signs of spasticity is to reduce discomfort, pain and/or uncontrolled changes in position. In other cases, drugs to reduce spasticity are used with the aim of improving voluntary movement, although direct evidence that the drugs have such an effect is meagre.

The objective of this study was to compare the effects of clonidine, cyproheptadine and baclofen on the walking pattern of subjects with chronic incomplete spinal cord injury.

Clonidine and cyproheptadine are included in the comparison because each one has previously been shown to improve walking in subjects with incomplete spinal cord injury. Furthermore, they have been shown to have different effects upon the walking pattern of chronic spinal-cord-transected cats but no comparative study on the walking pattern in human subjects has ever been undertaken. The study was made a three-way comparison by the inclusion of baclofen. Baclofen was included in the comparison because it is frequently prescribed for this population, because there has been almost no quantitative study of its effect on the recovery of walking, and because the findings in animal models suggest that its effects on recovery of walking should be carefully examined.

The design for this study required human SCI subjects whose injury had been sustained more than one year prior to entering the study to take each of the drugs separately with washout periods in between drugs. The results have allowed not only a comparison of the effects of clonidine, cyproheptadine and baclofen, but also provided further insight into the potential for recovery of walking in cases of chronic spinal cord injury. The comparison of the effects of these drugs constitutes an original contribution to the field of rehabilitation science, and the observations regarding changes in walking in chronic SCI subjects advance our understanding in the larger area of recovery of walking after spinal cord injury.

In the review of literature, epidemiological evidence is presented that the profile of neurological recovery in the SCI population has changed such that neurologically incomplete injuries are more common than neurologically complete injuries in many areas and this change has implications for the possibility of recovery of walking. Spasticity is a common problem and a large proportion of the SCI population, especially those with severe incomplete injuries, receive treatment for it. A historical review of pharmacological treatment for spasticity is presented in which it can be seen that there has been little study of these drugs' effects on walking. The findings regarding the pharmacological control of locomotion in spinal animals suggest that many of the neurotransmitter systems implicated in the modulation of locomotion are the same systems on which many of the centrally acting antispastic drugs rely for their

mechanism. It is thus argued that it is important to evaluate whether drug therapies prescribed for spasticity have any effect on the recovery of walking, and equally it is important to evaluate the effects of drugs on walking in human SCI subjects that have been shown to be important in modulating locomotion in animal models of spinal cord injury.

Many SCI subjects are too disabled to participate in studies of walking because they are incapable of overground walking. The section of the thesis entitled Manuscript #1 contains the published paper describing the harness support and treadmill that is used to evaluate the walking abilities of severely disabled SCI subjects. As is described in that section, the harness support device used in conjunction with the motorized treadmill permits the evaluation of subjects who would otherwise be too disabled to participate in a study of effects of drugs, or any other intervention, on walking pattern. In particular, it permitted the inclusion of four severely disabled subjects in the thesis project regarding the comparison of the effects of clonidine, cyproheptadine and baclofen on walking pattern in chronic incomplete SCI subjects. In light of the findings of the thesis project, it was very important to use the harness support device for subjects who required it because subjects of this severity showed the most marked effect of drugs.

The subsequent section entitled Manuscript #2 describes the design, execution and results of the thesis project. The comparison of cyproheptadine, clonidine and baclofen yielded new knowledge of the differences in these drugs while confirming some of the findings of previous studies. In addition, the findings of the thesis project suggest a number of implications for the adaptability of walking in SCI subjects in the years that follow the initial injury. The comparison of drug effects and the adaptability of walking in chronic SCI subjects are discussed in the latter part of this section of the thesis.

In the final section entitled Summary and Conclusions, the implications of the findings for further research and for clinical rehabilitation are discussed. As will be seen from the presentation of the results, it is important for future studies to address issues of the time course of drug effects and the mechanism of drug effect when the spinal cord is only partly

disrupted, among other issues. The implications for clinical rehabilitation are numerous. First, the disability of those with chronic incomplete spinal cord injury seems to be more adaptable than would be forecast from measures of their impairment. This has very positive implications for long-term recovery of walking. Moreover, there exist pharmacological strategies for improving walking in chronic SCI patients. These pharmacological strategies have different effects - a new finding from this study - and show the greatest effects in those who are severely disabled and not usually able to participate in gait training. In addition, the beneficial effects of these strategies may last longer than the treatments themselves, suggesting that they create a permissive effect that may be further developed in a rehabilitation context.

REVIEW OF LITERATURE

Spinal cord injury: epidemiology, neurological impairment and spasticity

Traumatic spinal cord injury, although relatively uncommon, has severe consequences for the survivors because of the high proportion with substantial disability. Most spinal cord injuries in Canada arise during damage to the vertebral column. The damage is sustained during a motor vehicle accident in approximately half of all cases, with sports injuries, falls and work accidents leading to most of the other injuries (Tator et al 1993). Epidemiological studies of spinal-cord-injured (SCI) cases in Canada and the United States have led to similar conclusions regarding the demographics of the SCI population: approximately four-fifths of the population is male, and over half are under 30 years of age at the time of injury (Burney et al 1993, Go et al 1995, Tator et al 1993).

The acute care and rehabilitation of SCI patients has greatly changed over the twentieth century. Early in this century, more than nine in ten SCI patients died soon after injury (Gutierrez et al 1993, Ohry & Ohry-Kossoy 1989). Improvements in survival arose partly from improved management of complications, and partly from improved management of the spinal injury. For example, Frankel and colleagues demonstrated that the method of reduction of spinal injuries was related to the outcome in terms of neurological impairment (Frankel et al 1969). In this report, they used a classification of neurological impairment that came to be commonly used in reporting severity of neurological impairment from spinal cord injury. The Frankel scale (see Table) was recently re-examined by the American Spinal Injury Association and International Medical Society of Paraplegia (ASIA/IMSOP) and a revised impairment scale was created (ASIA/IMSOP 1992, also Ditunno et al 1994). In the present review, the severity of impairment will continue to be referred to in terms of Frankel grades because much of the literature in this area was published prior to the revised system by ASIA/IMSOP (1992).

Reports of the extent of neurological impairment show varying absolute numbers but similar trends toward a SCI population in which most individuals have some sensory function and a large minority have some motor function caudal to the lesion level (Stover

TABLE FOR REVIEW OF LITERATURE

Classification of neurological impairment resulting from spinal cord injury

Frankel classification[1]			ASIA impairment scale[2]	
Title	Description		Title	Description
Complete	"... the lesion was found to be complete both motor and sensory below the segmental level ..."[1]	**A**	Complete	"No sensory or motor function is preserved in the sacral segments S4-S5."
Sensory only	"... some sensation present below the level of the lesion but ... the motor paralysis was complete below that level..."	**B**	Incomplete	"Sensory but not motor function is preserved below the neurological level[2] and extends through the sacral segments S4-S5."
Motor useless	"... some motor power present below the lesion but it was of no practical use to the patient."	**C**	Incomplete	"Motor function is preserved below the neurological level, and the majority of key muscles below the neurological level have a muscle grade less than 3."
Motor useful	"... some useful motor power below the level of the lesion. Patients in this group could move the lower limbs and many could walk, with or without aids."	**D**	Incomplete	"Motor function is preserved below the neurological level, and the majority of key muscles below the neurological level have a muscle grade greater than or equal to 3."
Recovery	"... patient was free of neurological symptoms [weakness, sensory loss, sphincter disturbance]. Abnormal reflexes may have been present."	**E**	Normal	"Sensory and motor function is normal."

1. Frankel et al, 1969. The "segmental level" refers to the neurological lesion, which was indicated to be not necessarily identical to the bony lesion but was not otherwise defined.
2. American Spinal Injury Association / International Medical Society of Paraplegia (ASIA/IMSOP), 1992. The "neurological level" is defined as "the most caudal segment of the spinal cord with normal sensory and motor function on both sides of the body."

& Fine 1986, Tator et al 1993, Ditunno et al 1995) and beyond the zone of partial preservation immediately caudal to the lesion (ASIA/IMSOP 1992, Mange et al 1992, Waters et al 1991). Stover and Fine (1986) reported that the proportion of SCI patients with incomplete injuries increased significantly from 1973-74 (38.1%) to 1983-84 (53.8%) in the U.S. centres included in their study. More recently, Go et al (1995) published data from the United States Spinal Cord Injury Model Systems (US-SCIMS) database that show that the proportion of incomplete injuries reached 50% in the period 1978-80 and has remained above 50% ever since. The proportion of tetraplegic (defined as having the neurologic injury level at one of the eight segments of the cervical cord) was slightly greater than half of all cases from 1973 to 1989, but in the period 1990-92, there were more new paraplegic cases than tetraplegic cases. Tator et al (1993) reported a similar increase in incomplete injuries in a Canadian context, from 35% in an early sample (1947-73) to 53.8% in a later sample (1974-81). The proportion of tetraplegics was 56.7% in the earlier period and 63.2% in the later period.

The differences in the proportions (of tetraplegia vs. paraplegia, and of incomplete vs. complete) across countries is likely due to differences in etiologies. Spinal cord injuries from violence are much more associated with paraplegia and are more likely to result in a complete injury. They accounted for 13.9% of the SCI cases in the US-SCIMS database in 1973-77, and 25.1% of cases in 1990-92 (Go et al 1995) whereas they accounted for under 10% of the cases in the Canadian study (Tator et al 1993). Spinal cord injuries from sporting activities, commonly from diving, are much more frequently associated with tetraplegia than with paraplegia, slightly more often incomplete than complete. Sports injuries accounted for only 12.7% of the US-SCIMS total, with a decreasing proportion over time, whereas in the Canadian report sports injuries accounted for 15.4% of the total in the earlier period (1947-72) and 22.9% in the later period (1973-81). It is important to note, however, in comparing the epidemiology across countries, that Go and colleagues (1995) postulate that the data in the US-SCIMS may overestimate severity of entire American SCI population due to more severe cases being entered in the database than are representative of the entire American SCI population.

In considering the reports of injury severity using the Frankel scale, it is important to note that the severity often changes during the first few months after injury. Tator and colleagues (1993) reported only on severity status at admission. Although they used an injury severity scale different from Frankel classification, the data may be converted to the latter to facilitate comparison with other reports. In the period 1973-81, 46.2% had Frankel A injuries, 14.9% Frankel B injuries, 7.4% Frankel C injuries, 28.0% Frankel D injuries, and 2.5% had normal motor and sensory function. Of all 14,791 patients in the US-SCIMS database, the proportions were approximately similar for status at entry to the system: Frankel A, 50.5%; Frankel B, 13.2%; Frankel C, 12.9%; and Frankel D, 21.6%. At discharge from rehabilitation, many patients have improved by one or more grades on the Frankel scale, especially among those who were admitted within 24 hours of injury. For patients with Frankel B injuries at admission, nearly half of those admitted soon after injury improved to a Frankel C or D grade by discharge. For patients with Frankel C injuries at admission, over half of those admitted soon after injury improved to a Frankel D grade by discharge. Patients admitted with a Frankel A or D grade generally remained at the same grade, although those admitted within 24 hours of injury were slightly more likely to improve a grade than those admitted later (Ditunno et al 1995). Based on the average length of stay for patients in the US-SCIMS database, discharge Frankel ratings were assessed 2-5 months post-injury in most cases.

There are additional reasons to believe that the proportion of SCI patients with incomplete loss of sensory and motor function will continue to rise. Large trials in the U.S.A. of methylprednisolone sodium succinate (MPSS) and of GM-1 ganglioside have shown that administration of these drugs to subjects with acute and sub-acute spinal cord injuries, respectively, leads to a reduced neurological impairment in the long-term. In the second U.S. National Acute Spinal Cord Injury Study (NASCIS-2), subjects who began the 24-hour MPSS protocol within eight hours of injury had significantly greater improvement in motor function, pinprick sensation and touch sensation at six weeks post-injury and again at six months post-injury than those subjects who received placebo (Bracken et al 1990). In addition, subjects in the MPSS group had a significantly greater increase in

motor score at one year than subjects who received placebo. Of additional interest to note in the follow-up analysis was that subjects who began their doses of MPSS more than eight hours after injury recovered less motor function over the subsequent year than subjects who had received placebo (Bracken et al 1992).

A randomized, placebo-controlled trial of GM-1 ganglioside has also shown promising results for reducing neurological impairment. Subjects began receiving the drug or a placebo within 72 hours of injury and continued the treatment for several weeks. Subjects in the GM-1 ganglioside group whose initial Frankel grade was A, B or C had a significantly greater chance of improving two Frankel grades by one-year follow-up than comparable subjects in the placebo group. Subjects in the GM-1 ganglioside group also showed significantly greater improvement in lower extremity ASIA scores than subjects in the placebo-treated group (Geisler et al 1991, Geisler 1993). No published data are yet available regarding an integrated strategy using both MPSS and GM1 ganglioside.

Further reduction in impairment may be possible in those with chronic injuries as a result of other pharmacological treatments. For example, short-term intravenous doses of 4-aminopyridine (4-AP) have been associated with transient reduction of impairment in incomplete SCI subjects (Hansebout et al 1993, Hayes et al 1993). 4-AP is a potassium channel blocking agent and it is believed to improve function in SCI subjects through improving nerve conduction in axons that are hypothesized to be intact across the lesion level but subject to conduction failure due to demyelination or dysmyelination. There may also be other mechanisms underlying the effects of 4-AP (Jankowska et al 1977, 1982). Hansebout and colleagues (1993) reported the effects of 4-AP in eight SCI subjects, two at each of Frankel A, B, C and D grades, and noted that the improvement in sensory and motor function was particularly evident in the two Frankel C subjects. They also noted that in some subjects the beneficial effects lasted for several days although the drug had been administered intravenously over a two-hour period and was likely to have been eliminated before the end of the beneficial effects. On the other hand, the acute administration of 4-AP to decerebrate cats has been shown to lead to a synchronization of neuronal activity, and when the 4-AP was preceded by chemical stimulation to elicit fictive

locomotion, the subsequent effect was a short-lasting change in the fictive locomotor pattern, followed by its disappearance and replacement by a synchronous bursting activity in the nerves being recorded (Dubuc et al 1986). Results were similar when a spinal cord transection was performed prior to drug administration (Dubuc et al 1986). The latter results suggest that although 4-AP may increase neuronal activity caudal to a spinal lesion, the drug's effects on movement behaviour will need further study.

Reports of large cohorts of SCI subjects regarding chronic disability are rarer than those regarding impairment. Thus far, from the US-SCIMS database, the functional outcomes reported have been scores on the Functional Independence Measure (FIM) (Ditunno et al 1995). The FIM was designed as a measure of overall functional status for patients of many diagnostic groups undergoing medical rehabilitation, and particularly to guide administrative decisions regarding utilization of resources and length of rehabilitation stay (Keith et al 1987). As such, the FIM is not very responsive to change in any single component of functional status such as walking. An adept wheelchair user earns the same FIM locomotion score as a person walking with a walker and leg braces or a person walking slowly without aids, so these data are not informative regarding walking as a functional outcome. Neither the Frankel scale nor the ASIA impairment scale expressly reflect walking. Nonetheless, data regarding impairment severity may be used to estimate the proportion of SCI patients who regain the ability to walk. Those with A or B ratings are obviously unable to walk with the exception of low paraplegics who walk with long leg braces. Those with E ratings are obviously able to walk. Generally, a C rating is assigned to those whose motor function is unsufficient for walking, and a D rating is assigned to those who are able to walk (see Table), although the walking may be limited in many ways. From the epidemiological studies in Canada and the U.S.A. (reported above), we may estimate that only one-quarter to one-third of SCI patients in rehabilitation regain some ability to walk by discharge from rehabilitation.

In the rehabilitation of SCI patients following the acute management of the spinal cord injury and any other injuries, the maximizing of independent movement is largely a matter of physical training, as described in numerous handbooks written by physical and

occupational therapists (e.g. Bromley 1981, Nixon 1985, Somers 1992, Whalley Hammell 1995). The training is aimed at reinforcing the muscles that the patient is still able to activate voluntarily, improving flexibility in selected areas, and practicing techniques of movement for functional goals. When walking is possible within the time frame of inpatient rehabilitation, training for walking is incorporated into the rehabilitation program. The importance of training has been recognized in studies of new rehabilitation approaches such as the use of a body-weight-support system or the administration of drugs to improve walking following spinal cord injury (both approaches will be discussed in more detail in the latter part of the present review). The studies have thus focussed on the role of, or incorporated into their research protocol, an interactive training approach to maximize the improvement in walking (Barbeau et al 1993b, Dietz et al 1995, Dobkin et al 1992, Fung et al 1990, Wernig & Müller 1992). Furthermore, there is a growing body of literature regarding the development of orthotic devices to assist walking. These devices may be mechanical, such as long-leg braces or the reciprocating gait orthosis, that have been developed particularly for paraplegics with little or no recovery of motor function in their lower limbs (e.g. Douglas et al 1983, Saitoh et al 1996, reviewed in Jaeger et al 1989). These devices may also be electrical, such as nerve or muscle stimulators to provide or assist voluntary muscle activity in key phases of the gait cycle (Bajd et al 1983, Kralj et al 1993). In addition, there has been some development of hybrid devices (Phillips 1989, Solomonow et al 1989).

Within the rehabilitation of active movement in SCI patients, reflex responses associated with spasticity are often seen to be impeding the control of movement and/or causing discomfort or pain to the patients. Spasticity has had many explicit or implicit definitions (for discussion, see Landau 1974, Thilmann 1993), although the most commonly cited definition in recent years is that spasticity is "a motor disorder characterized by velocity-dependent increase in tonic stretch reflexes ("muscle tone") with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex as one component of the upper motor neuron syndrome" (Lance 1980). The relationships among components of spasticity and deficits in voluntary movement are not clear although they are often

associated together. Treatment is provided to reduce spasticity, sometimes with the hope of improving voluntary movement, and other times with the primary aim of reducing discomfort or pain arising from the spasticity. The flexibility exercises that are part of standard rehabilitation reduce reflex responses (Odéen 1981) and maintain muscle length, but further antispastic treatment in the form of medications or surgical procedures are often provided. Maynard et al (1990) reported that among 466 patients with new traumatic spinal cord injury in the late 1980s, one-quarter had received some kind of medical or surgical antispastic treatment before discharge from rehabilitation. When the results were analyzed by Frankel category rather than by lesion level, it was evident that those with Frankel B or C severity of injury were almost twice as likely to have received antispastic treatment than those with Frankel A or D severity. Among patients from the total cohort for whom follow-up data were available (n=138), almost half had received antispastic treatment within a year.

Data from the US-SCIMS database also show high rates of treatment for spasticity among SCI patients. Almost one third of patients received some form of antispastic treatment by discharge and the proportion rose to almost half by the end of the first year post-injury. Amongst tetraplegics in the US-SCIMS, the percentages receiving antispastic treatment by the end of the first year post-injury were as follows: Frankel A, 59.5%; Frankel B, 67.9%; Frankel C, 64.6%; and Frankel D, 37.8%. Long-term follow-up data is more limited in the database, but it was observed that fewer than 5% of patients had undergone ablative surgical procedures within 5 years of injury, and it is suggested that most of the rest of the treatment is pharmacological in nature (Maynard et al 1995).

Taken together, the developments in spinal cord injury outcomes and treatments mean that it is increasingly important to evaluate the effects of antispastic treatments on motor behaviours, especially walking. First, where penetrating injuries are rare, more than half of all patients will likely have incomplete injuries and the proportion is likely to rise as progress is made in acute care procedures, such as methylprednisolone treatment. Thus, walking may be within reach for an increasing proportion of SCI patients. Second, within the SCI population, and especially within the group of patients with incomplete injuries,

treatments to reduce spasticity are used very frequently. The relationship between spasticity and voluntary movement is uncertain. Moreover, the relationship between treatments to reduce spasticity and voluntary movement is equally uncertain. In view of the changing epidemiology of spinal cord injury, it is increasingly urgent to explore these issues. As we shall see below, many of the treatments to reduce spasticity directly affect neural pathways that are important in the generation of movement. We turn first to a review of the development of pharmacological treatment for spasticity, then to a review of the pharmacology of locomotion, and subsequently to a review of walking function in SCI subjects and how the deficits may be addressed with pharmacological treatment.

Treatment for spasticity

Many treatments for spasticity over the years abolished or drastically reduced muscle tone, particularly destructive surgical procedures such as neurotomy, tenotomy and dorsal rhizotomy, but also applications of substances such as injected phenol to block peripheral nerves (Awad 1972, Khalili & Betts 1967). Oral drug therapy was relatively rare. In the second edition (1976) of his treatise on spinal cord injuries, Sir Ludwig Guttmann reviewed surgical ablative procedures as well as peripheral and intrathecal nerve blocks with alcohol or phenol, after having concluded that no drug thus far existed which had a long-lasting, relaxing effect on spasticity without having undesirable effects on the whole organism. Although later reviews were more optimistic about the possibility of clinically useful antispastic drugs, one finds numerous references to the idea of adjusting drug dose carefully, not only to reduce toxicity but also to avoid abolishing muscle tone if the patient relies on preservation of muscle function for independent movement (for examples, see reviews by Davidoff 1978, Young 1994).

In reviews of postulated spasticity mechanisms and methods of antispastic treatment there is a recurring theme that treatment to reduce spasticity may not improve voluntary motor ability. In particular, Landau pointed out that spasticity is often treated without a clear definition of the problem, and that it is far from axiomatic that reducing the clinical signs that were diagnostic to the neurologist will be therapeutic for the patient (Landau, 1974).

Twenty years later, Young observed that "With little evidence to support it, the theory that increased reflexes... may somehow submerge remaining voluntary function of motor neurons has long been a popular concept in spasticity treatment." (Young 1994). This popular concept seems to have originated from theories of motor control in which the influences of peripheral sensory inputs and descending inputs to the spinal motor systems are seen to be competitive or antagonistic to one another. In this view, the nervous system was viewed as having a hierarchical structure with more rostral areas exerting a tonic inhibition on spinal systems. The symptoms of spasticity or other involuntary movement in patients with cerebral or spinal cord lesions were interpreted as a release of function (term derived from Hughlings Jackson, 1889) or loss of restraining effects (e.g. Denny-Brown's views described in Langworthy 1970) on spinal pathways. The pyramidal tract, in particular, was believed to be important in exerting inhibitory control on spinal cord circuits, and the hyperexcitability in spinal cord circuits was thought to be primarily due to hyperactivity of gamma motor neurons. The concept of gamma motor hyperactivity can be traced back to Sherrington's experiments in decerebrate cats in which gamma motor hyperactivity was seen to be the cause of the induced rigidity (Sherrington, 1898). Many of these ideas about spasticity, however, have not been supported upon further investigation. Decerebrate rigidity has not been upheld as a useful model for spasticity and gamma motor hyperactivity is no longer believed to be an important factor in spasticity (for reviews, see Burke 1983, 1988). Furthermore, the pyramidal tract has not been found to have the proposed inhibitory role on spinal motor circuits without which spasticity would develop (for reviews, see Davidoff 1990, 1992, Burke 1988).

As Landau (1974) has pointed out, there have existed considerable variations in the definition of spasticity such that whether putative antispastic treatments were able to improve voluntary movement depended a great deal on the definition of spasticity stated or implied by the proponents of the treatment and, by extension, what symptoms were addressed by the treatment. The confusion over definitions has doubtless contributed to conflicting ideas about whether antispastic treatment in general will alter voluntary movement. Additional contributing factors are that clear distinctions have not always been

made among benefits conferred by treatments, and that the objectives of antispastic treatment are often different across different diagnostic categories. For severely disabled individuals whose diagnoses carry prognoses of progressively increasing disability and pain, antispastic treatments may make it possible for some movements, such as assisted transfers, to be more comfortable. It is only relatively recently that such a prognosis is less and less applicable for more and more SCI cases.

Let us return to the situation of SCI patients with spasticity problematic enough to warrant treatment as well as incomplete loss of motor function because it seems that this is a large and growing subset of the SCI population. It is an important and timely question whether treatment to address spasticity will affect the recovery of walking in negative or positive ways in these people. It does not seem likely that the answer will be the same for all antispastic treatments, and thus each treatment should be specifically examined for its potential to improve walking or any other voluntary movement behaviour that is relevant for the population.

Drug treatments for spasticity have been the focus of investigation in the present study and are thus the principal topic for review with respect to the aforementioned question regarding spasticity treatment and walking. Let us turn to a history of drug treatment for spasticity. In a brief review of antispastic drugs in his treatise on spinal cord injuries, Guttmann (1976) listed several drugs, only two of which are mentioned in subsequent reviews of antispastic drugs (Davidoff 1978, 1985, Noth 1991, Whyte & Robinson 1990, Young & Delwaide 1981, Young & Shahani 1986). One of these drugs is diazepam, a member of the benzodiazepines which are active at GABA receptors. Diazepam has been mentioned in many reviews of antispastic drugs in the last twenty years (Burke 1975, Davidoff 1978, Young & Delwaide 1981, Davidoff 1985, Young & Shahani 1986, Whyte & Robinson 1990, Noth 1991). The other is mephenesin which was mentioned more rarely (Burke 1975, Young & Delwaide 1981) and by the time of a review in 1981 (Young & Delwaide 1981) was considered an older drug and considerably less effective than dantrolene, diazepam or baclofen. Concurrently in the mid-1970s, new drugs were being developed, and reviews of that period listed baclofen, dantrolene sodium and the

phenothiazine and adrenoreceptor-blocking drugs (Burke 1975, Davidoff 1978). Drugs with a well-published history of use to treat spasticity are reviewed below, as well as some new drugs possibly relevant to the recovery of walking. The drugs have been divided into categories based on their known or postulated mechanisms.

Drugs with peripheral actions

There are two main categories of substances that act peripherally that have been used to reduce spasticity: agents to reduce the strength of muscle contraction; and agents to produce anesthesia of peripheral afferent receptors. The former approach appears to have been more widely used than the latter. For weakening the strength of muscle contraction, the drug of choice has been dantrolene (also called dantrolene sodium). In the dosage range used in humans with spasticity, dantrolene interferes with the excitation-contraction mechanism of skeletal muscle by interfering with the release of calcium from the sarcoplasmic reticulum (see review by Pinder et al 1977). By not affecting neural firing or the neuromuscular junction, dantrolene therapy has not been observed to change EMG recordings of muscle activity (Chyatte & Basmajian 1973). Rather, it reduces the force output of muscles. Its principal drawback as an antispastic drug is thus obvious -- it weakens all skeletal muscles, thereby risking a reduction in mobility for patients who rely on residual muscle function for movement. Trials of dantrolene in subjects with spasticity have generally found it to be superior to placebo in reducing spasticity, but improvement of voluntary function was rarer (Monster 1974). Its clinical use is also limited because it has been hepatotoxic in some patients, is contraindicated in those with liver dysfunction and is used with caution in all others.

More recently, there have been several reports published regarding the injection of botulinum toxin to weaken specific muscles affected by spasticity or other forms of hypertonia (Borg-Stein et al 1993, Snow et al 1990). The toxin acts to reduce muscle tone by blocking neuromuscular transmission. Botulinum toxin injections have the advantage over oral doses of dantrolene in that therapy can be directed only to muscles in which hypertonia is causing persistent discomfort or functional problems. However, the principal

risk is that dosage may be miscalculated and muscles overweakened. Published reports suggest that botulinum toxin has been used more for dystonia and its variants than for spasticity following spinal cord injury (reviewed in Tim & Massey 1992). In subjects with multiple sclerosis, botulinum toxin has been used to weaken leg adductor muscles in order to facilitate assisted transfers and hygiene (Borg-Stein et al 1993, Snow et al 1990). There is also a report of its use to reduce drop foot in spastic brain-injured subjects; five of the six ambulatory subjects in the study were reported to show gait improvements (Dengler et al 1992). In another report, seven of twelve hemiparetic subjects who received botulinum toxin injections into the calf muscles of the affected side improved their gait, particularly in terms of overground velocity, stride length and reduction of abnormal EMG timing (Hesse et al 1996).

Topical anesthetics have been used with some success to relieve spasticity. Sabbahi and colleagues (1981) reported the results of gait analysis in a hemiparetic subject before and after spraying a benzocaine solution over the affected lower limb. The subject showed improved movement of all three joints in gait subsequent to the anesthetic. Mills and Pozos (1985) demonstrated a large reduction in the amplitude of ankle clonus in two SCI subjects with topical application of xylocaine solution over all of the lower leg and proximal foot. It would seem, however, from inspection of review articles on spasticity and handbooks on rehabilitation of disorders with spasticity, that topical anesthetics are rarely employed but that the principle is applied more simply in the ice treatment and electrical stimulation treatment that are used to reduce spasticity.

Glycinergic drugs

Glycinergic drugs have been investigated as having possible therapeutic uses for reducing spasticity, in view of the findings that glycine is a major inhibitory neurotransmitter of the spinal cord (Young & MacDonald 1983). Glycine itself has been used for the treatment of spasticity with mixed results (Stern & Bokonjic 1974). Unlike other amino acids that act as neurotransmitters, glycine is able to cross the blood-brain barrier. The consequent activation of glycine receptors on interneurons and motor neurons of the spinal cord leads

to a decrease in cell firing and a damping of reflexes (Davidoff 1985, Young & MacDonald 1983).

Threonine, a precursor of glycine, has also been used for the treatment of spasticity. The rationale is that threonine will be converted to glycine and there will thus be an increase in glycinergic inhibition. In ambulatory subjects with multiple sclerosis, a modest decrease in spasticity was found in some subjects (Hauser et al 1992). Lee and Patterson (1993) found significantly reduced spasticity (as measured by the Ashworth scale, Ashworth 1964) associated with two weeks of threonine treatment in comparison to placebo treatment in subjects with spinal spasticity. A positive response was also noted in subjects with progressive spastic disorders of genetic origin (Barbeau A et al 1982). The authors noted that since glycinergic systems have been implicated in the manifestations of genetic spastic syndromes in rodents, glycinergic drugs should be especially investigated in genetic spastic syndromes in humans.

GABAergic drugs

The benzodiazepines, particularly diazepam, have been extensively used to treat spasticity (for reviews, see Young & Delwaide 1981, Davidoff 1985, Young & Shahani 1986, Whyte & Robinson 1990). Although diazepam has effects in various areas of the brain, thereby causing the principal side effects of somnolence and sedation, it has been shown to be equally effective at reducing spasticity in complete and incomplete SCI subjects as well as reducing reflexes in animals with complete cord transections, thus suggesting a spinal site of action (Cook & Nathan 1967, Hudson & Wolpert 1970, Schlosser 1971). It has been confirmed in a number of reports of both human and non-human subjects that diazepam reduces spinal reflexes by increasing presynaptic inhibition through stimulation of $GABA_A$ receptors (for review, see Davidoff 1985). It is still in clinical use, but its side effects, principally drowsiness and sedation, limit its usefulness.

Progabide is a GABA agonist that is thought to have actions at both $GABA_A$ and $GABA_B$ receptors (Mondrup & Pedersen 1984a). It has been identified as reducing spasticity, particularly in reducing tendon reflexes (Mondrup & Pedersen 1984a, 1984b). Like the

glycinergic drugs, progabide appears to have received little follow-up study, although the high doses (up to several grams per day) and the reported hepatotoxicity may have limited the clinical utility of the drug.

Since its introduction, baclofen (first called CIBA 34,647-Ba or β-(4-chlorophenyl)-GABA) has become the most important drug to treat spasticity arising from spinal lesions. The earliest reports of baclofen's usefulness in treating spasticity were published in the early 1970s (e.g. Jones et al 1970). At that time, it was understood that this drug was a GABA analogue and that it reduced mono- and polysynaptic reflexes in spinal and decerebrate preparations (CIBA research, quoted in Jones et al 1970). However, its mechanism remained partly mysterious for some time because bicuculline, a GABA antagonist, was not able to block its actions (reviewed in Davidoff 1978, Young & Delwaide 1981). It has since been understood that baclofen is active at bicuculline-insensitive GABA receptors, termed $GABA_B$ receptors (reviewed in Bowery 1989), and that it depresses spinal reflexes principally by reducing the release of excitatory transmitters from afferent neurons (reviewed in Davidoff 1985). This presynaptic action was demonstrated in several *in vitro* preparations, with consistent findings of reduced excitatory post-synaptic potentials in association with baclofen but no change in motoneuronal membrane properties (Davidoff & Sears 1974, Fox et al 1978, Pierau & Zimmermann 1973). An additional postsynaptic action of baclofen was later demonstrated with further study of *in vitro* preparations (Wang & Dun 1990) but the doses used to produce this effect are thought to be much greater than is ever achieved with oral doses of baclofen in humans.

Baclofen was quickly considered by many in the field to be the drug of choice for spasticity arising from spinal lesion (Burke 1975, Young & Delwaide 1981). It has been studied mostly in subjects with spinal cord injury or multiple sclerosis, in whom it has been associated with reduced flexor and extensor spasms and reduced resistance to passive movement (Duncan et al 1976, Sachais et al 1977). Baclofen has been found to be generally less effective at reducing signs of spasticity in subjects with cerebral lesions

(Jones & Lance 1976, Pinto et al 1972, reviewed in Whyte & Robinson 1990). In a recent review of $GABA_B$ receptor physiology, Wojcik and Holopainen (1992) raised the question whether injuries of the spinal cord might evoke the formation of supersensitive $GABA_B$ receptors in the spinal cord caudal to the injury. If so, this supersensitivity may account for baclofen's effectiveness against spasticity from spinal lesions and relative ineffectiveness against spasticity from cerebral lesions. However, see Hinderer (1990) for a discussion of baclofen's effects being mediated through its anxiolytic properties.

Baclofen's clinical success as an antispastic drug arises partly from its relatively benign side effect profile. It has been associated with somnolence, sedation, and fatigue, particularly during periods of increasing dosage. However, these side effects usually occur more rarely and more benignly than the same side effects with diazepam (Young & Delwaide 1981). The primary risk occurs with rapid change of dosage, overdosage having been associated with encephalopathy, seizures, respiratory depression, and coma (Delhaas & Brouwers 1991, Lee et al 1992), and abrupt withdrawal having been associated with hallucinations, seizures, visual disturbances, and psychosis (Kofler & Leis 1992, Rivas et al 1993).

Baclofen is typically used in doses under 100 mg/day, divided into three or four doses because it is rapidly absorbed and eliminated (Young & Delwaide 1981). To obtain relief in cases of severe spasticity, doses well over 100 mg/day are sometimes tried but the total dose is usually limited by an increase in the side effects of somnolence and fatigue. To avoid this problem and to increase the amount of drug delivered to the lumbar spinal cord, an intrathecal approach was used (for reviews, see Kroin 1992, Lewis & Mueller 1993, Ochs 1993, Penn 1988). In most reports, subjects are screened according to the clinical response to an intrathecal bolus of baclofen and an indwelling pump with attached intrathecal catheter are implanted when indicated. A large body of literature has developed regarding this approach (Abel & Smith 1994, Albright et al 1993, Armstrong et al 1992, Azouvi et al 1993, 1996, Becker et al 1995, Broseta et al 1989, Coffey et al 1993, Gardner et al 1995, Hankey et al 1986, Hugenholtz et al 1992, Kofler et al 1992, Kravitz et al 1992, Latash et al 1989, 1990, Lazorthes et al 1990, 1991, Loubser et al 1991,

Meythaler et al 1992a, 1992b, Müller et al 1987, Nance et al 1995, Nanninga et al 1989, Narayan et al 1991, Ochs et al 1989, Patterson et al 1994, Penn 1991, 1992, Penn & Kroin 1987, Penn et al 1989, Sahuquillo et al 1991, Siegfried & Rea 1987, 1988); most reports are in regard to spasticity from spinal injury or disease but more recently there have been a number of reports of intrathecal baclofen in use for spasticity from supraspinal disorders. Almost all evaluations of intrathecal baclofen's effect in comparison to pre-drug status and/or placebo treatment have been of resistance to passive movement (Ashworth scale) and spasm frequency. The reductions in these measures associated with intrathecal baclofen have been strikingly large, of a magnitude not usually seen before with any drug treatment. Most trials have thus used such measures primarily or exclusively to evaluate treatment outcome. Furthermore, the reduction in side effects that was forecast has generally proved true. Intrathecal baclofen treatment is nonetheless not without its risks -- the risk of sudden changes in dosage from catheter problems leading to overdosage or withdrawal, as well as the risks of infection associated with this invasive procedure.

It is rare that quantified changes in voluntary motor function following intrathecal baclofen have been reported (reviewed in Campbell et al 1995), not surprisingly because most subjects admitted to trials of intrathecal baclofen have been highly disabled. Furthermore, the impressive reduction in resistance to passive movement and spasm frequency have been deemed sufficient evidence of its effectiveness. Of the reported functional improvements, many are quantifications of improvements in areas such as transfers and dressing or merely anecdotal descriptions in which the mechanism of improvement is not clear. In a report published in 1993, Ochs estimated that the number of subjects treated with intrathecal pump worldwide was over 1000, and the number has doubtless grown since then. We have remarkably little quantitative data on voluntary function for such an increasingly utilized mode of treatment (cf. Armstrong 1992, Campbell et al 1995). There are, however, data regarding the mechanism of action of intrathecal baclofen. As with oral baclofen, it is believed to act presynaptically to reduce excitatory transmission onto motoneurons. In addition, it has been proposed to exert a postsynaptic effect on motoneurons close to the site of drug delivery within the cord

(Azouvi et al 1993, Bussel et al 1993, Dressnandt et al 1993, 1995) presumably from the high concentration of baclofen in this area, similar to the effect *in vitro*.

Adrenergic drugs

The use of adrenergic drugs for the treatment of spasticity has an unusual history because both antagonists and agonists have been put forward at different times as being useful. Most of the drugs in this category have been alpha-adrenergic drugs with the exception of propranolol, a beta-adrenergic blocker, which has been shown to relieve some signs of spasticity, particularly ankle clonus (Mai and Pedersen 1976). It is noteworthy, in light of other findings discussed below, that propranolol also possesses some serotonergic blocking properties. The phenothiazines, particularly those with alpha-adrenergic blocking ability such as chlorpromazine, were used to reduce muscle hypertonia arising from a number of neurological conditions. Although there were some cases of impressive success, particularly when chlorpromazine was combined with phenytoin (Cohan et al 1980), most reports concluded that phenothiazines and alpha-adrenergic blockers were generally ineffective as antispastic agents (reviewed in Davidoff 1978, 1985, Whyte & Robinson 1990). The strongly sedative effect of these drugs also limited their clinical utility, except for situations in which sedation was considered useful. The rationale underlying the use of alpha-adrenergic blockers was their ability to reduce the gamma motor activity found in animals with decerebrate rigidity. As pointed out by Davidoff (1978, 1985), factors other than gamma hyperactivity are implicated in decerebrate rigidity, and these drugs have not proven effective at changing segmental reflexes in spinal-transected animals. Moreover, as discussed earlier, gamma hyperactivity is no longer believed to play an important role in spasticity in humans with neurological disorders (Burke 1983, 1988).

In the early 1980s there was a shift in attention from alpha-adrenergic blockers to alpha-adrenergic agonists to reduce spasticity. Tizanidine, an alpha-2-adrenergic agonist and imidazoline derivative, was found to reduce the release of excitatory amino acids in spinal circuits and inhibit the tonic facilitatory effect of coeruleospinal pathways on spinal

circuits. In animals, tizanidine reduces polysynaptic spinal reflexes with little effect on monosynaptic reflexes (Davies 1982, reviewed in Coward 1994). The reduction in polysynaptic reflexes has been blocked by yohimbine, confirming that it is an alpha-2-adrenergic effect (Corboz et al 1991). Clinical studies have shown tizanidine to be clearly more effective than placebo or comparable to baclofen at reducing spasticity (i.e. Ashworth score) in subjects with multiple sclerosis (Lapierre et al 1987, Bass et al 1988). Nance and colleagues (1994) reported on a multi-centre study of tizanidine's effects in SCI subjects of Frankel A, B, and C levels. They found significant differences in several outcome assessments of spasticity between subjects receiving tizanidine (n=38) and subjects receiving placebo (n=40) after eight weeks of treatment (total daily dose up to 36 mg/day) (Nance et al 1994). Across studies, the principal side effects of tizanidine are generally reported to be dry mouth and somnolence (Lapierre et al 1987, Nance et al 1994).

Clonidine, like tizanidine, is also an alpha-2-adrenergic agonist, and the two drugs have some biochemical similarities (Coward 1994). Clonidine, however, was developed earlier and has been used for years in humans principally as an antihypertensive drug (Atkin et al 1992, Materson et al 1993), but also for other conditions (Rauck et al 1993, Singer et al 1995). In doses generally lower than those used for an antihypertensive effect, clonidine has been found to have useful antispastic properties, first reported by Tuckman and colleagues (1982). Several other case reports of clonidine's antispastic effects have been published (Nance et al 1985, Rosenblum 1993, Sandford et al 1992, Yablon & Sipski 1993). In three published studies, clonidine was found to be useful in reducing clinical signs of spasticity in about half of participating subjects (Donovan et al 1988, Maynard 1986, Weingarden & Belen 1992). Donovan and colleagues have performed the largest study thus far reported. Fifty-five SCI subjects took doses in the range 0.1 to 0.4 mg/day. Twenty-four of thirty-six tetraplegic subjects and seven of nineteen paraplegic subjects showed clinical improvement in spasticity, with no apparent difference in success rate in clinically complete versus incomplete injuries. Twenty-seven subjects elected to continue clonidine at the end of the study (Donovan et al 1988).

Two differences between tizanidine and clonidine in clinical application bear emphasizing. First, the doses of oral tizanidine required to produce antispastic effects similar to those reported for oral clonidine are approximately 100 times as large. This difference may be related to the finding that clonidine has a higher affinity for alpha-2 receptors than has tizanidine (Muramatsu & Kigoshi 1992). This differential affinity may underlie the second difference which is that clonidine has a greater antihypertensive effect associated with it, an effect that may lead to hypotension when clonidine is being used for spasticity. However, clonidine's antihypertensive effect has also been linked to its affinity for imidazoline receptors, and tizanidine has an affinity similar to clonidine for imidazoline receptors (Muramatsu & Kigoshi 1992). Furthermore, intrathecal clonidine and intrathecal tizanidine have been shown to reduce nociception, blood pressure and heart rate at similar doses in dogs (Kroin et al 1996), suggesting that part of the difference in effects from oral doses may be related to differences in central and peripheral effects. Thus, the reasons for differences in clinical effects of tizanidine and clonidine will require further investigation.

Other drugs with central actions

Cyproheptadine is a serotonin antagonist that has been in therapeutic use for many years for other medical conditions (Goldberg et al 1979, Goldman 1976, Krieger et al 1975, Wanderer et al 1977). Its use as an antispastic drug arose because of its success at blocking high levels of muscle activity in the hindlimbs of chronic spinalized rats induced by application of serotonergic drugs (Barbeau et al 1981). Barbeau and colleagues (Barbeau H et al 1982) found that cyproheptadine was able to markedly reduce clonus in four subjects and reduce flexor spasms in five subjects (total: n=2 SCI subjects, n=4 subjects with multiple sclerosis). Nance (1994) studied the effects of cyproheptadine, clonidine and baclofen in 25 SCI subjects with an average Ashworth score >2 across several muscle groups. All three drugs were associated with a decrease in the average Ashworth score and in the amplitude of first swing in the pendulum test. The decreases were significantly different from the no-drug condition but there were no significant differences among the drugs (Nance 1994). When used to treat spasticity,

cyproheptadine's principal side effect is one of its more useful effects in other patient populations: that is, it is associated with an increase in appetite.

Morphine has been used as an analgesic for many years and has been recently used to control spasticity, mostly through an intrathecal route (Erickson et al 1985, 1989, Siegfried & Rea 1988). Morphine is able to reduce both polysynaptic and monosynaptic reflexes. Cannabis has also been reported to reduce spasticity, reported anecdotally from patients who smoke marijuana, and also reported following investigation of synthetic Δ^9-tetrahydrocannabinol (THC) (Petro & Ellenberger 1981). THC is believed to reduce spasticity through inhibition of spinal polysynaptic reflexes, and was seen to be effective at oral doses too low generally to produce side effects of euphoria. However, the potential for abuse at higher doses limits its clinical utility (Petro & Ellenberger 1981).

Thus, there are several pharmacological strategies that may reduce spasticity in subjects with complete and incomplete spinal cord injury. The reported effects have included not only reduced resistance to passive movement as measured by laboratory and clinical examination, but also changes that increase the comfort of the subjects. However, as emphasized above, an increasing proportion of persons with new SCI have the potential for useful motor function caudal to the injury level, including walking, and it is thus increasingly important to evaluate systematically whether treatments administered for complications from spinal cord injury are favourable or unfavourable for the recovery of walking. The Figure provides a schematic illustration of the proposed roles of antispastic drugs. As we turn to the evidence for the roles of spinal neural systems in locomotion, we shall see that many of the neurotransmitter systems implicated in the mechanism of action of antispastic drugs are also implicated in the control of locomotion, thereby reinforcing the importance of evaluating the effects of present and proposed antispastic treatments on walking.

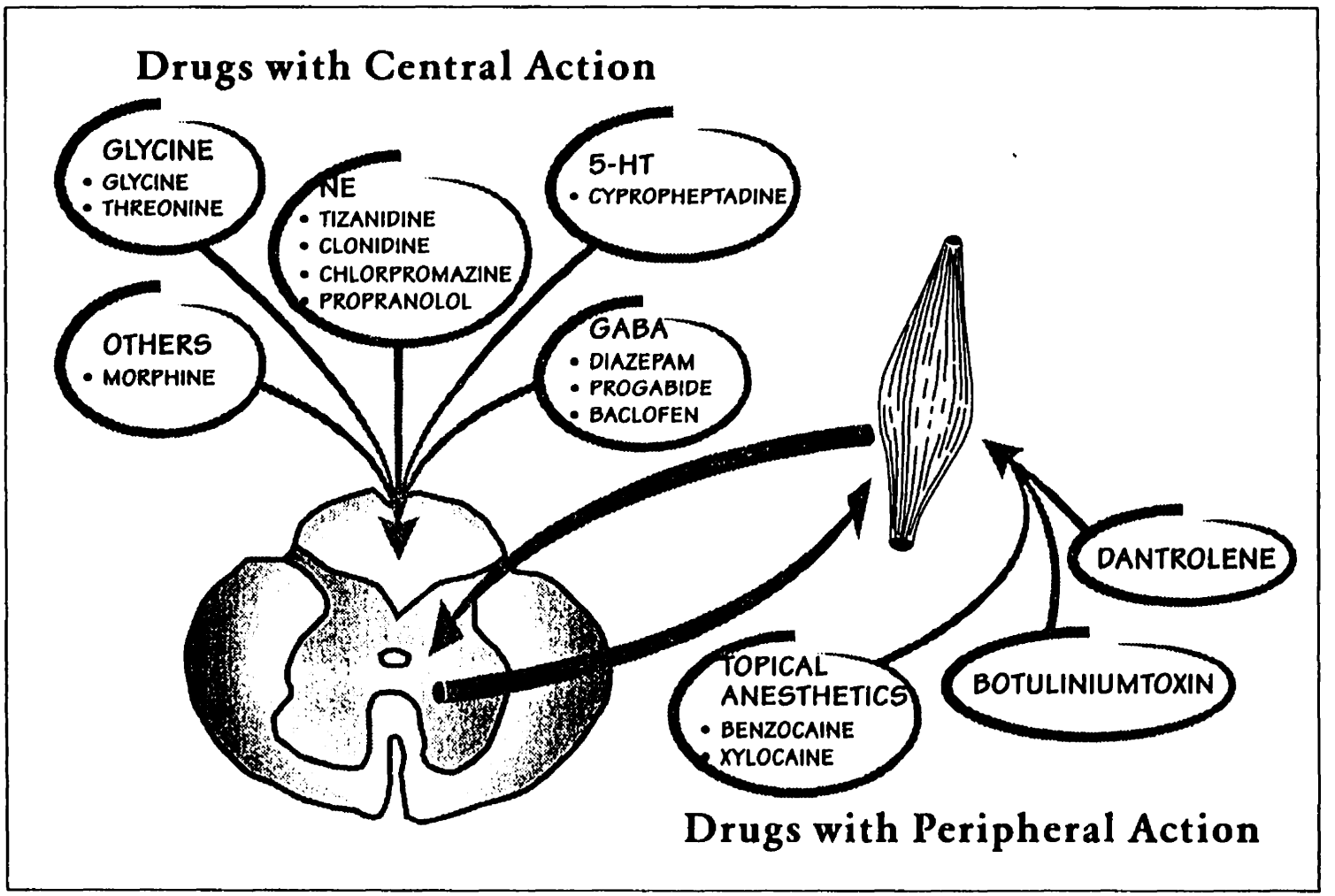
Control of locomotion by spinal neural systems

It has been understood since early in this century that the spinal cord circuits of mammals (principally studied in cats and dogs) are able to generate rhythmic activity. Sherrington

Figure for Review of Literature

A schematic illustration of the sites of action of drugs that have been used to treat spasticity in various neurological disorders, including spinal cord injury. See text for more detailed description of drugs. Abbreviations: 5-HT = 5-hydroxytryptamine = serotonin; NE = norepinephrine; GABA = gamma aminobutyric acid.

Figure for review of literature



(1910) described stimuli that were able to elicit flexion reflexes and crossed extension reflexes, and how these reflex movements in alternation produced a stepping pattern. Although his extensive use of the term "reflex stepping" suggests support for the reflex chaining hypothesis of movement generation (see Grillner 1981 for historical review), Sherrington argued from numerous observations of the maintenance of the rhythm that it must be "central in its seat" (1910, p. 87). Further support for the stepping rhythm's being generated centrally was provided by Brown (1911) who demonstrated in decerebrate cats the presence of alternating muscle activity between antagonistic muscle pairs of the hindlimbs, although input from all muscle and cutaneous afferent nerves had been eliminated. Brown concluded that the "phasing of the acts of progression [i.e. locomotion] is determined neither by the peripheral skin stimuli nor by the self-generated proprioceptive stimuli of the muscles..." (Brown 1911, p. 316).

It is important to note that peripheral afferent input provides an important source of input for ongoing modulation of the locomotor pattern (Engberg & Lundberg 1969, concepts reviewed in Grillner 1981, 1985). In addition, rostral components of the central nervous system (CNS) participate in locomotion particularly, for example, when precise limb placement is required (see reviews: Grillner & Dubuc 1988, Armstrong 1986). However, it is also important to note the implications of the findings of Sherrington and Brown (among others). That is, elements exist within the spinal cord to produce patterns of rhythmic activity among motoneuron pools and these patterns can give rise to locomotion, among other motor behaviours. The usual conceptual term for these rhythmic pattern-generating elements is central pattern generator (CPG). In the neurophysiology and motor control literature, one can also find references to CPGs for respiration and mastication, among other behaviours, but for the present review we will consider primarily the literature regarding CPGs for locomotion. In some of the studies, fictive locomotion was studied rather than actual locomotion. Fictive locomotion may be defined as locomotor-patterned activity recorded in motoneurons or motor nerves in an animal whose limb muscles do not move for reasons of the motor nerves having been sectioned or the muscles rendered motionless by curarization or other chemical treatment.

Depending upon experimental conditions, fictive locomotion can closely resemble real locomotion.

Important understanding of spinal CPGs for locomotion in mammals arose from the study of decerebrate cats. Shik and colleagues (1966) demonstrated that decerebrate cats demonstrate coordinated stepping on a treadmill when a region of the brainstem was electrically stimulated. The stimulation, in what was subsequently termed the mesencephalic locomotor region (MLR) (for reviews, see Grillner 1981, Jordan et al 1992), was not patterned but was simply repetitive pulses. At low intensities of stimulation, the cats displayed a walking pattern. As the stimulation increased, the locomotion pattern sometimes changed to a trot or gallop, depending upon the strength of the stimulation and upon the speed at which the treadmill belt was moving (Shik et al 1966). In the several forms of locomotion, different timing and magnitude of muscle bursts are required, both in absolute terms and in the relation of muscle bursts to one another. The findings thus demonstrate that circuitry within the spinal cord is able to generate complex patterns in response to a simple variation in induced activity in a brainstem region. The study of MLR-induced locomotion in decerebrate preparations has progressed to the point of identifying cell groups and neurotransmitters involved, as well as afferent input to the MLR that may reset the rhythmic output of the spinal CPGs (for review, see Jordan et al 1992). However, for the present review, we will focus on the implications of spinal CPGs for locomotion and the research efforts to activate these circuits following an induced transection of the spinal cord.

It is possible in many species, including lower vertebrates, to trigger locomotion following spinal cord transection (SCT) (Grillner 1981). In mammals, however, locomotion was not seen spontaneously following SCT and pharmacological methods were developed to elicit activity of the CPGs through stimulating receptor sites caudal to the lesion. Forssberg and Grillner (1973) demonstrated that an injection of clonidine to cats with acute SCT led to a regular stepping pattern of the hindlimbs on a moving treadmill belt. For some cats, the clonidine was all that was required for expression of locomotion; for others, additional stimuli such as lifting of the tail were required (Forssberg & Grillner 1973). Barbeau and

Rossignol (1991) replicated these results, showing that locomotion was induced with injection of clonidine in the first 4-7 days post-spinalization. The role of noradrenaline in initiating locomotion in cats with acute SCT was recently given further support by the finding that intrathecal application of noradrenaline was able to induce and maintain a fictive locomotor pattern (Kiehn et al 1992). Thus, we have evidence not only of spinal locomotor-generating networks in the cat, but also that the noradrenergic system plays a role in initiating locomotion.

Indeed, it was not clear for some time whether locomotion could be consistently demonstrated in the cat with SCT without resorting to continuous cutaneous stimulation or pharmacological stimulation. Although cats spinalized as kittens generally regained some independent hindlimb locomotion (Forssberg et al 1980, Goldberger 1986, reviewed in Grillner & Dubuc 1988), cats spinalized as adults were thought not to regain independent locomotion (Eidelberg et al 1980, Goldberger 1986). However, it was subsequently demonstrated that cats spinalized as adults were able to regain independent hindlimb treadmill locomotion that resembled in many respects the pattern seen in normal adult cats if appropriate training was provided (Barbeau & Rossignol 1987, Belanger et al 1988, Lovely et al 1986). The training involved near-daily experience on the treadmill with support of the hindquarters provided by an experimenter holding the cat by its tail. The support provided and the treadmill speed were each adjusted according to the cat's ability to cope with the demands of the task. The cats achieved a stable locomotor pattern within a training period of 3 weeks to 3 months. The locomotor pattern at this time was restricted to treadmill walking and the cats were unable to cope with higher treadmill speeds that would necessitate fast walking, trotting or galloping. However, within the range of speeds of which they were capable, their locomotor patterns resembled those of normal cats (Barbeau & Rossignol 1987). Thus, the locomotor-generating networks of the spinal cord may be expressed in the chronic spinal cat with interactive training.

In view of the findings that either clonidine or training may assist recovery of locomotion in cats with SCT, the combination of clonidine and training might be expected to increase the rate of recovery of locomotor behaviour in acute spinal cats. Recently, it was shown

that daily clonidine injection combined with locomotor training permitted the expression of a locomotor pattern much earlier than it would be expressed with training alone. The cats were trained in conjunction with bolus doses of intraperitoneal or intrathecal clonidine and they achieved independent rhythmic hindlimb stepping on the treadmill without clonidine in 6-11 days (6 days of intrathecal clonidine in 1 cat, 9-11 days intraperitoneal clonidine in 3 cats) (Barbeau et al 1993a).

Noradrenergic drugs have proven thus far to be unique in their association with initiation of locomotion in cats with SCT (Barbeau & Rossignol 1991). However, the finding that chronic spinal cats could be trained to have a stable locomotor pattern permitted the exploration of several pharmacological interventions, including clonidine again, in order to understand the modulation of an established locomotor pattern. When clonidine was administered to chronic spinal cats who had been trained to perform hindlimb treadmill walking, they showed a substantial increase in step cycle duration for the same treadmill speed, along with an increased excursion of the hip, knee and ankle. The electromyographic (EMG) records show a marked increase in burst durations, particularly of the flexor muscles (Barbeau et al 1987a, Rossignol et al 1986). The effects could be partially reversed by yohimbine, a noradrenergic antagonist, confirming that it is through noradrenergic receptors that clonidine exerts a modulatory effect on the locomotor pattern. It is interesting to note that when high doses of clonidine are administered to chronic spinal cats with a well-established locomotor pattern, the result was often a deterioration of locomotor pattern with such deficits as excessive flexion and paw drag. On the other hand, when clonidine was administered to chronic spinal cats that had developed a poor locomotor pattern, the result was an improvement in locomotor pattern (Rossignol et al 1996).

Serotonergic drugs have also been found to have a modulatory effect on the locomotor pattern of chronic spinal cats. Barbeau and Rossignol (1990) found that administration of serotonergic agonists or precursors led to a marked increase in EMG amplitude of both flexors and extensors. Consequently, the cats showed more brisk movements and had a larger angular excursion at the hip, knee and ankle as well as a slightly longer cycle

duration. The cats showed movements during walking that resembled clonus and spasms sometimes seen in SCI subjects. In addition to the effects on the locomotor pattern, the serotonergic drugs led to an increased response to cutaneous stimulation of the paw. Administration of cyproheptadine, a serotonergic antagonist, was able to partly reverse the changes in walking and reflex responses (Barbeau & Rossignol 1990).

In studies of cats with chronic SCT who have been trained to walk on a treadmill, there has been less reported regarding GABAergic drugs. One exception is the finding that the administration of baclofen (intrathecally or intraperitoneally) led to paw drag, reduced weight support and other deficits. Higher doses of baclofen, led to a cessation of the locomotor pattern. The effect could be partly reversed by administering a GABA antagonist (Chau et al 1995). To understand more of the role of GABA in locomotion, we turn to the evidence from locomotion studies in other vertebrates.

Although much has been learned about CPGs for locomotion from the study of cats, some investigators have turned to simpler models to gain a more detailed understanding of the spinal mechanisms of locomotion. The lamprey is of particular interest because it has a relatively simple nervous system and its brainstem and spinal cord can be removed and maintained *in vitro* for up to several days, permitting extended study (reviewed in Grillner 1985, Grillner et al 1991, 1995). The spinal cord of the neonatal rat has also been studied in an *in vitro* preparation (Cazalets et al 1992, 1994, 1996, Kiehn & Kjaerulff 1996). The findings from fictive locomotion in these models have led investigators to propose that the principal neurotransmitters regulating the spinal locomotor networks themselves are glutamate and glycine, and that other neurotransmitters play modulatory roles. In particular, the differences noted for the modulatory effects of GABAergic and serotonergic drugs are important because of the use of these classes of drugs in SCI humans. In the lamprey spinal cord, agonists of $GABA_B$ receptors, including baclofen, produce a reduction in locomotor drive, a depression of burst activity and a modification of intersegmental coordination toward a reduced phase lag between adjacent segments (Tegnér et al 1993). In the neonatal rat spinal cord, GABAergic inputs slow down or inactivate the locomotor pattern (Cazalets et al 1994). Serotonin applied to the lamprey

spinal cord produces a delayed burst termination with longer bursts of activity and a longer phase delay (Harris-Warrick & Cohen 1985, reviewed in Grillner et al 1995). Unlike GABA, however, serotonin has no effect on synaptic transmission from network interneurons (Matsushima & Grillner 1992). In the neonatal rat spinal cord, serotonergic inputs were able to alter the relative timing and burst duration of muscles participating in the locomotor pattern (Cazalets et al 1992, Kiehn & Kjaerulff 1996). The evidence regarding serotonin have prompted recent reviewers to hypothesize that serotonin plays a role across many vertebrate species in facilitating rhythmic motor output (Jacobs & Fornal 1993, Wallis 1994).

Regarding therapy for walking following spinal cord injury in humans, several avenues of exploration are suggested from the evidence concerning the pharmacological control of locomotion in animals. First, the evidence in chronic spinal cats is compelling for the role of noradrenergic agonists such as clonidine in the recovery of locomotion. Second, the evidence in many species for the role of serotonin suggests that serotonergic drugs may be useful in modulating locomotion. However, it is unclear whether to block or "boost" the serotonergic inputs: in some paradigms locomotion was brought about by increasing serotonergic inputs, whereas in spinal cats who has already recovered some walking, the serotonergic antagonist cyproheptadine was able to block the motor behaviours that resembled the signs of spasms and clonus. Third, the evidence in the lamprey and neonatal rat models suggests that GABAergic inputs serve to modulate, but perhaps ultimately to inhibit, locomotion. As with serotonin, the roles of GABAergic drugs in the modulation of walking are not clear. Finally, activation of pattern-generating circuits may be produced most directly through increasing glutamatergic inputs and/or reducing glycinergic inputs. However, there are no immediate clinical possibilities developed in these areas.

Thus, although details of their mechanisms have been partially elucidated recently, concepts of spinal CPGs for locomotion were developed many decades ago. However, concepts of activating spinal CPGs are not commonly used in the rehabilitation of SCI patients (cf. Dobkin 1993). Several reasons may be identified for the lack of application. The first is simply that, until relatively recently, a small proportion of SCI patients

survived long enough for rehabilitation of walking to be considered (Ohry & Ohry-Kossoy 1989). Second, reports of patterned movement in the lower limbs of humans following spinal cord injury were rare and, until recently, incompletely described (for discussion see Eidelberg et al 1981, compare with Bussel et al 1988, Calancie et al 1994). Third, most of the early information about CPGs for locomotion was obtained from acutely spinal-cord-transected animals, and the state of the spinal cord in weeks, months or years following blunt trauma is not entirely comparable to the state following acute transection. Several investigators have pursued animal models of the spinal cord trauma typically sustained by humans in order to fill this gap in our understanding (Anderson & Stokes 1992, Fernandez et al 1991, Wrathall 1992). Fourth, an early investigation of spinal CPGs in primates was unable to demonstrate a locomotor pattern in macaque monkeys with a complete SCT although the methods were similar to those successfully used in cats, raising the possibility that CPG circuitry does not exist in primates (Eidelberg et al 1981). Fifth, the sequence of development of stepping patterns and later walking in human infants has been taken as evidence that the mechanism of locomotor control is different in humans than in other animals. The first three reasons are diminishing in importance as the SCI population changes and as advances in research are made. The fourth and fifth reasons have been more controversial: we first turn to the evidence regarding the existence of CPG-type circuitry in non-human primates and subsequently to the evidence regarding the development of walking in humans.

Eidelberg and colleagues (1981) published a report of attempts to elicit locomotion in macaque monkeys following mid-thoracic spinal cord transection (SCT). Among the monkeys with complete SCT, some were investigated for evidence of fictive locomotion acutely after SCT, and others were investigated for evidence of treadmill locomotion for a minimum of six weeks following SCT. In none of these monkeys was evidence of locomotion seen, although similar pharmacological strategies were employed to those described previously to trigger locomotion in cats with SCT. Among ten monkeys who had received partial SCT, six recovered the ability to support weight and perform treadmill stepping, and two others showed some weak stepping ability although weight

support remained poor. The authors proposed that pattern-generating circuits probably exist in the primate spinal cord but require greater input from rostral structures than are necessary in non-primate mammals. In particular, their analysis of pathology in the monkeys with partial SCT led them to suggest that ventrolateral pathways are most important in recovery of locomotion in monkeys (Eidelberg et al 1981). A subsequent re-analysis of the data obtained from the ten monkeys with partial SCT led to a partial revision of the earlier findings. That is, they concluded that some locomotion is possible in primates following severe incomplete spinal cord lesions and that the correlation of pathological findings with locomotor recovery was weak (Vilensky et al 1992). More recently, a report was published of fictive locomotion following SCT in a different primate species, the marmoset. Hultborn and colleagues (1993) showed evidence of rhythmic alternating activity between the two hindlimbs and between flexors and extensors in individual hindlimbs. The animals had been previously decerebrated, then spinalized at a low thoracic level and paralyzed, with recordings obtained from hindlimb motor nerves. The fictive locomotor pattern was obtained in only two of the three marmosets studied and was seen only following injection of clonidine and sometimes also naloxone. Nonetheless, the findings suggest that spinal locomotor-generating circuitry does indeed exist in primates.

Stepping patterns may be elicited in human infants shortly after birth by touching their feet to a supporting surface. These movements become progressively more difficult to elicit in the first few months, and bipedal walking appears later, generally at approximately one year of age. The disappearance of locomotor-type movements has been interpreted as reflecting an inhibition of spinal CPGs that would otherwise produce quadrupedal locomotion through establishment of functional contacts from rostral systems to spinal cord circuits (Forssberg 1982, 1985, 1986). There is evidence, however, from other studies of human motor behaviour to contradict this hypothesis. Thelen and Fisher (1982) observed marked similarities between neonatal stepping and infant kicking. Thelen (1986) also found that seven-month-old infants are able to produce well-coordinated locomotor patterns when supported over a treadmill. Thelen proposes that the apparent

disappearance of stepping is due to the disparity, at that age, between strength and mass. Thus, there is still good reason to believe that some spinal circuitry for rhythmic, alternating movements exists in humans as it does in other vertebrates.

It will not easily be resolved whether there are any circumstances in which the human spinal cord deprived of all rostral connections would be capable of generating a rhythmic pattern of neural output leading to walking. However, spinal pattern-generating circuits have been demonstrated in all non-primate vertebrate species investigated thus far, and there is evidence that similar circuits exist in primates although they may require greater and/or different inputs for activation than those of other mammals. These required inputs may include projections from rostral areas of the nervous system. Fortunately, the majority of people with spinal cord injury from blunt trauma have anatomically incomplete transections of the cord. As we have seen (above) in the epidemiological data, half or more of new SCI cases have incomplete loss of sensory and/or motor function, thus certainly have only partial transections of the spinal cord. Furthermore, post-mortem findings following cord injury from blunt trauma suggest that many of those with complete loss of sensory and motor function caudal to the lesion have anatomically incomplete injuries of the cord (Kakulas 1988, Bunge 1993). Therefore, in a large and probably increasing proportion of newly injured SCI patients, there exists a possible anatomical substrate for recovery of walking that is not developed into functional walking with current rehabilitation practices.

Although we have not yet identified the optimal method of triggering walking in SCI individuals who cannot walk, or of modulating walking patterns to improve walking in SCI individuals with limited walking, a consideration of the evidence regarding pharmacological control of locomotion in other vertebrates leads us to re-evaluate strategies for control of spasticity because similar neurotransmitter systems are involved. A re-evaluation is particularly important because of the high rates of spasticity treatment, usually pharmacological, for SCI patients. It may be possible to use drugs that both reduce spasticity and seem likely candidates for activating or modulating spinal locomotor circuits. At a minimum, we may avoid using drugs to control spasticity that are likely to

reduce the output of locomotor-generating circuits, although such drugs may still have a role in the management of spasticity in conditions with progressive neurological deterioration precluding walking.

We now turn to the literature regarding the recovery of walking following spinal cord injury. First, we will review what has been found regarding the nature of the walking deficits, and second, we will review the evidence for pharmacological therapy for recovery of walking.

Walking patterns in SCI subjects and effects of drugs

The walking patterns of SCI subjects have been found to deviate from normal walking patterns in several ways. Many of those who recover functional walking continue to walk slowly and may require mechanical aid(s) to walk. These aids may include mechanical orthoses on the legs, and possibly on the lower trunk, and walking aids such as walkers or crutches. Walking can be a laborious process for some of them, and walking aids are sometimes discarded in favour of a wheelchair for reasons of efficiency (Waters & Lunsford 1985, reviewed in Jaeger et al 1989). The latter has been observed particularly in people with low paraplegia who walk with long-leg braces locked at the knees, but the principle holds true for most people who can propel a wheelchair more efficiently than they can walk. Several deviations that are common in walking patterns in SCI subjects are readily measurable with simple instrumentation including reduced velocity, cadence and stride length. Waters and colleagues (1989, 1994) have documented reductions in velocity and cadence as well as increases in oxygen cost and peak axial load through walking aids. In addition, they showed that those changes were related to the extent of neurological impairment in SCI subjects.

Other deviations in the walking pattern of SCI subjects have been measured in the muscle activation patterns and the joint angular excursion patterns. The literature regarding specifically SCI subjects is relatively small, so we will also consider deviations reported in subjects with spasticity and paresis from other neurological disorders. One of the first comprehensive studies of walking pattern in subjects with spasticity and paresis was

reported by Knutsson and Richards (1979). They described three categories of gait deviations in hemiparetic subjects. The first category included subjects who exhibited early activation of the triceps surae soon after foot contact in association with greater plantarflexion and knee flexion than is seen in normal gait. The second category comprised subjects who had low levels of activation across the lower limb muscles recorded, generally with hip and knee flexion and ankle dorsiflexion. In some of these subjects, activation of quadriceps was seen in mid-stance and was termed a "spastic crutch" pattern. This abnormal timing of quadriceps activity corresponds to the period of single-limb stance on that side. In the third category were subjects with frequent episodes of sustained co-activation of antagonist pairs of muscles. Knutsson and Richards were unable to classify four of their twenty-six subjects into the three categories, and all of these subjects had complex abnormal patterns of muscle activation.

It has been proposed that an increase in passive stiffness of muscles is at least partly responsible for disordered motor patterns in gait. Dietz and colleagues (1981) noted that spastic subjects exhibited a pattern of greater EMG activity in the tibialis anterior muscle without a corresponding increase in the amount of dorsiflexion during gait. Their hypothesis of increased passive stiffness of the triceps surae muscle is supported by findings of increased passive stiffness in the triceps surae of the hemiparetic side observed by Sinkjaer and Magnussen (1994) in responses to superimposed stretch during voluntary isometric contraction. However, the subjects described by Dietz and colleagues (1981) did not show as much abnormal EMG timing or angular excursion patterning as some of those reported by Knutsson and Richards (1979) or those reported in the studies described below. An increase in passive stiffness of some muscles, particularly the triceps surae, may well be present but is unlikely to account for all of the gait deviations that have been reported in other studies.

Kerrigan and colleagues (1991) reported deviations in gait pattern in subjects who had sustained cerebrovascular accident or traumatic brain injury and who had been referred to their laboratory because of stiff-legged gait. They reported that most of these subjects had abnormal activation of one or more of the quadriceps muscles in late stance or early swing

phase, and several had abnormal activation of one of the hamstrings muscles in late stance. All of the subjects had less than normal knee flexion in their walking patterns, as that was a criterion for inclusion in the study of stiff-legged gait.

Conrad and colleagues (1985) compared treadmill walking patterns in ten subjects with various disorders having symmetric spasticity and little or no paresis and ten healthy subjects. Walking speed was controlled for all subjects to 0.56 m/s which was presumably considered slow by the normal subjects but allowed better comparison of the timing of gait events between the subject groups. The temporal data show longer step duration and double foot support duration for the normal subjects than have been reported elsewhere but this is presumed due to the low speed. The paraspastic subjects displayed similar mean values for the aforementioned temporal factors as well as for stance-swing ratios and phases of foot contact; however, the variability among paraspastic subjects was considerably higher than the variability among normal subjects. The variability among paraspastic subjects was especially high when they were required to walk without holding a railing. The kinematic data for the knee and ankle show similar findings to those reported by Knutsson and Richards (1979) in their second category (i.e. prolonged flexion). However, Conrad and colleagues (1985) did not ascribe the increased flexion to paresis but rather to a disordered pattern of muscle recruitment. They found that there were frequently bursts of activity in quadriceps and/or hamstrings at the stance-swing transition as well as prolongation of the normal early stance burst of hamstrings into most of the stance phase. The latter EMG findings parallel the findings of Kerrigan and colleagues (1991) in stiff-legged gait despite the differences in kinematic pattern. There was early stance activation of gastrocnemius in several paraspastic subjects and a general flattening of the activation profile such that the muscle was active throughout most of stance phase. The tibialis anterior also showed a disordered activation pattern in being active longer in the first half of stance phase than was seen in the normal subjects. The authors propose that the disordered gait patterns are due to defective central generation of muscle activity and increased influence of peripheral factors such as muscle lengthening on muscle activation patterns (Conrad et al 1985).

Fung and Barbeau (1989) described treadmill walking patterns in eight subjects with spasticity and paresis due to traumatic spinal cord injury in all but one case. In the four subjects who were able to manage only the lowest treadmill speed (0.26 m/s), the EMG profiles were markedly abnormal. In particular, the tibialis anterior and gastrocnemius muscles displayed bursts of activity in phases of the cycle in which they are not normally active. Gastrocnemius was active in early stance in three subjects and in swing in two subjects. Tibialis anterior was active in mid-stance in three subjects. The timing of the hamstrings muscle in one subject showed maximum activity in late stance to early swing, in contrast to the normal pattern of maximum activity in late swing to early stance. The abnormal profiles of muscle activation in these four subjects bear some resemblance to the stiff-legged subjects described by Kerrigan and colleagues (1991) as well as to the subjects with co-activation described by Knutsson and Richards (1979) and those described by Conrad and colleagues (1985). In addition, the activation of gastrocnemius in early stance is similar to the first category of abnormal gait reported by Knutsson and Richards. The four other subjects with spasticity and paresis reported by Fung and Barbeau (1989) exhibited less marked abnormalities in their EMG profiles although all had shifts in the timing within the cycle of maximum EMG activity of at least one muscle recorded.

Among the spastic paretic subjects described by Fung and Barbeau (1989), two of the subjects among those with more abnormal EMG profiles in walking required harness support over the treadmill in order to sustain reciprocal stepping. The harness system supported approximately 40% of their body weight during their treadmill walking trials. The use of such a harness system is based on the observation in training spinalized cats that providing partial body weight support of the hindquarters allowed the cats to express a locomotor pattern that would not otherwise be visible due to loss of equilibrium. The harness designed to provide body weight support (BWS) to human subjects was adapted first from a parachute harness (Barbeau et al 1987b) and later from a mountaineering harness (Norman et al 1995). A study of normal subjects walking with harness support revealed that the pattern of walking was essentially the same with BWS as it was without it, with a few differences in relative stance duration, total angular excursion and EMG

amplitude. There were no differences in cycle time, EMG timing or overall angular excursion profile when speed was controlled across conditions (Finch et al 1991).

Visintin and Barbeau (1989) evaluated the treadmill walking pattern of spastic paretic subjects, all but one of them from spinal cord injury, at full weight-bearing (FWB) and with 40% BWS. During the FWB condition, they found similar abnormalities in EMG timing and angular excursion profiles to those reported in other studies of gait in subjects with spasticity and paresis. Some of these abnormalities were alleviated with 40% BWS. For example, there was commonly less knee flexion during mid-stance and less gastrocnemius activation at foot contact during the sequences at 40% BWS than in those at FWB. Thus, similar to the findings reported for normal subjects (Finch et al 1991), the use of a harness system for partial BWS does not substantially change the walking pattern except possibly to alleviate some deficits. When deviations in EMG timing and angular excursion profiles are found in SCI subjects during harness-supported treadmill walking, they are therefore not likely to be due to the harness system. Indeed, it is important to bear in mind that subjects whose walking ability is studied with the use of a harness system may be incapable of any overground walking and are thus more disabled than most subjects in other studies of spastic paretic gait. That is to say, the harness does not induce most of their deficits, but rather permits an evaluation of walking that would otherwise not be possible, and allows us to observe some of the deficits that may be contributing to their inability to walk overground. The findings that a harness system permits a walking pattern that is approximately normal in cycle time, EMG timing and overall angular excursion profile are important because some of the studies of drug effects on walking in SCI subjects have made use of such a harness system for some subjects.

As noted in a previous section on drug treatments for spasticity, there are a few reports that drugs with peripheral actions have been associated with improvement in walking in some cases. These treatments are, however, limited in their scope because greater and more widespread weakness or reduction in sensory input will doubtless eventually lead to a deterioration in walking. That is not to disparage their clinical usefulness for some cases. Nonetheless, for the purposes of the present review, we will focus on drugs with central

actions and their effects on walking in subjects with spasticity and paresis. The first systematic investigations of the effects of antispastic drug therapy on walking were for baclofen and tizanidine. Corston and colleagues (1981) reported the effects of tizanidine (then known as DS103-282) and baclofen compared with placebo in a double-blind crossover trial in ten subjects with spasticity and paresis from various causes. Maximum total daily doses were 60 mg for baclofen and 24 mg for tizanidine, both near the low end of the range of doses reported in other studies. Knee and ankle angular excursion data were obtained during overground walking. (The use of walking aids was not specified.) They found few significant differences in mean ankle and knee angles at key points of the gait cycle, and all represented a mean change of 1.5° or less. They concluded that only minimal subjective and objective changes occurred in their subjects, with baclofen having a marginally better effect than tizanidine.

Although there have been numerous reports of baclofen's effects in SCI subjects, especially since the intrathecal delivery mode has come into widespread use, it is difficult to be sure of its effects on walking. In many of the reports of intrathecal baclofen's effects, the subjects have been severely disabled and the evaluation of walking was not performed. In other reports, there is anecdotal information about intrathecal baclofen's effects on walking. In some cases, subjects have been reported to have improved at walking (Azouvi et al 1996, Broseta et al 1989, Latash et al 1990, Lazorthes et al 1990, Meythaler et al 1992b, Penn 1988, Saltuari et al 1992). In other cases, subjects have experienced deterioration of walking in response to a bolus dose of intrathecal baclofen (Abel & Smith 1994, Loubser et al 1991, Sahuquillo et al 1991), and many other reports discuss the importance of titrating the dose carefully in subjects with voluntary motor control to avoid reducing the subjects' movement capacity (for review, see Campbell et al 1995).

In contrast to the literature regarding baclofen, there have been some detailed reports of the effects of alpha-adrenergic agonists on walking. Knutsson (1983) reported the effects of tizanidine (total dose 32 mg/day) on the walking pattern of a SCI subject. In the control evaluation, the subject's ankle was plantarflexed at foot contact and moved toward dorsiflexion throughout the cycle, although rarely achieving more than a limited amount of

dorsiflexion. The triceps surae showed activation at foot contact with a prolonged burst throughout stance and co-activation of tibialis anterior. The quadriceps showed little activity at foot contact and a prolonged burst from approximately mid-stance to early swing. In the tizanidine evaluation, the ankle excursion profile remained similar but was shifted into a more dorsiflexed range, with generally a neutral position at foot contact. This change was accompanied by a reduction in triceps surae activity at foot contact and reduced tibialis anterior co-activation through stance phase. The abnormal quadriceps profile remained although it was reduced in amplitude.

Stewart and colleagues (1991) reported the effects of a double-blind, placebo-controlled study of clonidine on the walking pattern of SCI subjects (total dose range: 0.10 to 0.50 mg/day). Six of the nine subjects had clinically complete spinal cord injury and their walking pattern did not change with clonidine. That is to say, they continued to require assistance for moving their legs in a stepping pattern while they were supported by a harness system over the treadmill. The finding that clonidine was unable to trigger walking in complete SCI subjects was recently replicated in two subjects (Dietz et al 1995). Of the three incomplete SCI subjects reported by Stewart and colleagues (1991), one showed a marked improvement in walking ability. The improvement included more normal muscle activation patterns with decreased co-activation, as well as reduced trunk flexion, greater hip extension in late stance, more ankle dorsiflexion through early to mid-stance, and a general reduction in the variability of the walking pattern. The other two subjects were much less disabled at entry to the study and showed minimal changes with clonidine. Bastings and colleagues (1995) also reported a more normal muscle activation pattern during walking in a spastic paretic subject who had been taking clonidine for two weeks (dose: 0.375 mg/day), particularly in improved reciprocal activation of the tibialis anterior and soleus muscles.

Recently, a brief report was published on the effects of an intrathecal injection of a bolus of clonidine on the overground walking pattern of incomplete SCI subjects (Rémy-Neris et al 1996). Within a half-hour of the injection, subjects showed an increase in maximal overground walking speed (using parallel bars) that was maintained or increased over

successive evaluations of walking during the subsequent six hours. Self-selected walking speed remained unchanged even in the presence of change in maximal walking speed, suggesting that short-term clonidine treatment may permit improvement in the walking speed, but does not create it in the absence of additional effort by the subject. The increases in maximal walking speed were associated with increases in step length. During the same time period, the response to flexor reflex stimulation and the resistance to passive movement of the limbs were reduced. In the same subjects, the changes in walking speed, reflexes and resistance to passive movement were insignificant on days when placebo injections were given. The reduction of signs of spasticity concurrent with changes in walking speed suggest that intrathecal clonidine may be a highly useful medication for SCI subjects, although the nature of the relationship among components of spasticity and aspects of walking behaviour will need further investigation.

Cyproheptadine has also been studied for its effect on walking pattern in spastic paretic subjects (Wainberg et al 1986, 1990). Wainberg and colleagues (1990) reported the effects of cyproheptadine (maximum dose 24 mg/day) on spastic paretic subjects. Six SCI subjects participated in a double-blind, placebo-controlled trial. Three of the SCI subjects and one subject with idiopathic spastic paresis then participated in an open trial. The EMG changes seen with cyproheptadine included a decrease in clonic discharge in gastrocnemius in both harness-using and non-harness-using subjects. In addition, the quadriceps EMG burst was more restricted to stance phase. The kinematic changes included a more normal ankle excursion pattern with less plantarflexion at foot contact, as well as a more normal knee excursion in swing. As with clonidine (Stewart et al 1991), the greatest effects were seen in the most disabled subjects of those with partial motor function (Wainberg et al 1990). Frankel grades are not given for these subjects, but the description of them suggests they would be assigned a Frankel C grade.

In summary, practical considerations such as speed and need for assistance seem to determine the extent to which a SCI individual will use walking as a mode of locomotion. Thus, therapeutic interventions must be associated with change in one or more such variables in order to be clinically useful. On the other hand, the nature of deficits in the

quality of the walking pattern of SCI subjects has generally been described in terms of muscle activation patterns and angular excursion patterns. Studies of drug effects over short periods (e.g. several weeks) have generally relied on muscle activation patterns and/or angular excursion patterns to show effects that distinguish successful drug treatment from placebo or unsuccessful treatment. The rationale is that subtle changes in pattern will logically presage changes in speed and other practical considerations if the latter cannot be measured over such a short period. However, if drug therapy or other intervention permits a change in functionality of walking, this would be very important to report. Thus, a study designed to compare effects of different drugs on walking in SCI subjects should examine both the quality of the gait pattern as well as its functionality. To distinguish among the effects of drugs on quality of gait pattern, muscle activation and angular excursion patterns may be examined while speed is controlled. To identify changes in functionality of walking, variables such as speed and need for assistance should also be examined.

Concluding remarks and rationale for present study

There are several reasons to examine more closely the possible means of recovery of walking in the SCI population. It remains a population of mostly young people who, if they survive the acute period post-injury, are likely to live for several decades. It is increasingly becoming a population of people among whom most have partial preservation of sensory and/or motor function and many more probably have anatomically incomplete injuries. New treatments for acute spinal cord injury, as well as many treatments under development, are likely to reduce the damage to the cord, particularly to the white matter tracts passing through the zone of injury, thus improving the reciprocal connections between the spinal cord and more rostral structures. There is thus a large and growing proportion of the SCI population for whom walking is or will be attainable.

Since the development of effective antispastic drugs, a large proportion of SCI patients are prescribed such therapy and some are still recommended for surgical approaches to reduce spasticity. Although antispastic treatment is fairly common across the spectrum of

severity of the spinal cord injury, the rates of antispastic treatment appear to be highest among those with severe partial injuries. The basis for most of the drug and surgical therapies has been the reduction of motor responses attributable to reflexes, either by reducing peripheral inputs or motor output directly, or by reducing reflexes through a central effect. There is little evidence that most clinical efforts to normalize the motor patterns of SCI patients take into account the findings regarding the pharmacology of locomotion in the spinal cord of other animals. The principle of considering simultaneously a drug's effects on spasticity and its effects on walking is increasingly important for drug therapy.

A network of pattern-generating elements exist within the spinal cord of numerous species of animals, almost certainly including humans. The essential neurotransmitters in the locomotor network itself appear to be glutamate and glycine. There are no immediate clinical options for altering transmission in these pathways to improve walking without having highly undesirable side effects. There are more immediately promising avenues of therapy regarding the neurotransmitters that have been shown to have modulatory effects on locomotion. With regard to noradrenaline, the evidence of clonidine's effects on initiating and modulating walking in cats suggests that the clonidine may be useful in the recovery of walking in SCI humans, and this suggestion has been supported by some of the findings in SCI humans. The finding in both cats and humans that it reduces motor responses to cutaneous reflexes makes clonidine additionally useful. However, the finding that clonidine led to a deterioration of a well-established locomotor pattern suggests that dosage should be titrated particularly carefully in subjects who have already recovered some ability to walk. Tizanidine is sufficiently similar to clonidine that it may have the potential for similar effects on walking, although this will require further research. Furthermore, the findings regarding the effects of noradrenergic drugs in locomotion suggest that it is difficult to consider any longer the possibility of using noradrenergic antagonists to reduce spasticity in SCI humans who have some potential to recover walking.

Serotonin has also been shown to have a neuromodulatory role in locomotion, particularly at the level of motor output of spinal pattern-generating systems. In the chronic spinal cat with an established locomotor pattern, an increase in activation of serotonergic receptors was associated with a modulation of locomotion including brisk movements that resembled spasms seen in SCI humans. Cyproheptadine, a serotonergic antagonist, was able to block these effects. Cyproheptadine has also been shown to reduce signs of spasticity and improve walking in human subjects with spasticity and paresis. GABA has also been shown to have a neuromodulatory role in locomotion. Activation of GABA receptors has reduced motor output, in some ways similar to blocking serotonergic receptors, but has in addition been shown to reduce locomotor drive. These findings suggest that GABAergic drugs may be very useful in reducing signs of spasticity, as indeed baclofen has proven to be, but that their effects on walking will require careful investigation.

In conclusion, the present study was designed to address the issue of modulating walking patterns with drugs that may also be used to treat spasticity. The rationale for each of clonidine and cyproheptadine have been developed from studies of the recovery and modulation of locomotion in spinalized animals. Each of them has been studied in human subjects with spasticity and paresis, mostly from spinal cord injury, and each has been shown to have a beneficial effect on walking pattern. Neither drug has been compared to other drugs in their effect on walking and the present study was designed to allow a comparison of effects within a group of SCI subjects who all try each of the drugs. The decision was made to make the study a three-way comparison including baclofen because the latter is the most commonly used and widely supported drug to treat spasticity in patients with spinal lesions, but there has been almost no study of its effect on walking pattern. Furthermore, the findings regarding GABAergic effects on locomotion in animal models of spinal cord injury suggest that we need to examine carefully whether baclofen has an effect on walking. It is hoped that, with a thorough consideration of both clinical considerations and implications of basic research, the potential for walking may be

extended to a larger and larger proportion of people who have sustained spinal cord injury.

MANUSCRIPT #1: A treadmill apparatus and harness support for evaluation and rehabilitation of gait

Abstract

This report describes a treadmill apparatus for the evaluation and rehabilitation of gait in disabled persons. The apparatus incorporates a body weight support system as well as mechanisms to change certain conditions: treadmill belt speed, upward- downward and lateral slopes, and provision of obstacles. The apparatus enables elements of a treadmill walking pattern to be visible in persons for whom gait evaluation or rehabilitation may not otherwise be possible. It also allows for exploration of factors that limit the adaptability of gait in persons after disease or injury by changing the mechanical demand of the locomotor task.

Introduction

A motorized treadmill can be a useful tool in both gait research and gait rehabilitation. Although differences exist between treadmill walking and overground walking, there are similarities as well (Arsenault et al 1986, Murray et al 1985, Strathy et al 1983). Furthermore, the use of a treadmill to evaluate walking has several advantages in certain situations. One such advantage is that it allows for someone to walk continuously within a restrained space. Another advantage is the ability to use a harness support system for partial weight bearing for individuals who have impaired motor function and in whom gait is otherwise difficult to evaluate. An earlier system constructed to provide body weight support over a treadmill was described in a previous study (Barbeau et al 1987b). It can also be advantageous for evaluation or training purposes to have close control of gait speed, which is provided by a motorized treadmill. In addition, many treadmills can provide an uphill walking surface, thus providing a different locomotor task. Unfortunately, some commercially available treadmills have a minimum speed that is faster than the maximum speed of many people with gait disorders. Furthermore, most such treadmills can only provide two of the environmental conditions found in the external world: namely, level and uphill conditions. The treadmill of the earlier system (Barbeau et al 1987b) had these speed constraints and was unable to provide slope conditions. In order to provide steady slow treadmill speeds, and to provide additional environmental demands, a special treadmill apparatus was designed.

The first purpose of this report is to describe a treadmill apparatus that has been designed to allow partial weight bearing with harness support and to provide the conditions of (1) level walking, (2) walking speeds ranging from nearly 0 to fast walking, (3) walking on uphill, downhill, left lateral or right lateral slopes, and (4) stepping over obstacles. The second purpose of this report is to outline some examples of the research results and discuss the potential clinical applications of such a treadmill system.

Methods: system description

The entire treadmill apparatus (without the obstacle delivery apparatus attached) is a steel structure 2.4m long, 2.95m high and 1.2m wide. For clarity of description, these directions will be termed X, Y and Z, respectively. All components of the apparatus were constructed by Industries Auteca Limitée except where indicated otherwise. The body-weight-support system, the treadmill belt movement and the slopes are all controlled by a hydraulic motor which has a power output of 1.64kW.

Treadmill Structure

The essential structural features of the treadmill apparatus are illustrated in the schematic diagram (fig 1). The treadmill belt is a loop of synthetic rubber and nylon 3.75m long which passes around 2 cylinders of 0.31m diameter. The belt is supported as it passes along the top surface between the two cylinders by a steel plate (1.26m x 0.51m). The unit formed by the belt, the two cylinders and the plate is supported by an axle along its width which allows the unit to be adjusted for uphill or downhill walking (maximum 16° (=29%) each direction). This Z-axis axle (fig 1, part 2c) is supported by a C-shaped piece which is in turn supported at three points. At the ends of the C, under the attachments of the Z-axis axle, two support columns are attached to a circle sector of steel that slides over wheels mounted in the treadmill structure's base (fig 1, part 2e). At the middle of the C, the treadmill unit is supported by the X-axis axle (fig 1, part 2d) which allows lateral slopes (maximum 11° (=19%) each direction).

Parallel bars are attached on vertical beams at one end of the apparatus and are adjustable from 0.48m to 0.98m in height from the walking surface. The bars are independent of the slope mechanisms and thus remain at the same height and level when either of the slopes is altered. Additional bars can be mounted perpendicular to the parallel bars for those subjects who prefer such an arrangement (not shown in fig).

Figure 1: schematic diagram of treadmill

① Obstacle delivery apparatus

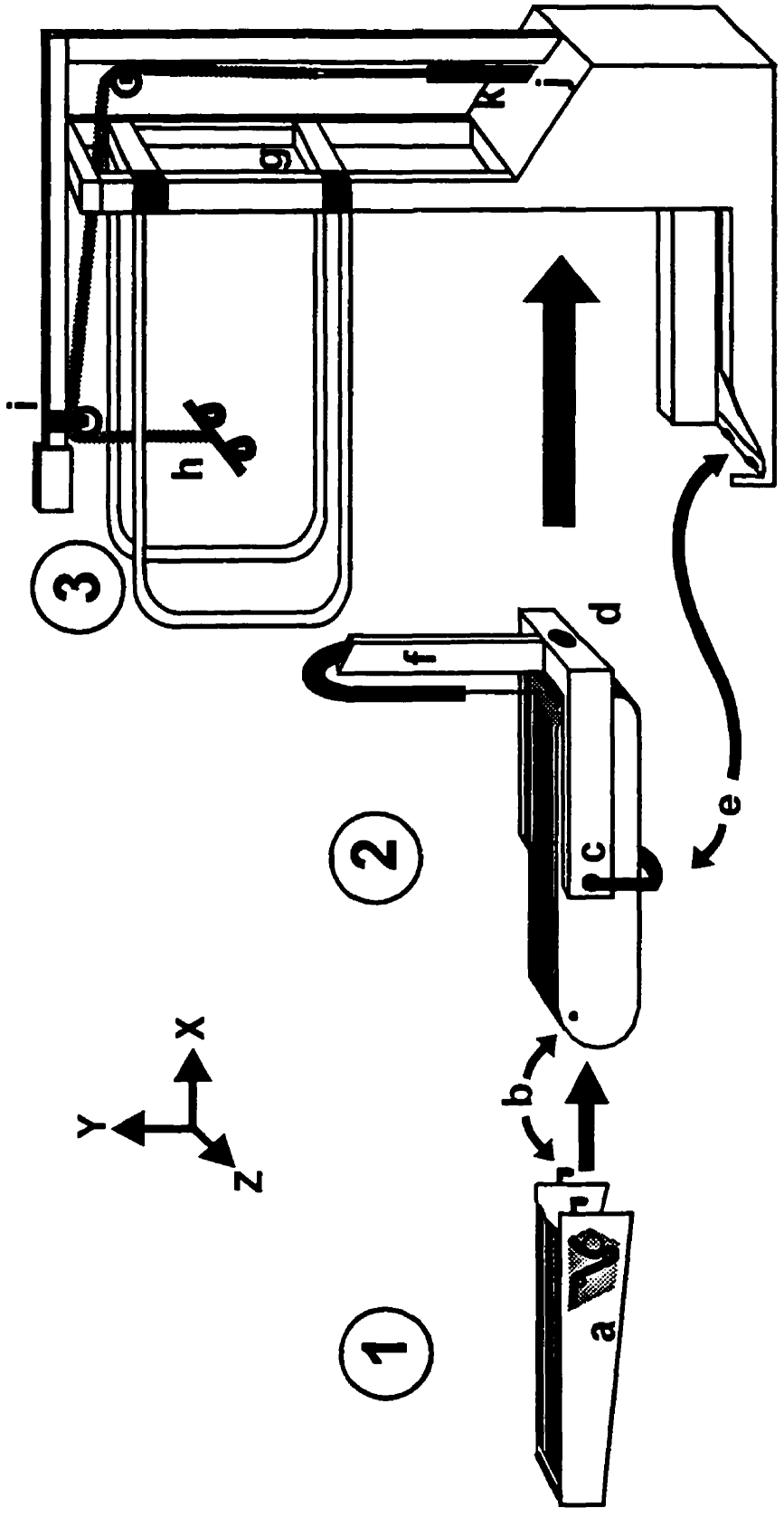
The obstacle delivery apparatus is attached to the rest of the treadmill apparatus only when needed.

② Treadmill and axles / ③ Power unit and support structure

② and ③ are permanently attached to one another, and have been separated in the schematic only to illustrate the slope mechanisms more clearly.

a. Cut-away view to illustrate the internal mechanism of rollers that allows the rubber loops to be driven by the treadmill belt. (See text.)
b. Metal hooks on the obstacle delivery apparatus for attachment to the treadmill.
c. Z-axis axle for uphill and downhill slopes.
d. X-axis axle for lateral slopes, physical connections from ② to ③, as indicated by large arrow.
e. The partial circle under the upright supports rests on two wheels in the support structure (the near horizontal beam of the support structure has been partly cut away for illustration).
f. The upright beam houses electrical and hydraulic connections (further connections to power unit are not illustrated, but they follow the direction indicated by arrow, immediately above X-axle direction).
g. Parallel bars are mounted on a sliding mechanism. (Additional crossbars and detachable reinforcements not illustrated.)
h. Metal bar with clips is the point of attachment for the harness (latter illustrated in Figure 2).
i. Pulley can be fixed in any of 13 positions along the beam.
j. Load cell for the body-weight-support system.
k. Control panel

Figure 1



Speed

The hydraulic motor has two gears for control of treadmill speed. The first gear allows speeds ranging from 0.02m/s to approximately 0.70m/s whereas the second gear allows speeds up to 2.0m/s. A two-gear system was developed in order to have a higher gear ratio and therefore higher torque for low treadmill speeds. Thus, the resistance arising from most subjects on the belt causes little fluctuation in belt speed. The resistance can arise simply from the mass of the subject or from extensor spasms in certain subjects. The motor is constructed such that the treadmill belt can rotate in either direction. Thus, for forward walking, either the right or left side of a subject can be filmed without moving the cameras or the treadmill.

Slopes

Through the axles described earlier, the treadmill walking surface can be inclined along its Z-axis for uphill and downhill conditions or can be inclined along its X-axis for lateral slope conditions. It can be inclined in two directions at once, and it can be put in a mode in which either or both of the slope functions is cyclically fluctuating between limits set by the experimenter.

Obstacle Delivery Apparatus

In one direction of treadmill belt rotation (the positive X-direction in fig 1) the treadmill can be configured for the delivery of obstacles. A treadmill extension can be hooked into place at the end of the treadmill (fig 1, part 2b). It is suitable for lightweight obstacles such as boxes of plastic or foam. The surface of the extension apparatus is 1.65m long and it has loops of rubber around rollers (0.04m diameter) at either end. The centre loop is 0.09m wide and is looped through a series of three rollers underneath the surface. The rollers are mounted on a spring mechanism that ensures that the free side of one roller is in contact with the treadmill belt (fig 1, part 2a). When the extension apparatus is attached to the treadmill, the motion of the main treadmill belt drives the roller to produce movement of the centre loop at the same speed as the treadmill belt. The movement of the center loop causes the other loops to rotate with it.

Thus, an object placed at the end of the obstacle delivery apparatus will be about 2m away from the walking subject, clearly visible, approaching at the same speed as the treadmill belt movement, and will transfer smoothly to the belt. The small gap between the rubber loops and the treadmill belt requires that objects be at least 0.15m in length along the direction of travel of the belt (X-axis).

Body-Weight-Support System

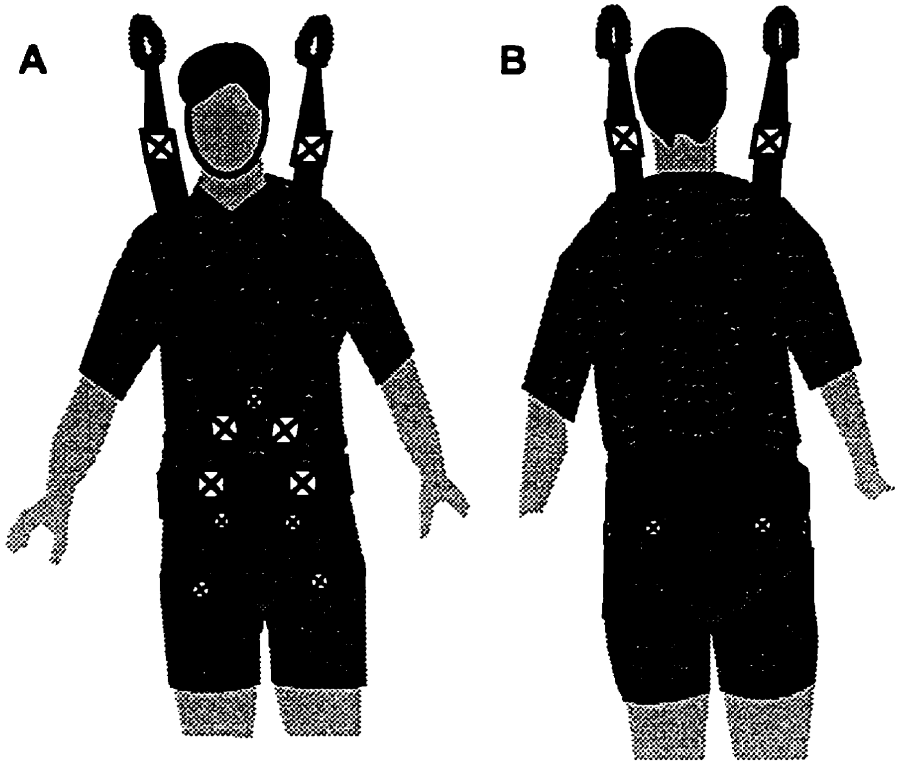
An electrically controlled body-weight-support system has been described previously (Barbeau et al 1987b). Although the principles remain the same, modifications have been made for subject comfort and for compatibility with the upgraded treadmill system. The previous harness successfully discouraged the hip flexion and abduction patterns encouraged by standard parachute and mountaineering harnesses but frequently caused pressure in the perineum which could become intolerable. The present harness (designed by Richard Lefebvre, Kinésiologue) is illustrated in figure 2. It consists of padded straps for each upper thigh, each attached by three vertical straps to a padded pelvis belt from which arise two wide straps to go over the shoulders. The thigh straps and their vertical attachment straps are all secured by buckles which can be detached quickly if required (Fastex SR1). The pelvis belt is secured by two large buckles (Fastex SR2). All buckle locations are indicated schematically in figure 2. Because the pieces are all detachable, the harness can be applied in a sitting position for those subjects who cannot stand while it is applied. The principal movement restriction it causes is a reduction in extremes of hip flexion and extension (Barbeau & Blunt 1991). Because the subjects for whom it is intended are generally not capable of walking with long strides, the hip excursion restriction is usually of no practical significance.

The shoulder straps have buckles identical to those on the pelvis belt (Fastex SR2) and they attach to short straps which hang from a steel bar which descends from a length of automotive seatbelt strapping. The latter strap runs over two pulleys and is attached to a hydraulic cylinder. The pulley closer to the harness can be adjusted in its position along the length of a beam parallel to the treadmill walking surface (i.e. X-direction)

Figure 2: harness

Drawing adapted from video images of person wearing the harness attached to its overhead supports. The person is standing on the treadmill with hands on parallel bars. The locations of quick-release (Fastex) buckles are indicated. A. from the front; B. from the rear.

Figure 2



Fastex SR2 buckle

Fastex SR1 buckle

and 2.25m above it. For any fixed position of the overhead pulley and strap length, a change in the hydraulic cylinder changes the resting height of the harness from the treadmill surface and thus changes the support received by the subject. However, for any harness height, the support received can vary according to the support moments generated by the subject's legs (on the walking surface) and/or arms (on the parallel bars). At the base of the hydraulic cylinder rests a load cell (Intertechnology, Inc.) which is linked to a digital display showing the total mass (kg) supported by the pulley system. The load cell output can also be recorded as an analog signal in conjunction with other analog signals. The load cell has been calibrated to measure up to 227kg and the harness is adequately comfortable for complete suspension of the subject. Thus, a subject using the harness can be suspended completely for a brief period in order to ascertain his/her full weight. Subsequent readings of support in kilograms can then be calculated as a percent of body weight.

Evaluation of Subjects

The treadmill apparatus is used principally for the study of gait patterns and how these patterns change in association with experimental and/or therapeutic interventions. The patient populations of interest in the laboratory are primarily those with spasticity and paresis from central nervous system lesions. For example, spinal-cord-injured (SCI) subjects have been evaluated before, during, and after periods of medication (Norman & Barbeau 1993b) or gait training with the assistance of functional electrical stimulation (Ladouceur et al 1993). Also, SCI subjects have been compared with normal subjects in their ability to adapt their gait pattern to different speeds and slopes of treadmill motion (Pépin & Barbeau 1992).

In evaluation of subjects using the treadmill apparatus, gait pattern is quantified using any or all of the following means: (1) speed and slope of treadmill belt motion; (2) body-weight-support levels; (3) muscle activation patterns from surface electromyography; (4) kinematic measurements from digitization of video recordings; (5) temporal parameters from footswitch signals; and (6) modulation of reflexes.

For the following case reports, gait pattern was evaluated in terms of speed and support levels. In each case, the subject remained seated while the harness was applied. The treadmill was rendered wheelchair accessible by inclining it about the Z-axis axle, such that the left side (as the treadmill is viewed in fig 1) was lowered and the right side raised. A wooden ramp was placed at the lower end, and the subject was wheeled directly on to the treadmill which was then returned to the level position. The subject was assisted to rise to a standing position by the harness system. For the sequences in which a subject required assistance to move his legs, the height of the walking surface from the floor (0.55m) was an advantage in that the person(s) assisting the subject's leg movement remained standing for the task. All procedures were approved by the ethics committee of the university, as well as by the ethics committees of the rehabilitation institutions at which these individuals had previously been inpatients.

Results

The following case reports illustrate how the present apparatus can be used to examine gait pattern for both experimental and rehabilitation purposes. Both case reports describe subjects who were participating in a study of medication effects. Although medications were associated with changes in gait pattern in some cases, it is not the intent of this paper to describe medication effects because they are described elsewhere. Rather, the following cases were selected on the basis of what they illustrate about the locomotor capacity that can be revealed with the use of such a treadmill and support apparatus.

Case Report 1

The subject was a 20-year-old man who had sustained a C4-C5 spinal injury 5 years before evaluation at the laboratory. His neurological level of injury (NLI) was C5 with an impairment (Frankel) grade of C (Ditunno et al 1994). His trunk and lower limb muscles were all grade 2 or less. He could propel himself in a lightweight wheelchair

over level surfaces. He required assistance for all transfers and was unable to stand, even with the assistance of several people.

In the first evaluation, the harness system provided him with support, sometimes to near his total body weight (95kg) when effort or cutaneous stimuli provoked flexor spasms in his lower limbs. He had sufficient use of his arms that he could place his hands on the parallel bars and reduce the tendency for his trunk to swing (i.e. rotation about the Y-axis) when he attempted to move his legs. He did not have sufficient strength to support any more than a small proportion of his weight through his upper limbs.

When the subject was raised to a near-standing position, his posture was typical of what is observed in subjects who require support of more than half of their body weight through the harness system. His hips and knees were flexed and contact with the treadmill belt was made only with the forefoot on each side. Lowering the height of the harness resulted merely in increased flexion at all lower limb joints but no change in the amount of weight registered by the system. Attempts at stepping at low harness levels were unsuccessful because it was prohibitively difficult to swing one foot past the other. By contrast, raising the height of the harness resulted in greater knee extension and ankle plantarflexion and an increase in the amount of weight registered by the transducer. Attempts at stepping were unsuccessful because his feet did not make adequate contact with the treadmill belt. The height of the harness was initially determined by the experimenters and then by the subject as he gained experience with the apparatus.

After the harness height had been stabilized, the treadmill belt was started at its minimal speed, and the subject was assisted in advancing his lower limbs, one at a time. He was able to tolerate a few minutes at a time, with breaks to sit and rest in between. After several sequences, the treadmill speed was increased to 0.05 m/s and the subject succeeded in stepping without assistance.

In one of his subsequent evaluations, his posture remained essentially the same (fig 3) although the body-weight-support system registered lower values of mass supported for

comparable speed (fig 4A). During this evaluation, he could follow treadmill speeds up to 0.20m/s with relative ease and up to 0.25m/s with difficulty (fig 4B). He remained incapable of overground locomotion (fig 4C)

Case Report 2

The subject was a 32-year-old man who had sustained a C4-C5 spinal injury 14 months before evaluation at the laboratory. His NLI was C5 with an impairment grade of C. The strength of his trunk and lower limb muscles was mostly grade 2-3. He could propel himself independently in a lightweight wheelchair over level surfaces, but he required assistance for all transfers. He was able to rise to a standing position with assistance and could maintain standing for brief periods, by leaning with his forearms on a rolling walker equipped with horizontal forearm supports.

The ranges of treadmill speed and percentage of his body weight supported by the apparatus are shown in figures 4D and E. Data from two of his evaluations are illustrated. In the first of those two evaluations, he was initially assisted in advancing his lower limbs, similarly to the subject described in the first case report. He required assistance for most of the evaluation, although he could perform short sequences without assistance. Although his need for assistance was similar to the previous case report, his posture was different. He remained more upright throughout almost all sequences, with his knees and hips generally more extended. During most of stance phase on each side, his entire foot was in contact with the treadmill belt. The lower body weight support values are reflective of his greater ability to maintain stance.

For the latter of the two evaluations, he was able to manage higher treadmill speeds while still using the harness system for partial support. He did not need any assistance to advance either foot as the treadmill belt moved. At this time he was also able to walk on a smooth floor using a rolling walker with forearm supports at a speed of 0.10m/s (fig 4F), although for shorter periods of time than was possible on the treadmill with harness support.

Figure 3: Drawing to illustrate subject's posture

The drawing was traced from a video image of the subject of Case Report 1 during independent stepping with harness support on the treadmill in the later evaluation. For simplicity of illustration, only the harness clips, parallel bars and belt of the treadmill apparatus are shown, and all elements of measuring and recording equipment have been deleted from the image.

Figure 3

Figure 4: Body weight support and speed data for the subjects of the case reports.

A.B,C: Case Report 1. D,E.F: Case Report 2

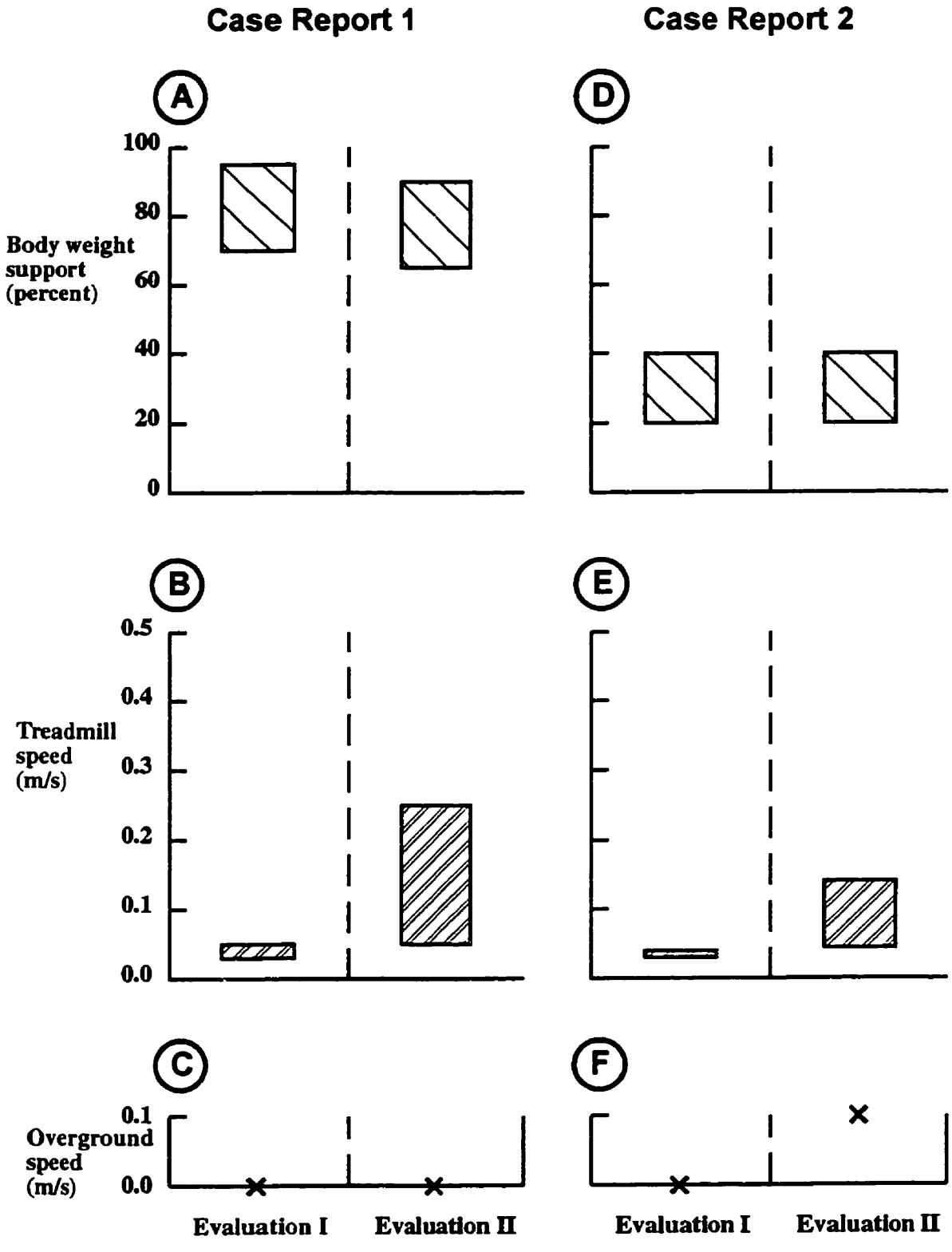
A&D: the range of body weight support used during independent sequences on the treadmill, as a percentage of total body weight.

B&E: the range of treadmill belt speeds for which the subject could continue stepping: a minimum of ten steps in the earlier evaluations; a minimum of twenty steps in the later evaluations.

C: The subject of Case Report 1 remained incapable of overground walking.

F: The subject of Case Report 2 developed the ability to walk overground with a rolling walker with forearm support troughs.

Figure 4


Case Report 1
Case Report 2
A
D
100
80
60
40
20
0
Body weight support (percent)
B
E
0.5
0.4
0.3
0.2
0.1
0.0
Treadmill speed (m/s)
C
F
0.1
0.0
Overground speed (m/s)
Evaluation I
Evaluation II
Evaluation I
Evaluation II

Discussion

The rationale for the development of the present system to provide partial support of body weight during locomotor training arose from results obtained from locomotor training in adult cats spinalized at a low thoracic level (Barbeau & Rossignol 1987). An interactive training approach was developed with the spinal-transected cats, such that each cat received support to reduce the weight borne by the hindquarters during treadmill locomotion. The support was progressively reduced, in accordance with the cat's improving abilities to control the posture and movement of the hindquarters. The principle of providing mechanical support during therapeutic exercise is well-known in rehabilitation (Kisner & Colby 1990, Palmer 1992). However, a means of doing so is often not feasible for severely disabled people in the rehabilitation of gait. The apparatus described here was designed partly to investigate the factors that limit overground gait. It also may provide a means for many of these people to participate in rehabilitation efforts to restore gait.

A conceptual framework for gait rehabilitation requires an understanding of what is required for any locomotor pattern to be successful. Forssberg (1982) identified that the neural control of locomotion must involve the production of a basic locomotor rhythm, support against gravity, propulsion, equilibrium control and adjustment for environmental contraints and goals. Within the literature regarding neural control of locomotion in animal models, the presence of patterned motor output following induced neurological damage is taken as evidence of recovery of function. However, for the rehabilitation of patients with gait disorders, functional recovery encompasses not only patterned motor output but also the ability to use the motor output for tasks or activities the patients wish to accomplish. Patla (1991a,b) proposed a model in which the core locomotor patterns of rhythmic activation of the limbs form only the most rudimentary elements of locomotion. In this model, components of propulsion, equilibrium control and adaptations for contexts and goals, and minimization of both tissue stress and energy expenditure form layers on top of the core locomotor pattern. It

is only when all of the components are adequately addressed that rehabilitation may enable patients to achieve functional recovery of gait as a mode of locomotion.

Neurological trauma or disease can disrupt an individual's capacity for gait as a mode of locomotion. The disruption can arise from deficits in several or all of the components. In searching to improve rehabilitation strategies, it is important to characterize the nature and extent of the gait deficit in neurological populations, and to provide a basis for evaluating interventions such as medications, surgery, physical therapy techniques or application of orthotic devices. It is also important to develop strategies for rehabilitation which allow for the possibility of adjusting the level of difficulty of the components of locomotion, thus providing locomotor tasks which appropriately challenge the individual. It was for these purposes that the present apparatus was designed and constructed.

The Use of the Apparatus to Describe and Quantify Gait Pattern

Previous versions of the harness system have proven to be a valuable tool in the evaluation of other rehabilitation interventions. Pharmacological interventions, for example, appear to produce the most striking changes in very disabled subjects (Fung et al 1990, Stewart et al 1991, Wainberg et al 1990). According to the model described earlier, such subjects are struggling to express the core locomotor pattern and have little or no capacity for other components of successful locomotion. The use of the harness and treadmill apparatus has important implications for comparison of data with data obtained in other contexts. For most situations in which harness support was provided as part of the evaluation method, the subjects would have been incapable of participating in a gait evaluation without such support, as was certainly the situation for the subjects of the case reports. Presumably, the constraints of support against gravity and equilibrium control were lessened by the harness support, and the constraint of propulsion was lessened by the motorized treadmill, such that some elements of walking were expressed in a way that was not otherwise possible. Such subjects are substantially

more disabled than most of those upon which most of the literature of spastic paretic gait is based (Conrad et al 1985, Dietz et al 1981, Fung & Barbeau 1989).

The expression of some elements of a walking pattern may not constitute functional recovery as it is generally defined by the rehabilitation community, since the pattern can only be observed in the context provided by the harness and the treadmill. However, it is worthwhile to explore locomotion at this level since a core locomotor pattern is a necessary component of any future functional recovery. As the fields of neuroscience and biomedical engineering contribute potential treatment options for neurological disorders, tools will be needed to assist in identifying whether such treatment options alter the potential for recovery of locomotion.

Similarly, adaptation to treadmill walking conditions, such as obstacles, speed changes or slope changes, are slightly different from the adaptations needed in functional overground walking. However, for individuals who have already recovered some capacity for walking, such closely controlled tasks may reveal changes in their capacity for adaptation in response to experimental or therapeutic interventions. For therapeutic interventions, it can be hypothesized that changes would be manifest in such controlled conditions before they would translate into global functional improvements, although research is required to address these issues.

The gait of individuals with neurological dysfunction differs from normal gait in several ways. Differences have been reported in muscle activity patterns and joint angle patterns (Conrad et al 1985, Dietz et al 1981, Fung & Barbeau 1989). However, there exist differences in the gait patterns of normal subjects when they are required to walk at speeds other than self-selected comfortable walking speeds (Nilsson et al 1985, Shiavi et al 1987). For those individuals who can only walk slowly, it is important to determine the extent to which the abnormalities seen in their locomotor patterns are a result rather than a cause of the slow speed. Preliminary results have shown, for example, that longer stance and cycle durations and smaller angular excursions were observed in normal subjects walking at speeds similar to those of spinal-cord-injured subjects (0.1 to

0.3m/s) (Pépin & Barbeau 1992). Thus, some characteristics of the gait of disabled subjects are readily evident in normal subjects who are walking at comparable speeds. Since the speed of travel is an important determinant of whether walking is preferred to wheelchair use, it is important to understand the factors which limit a person's speed. In addition, because many environments include nonlevel surfaces, it is important to understand the factors which limit a person's ability to manage such environments. Research into the above issues will be useful for the ongoing development of concepts and tools for gait rehabilitation.

The Use of the Apparatus for Rehabilitation

When neurological trauma or disease disrupts an individual's ability to walk, gait rehabilitation efforts can be constrained. If an individual is incapable of independent equilibrium control while stepping, and cannot safely be guarded by the rehabilitation staff, attempts to walk are generally not feasible. The subjects described in the case reports provide examples of how locomotor evaluation and training could be made feasible by a harness and slow-speed treadmill. Although the case reports of this report describe individuals with severe gait deficits, systems with body weight support have been used with individuals of a wide range of disability from a number of different causes. Thus, it is envisaged that the apparatus described here may prove to be very useful for gait rehabilitation. However, the topic has been well reviewed already. The effects of using a harness system in locomotor rehabilitation are discussed in previous publications from this laboratory (Barbeau & Blunt 1991, Barbeau & Fung 1992, Barbeau et al 1987b, 1993b, Finch et al 1991, Fung et al 1990, Visintin & Barbeau 1989, 1994) and elsewhere (Dobkin et al 1992, Harburn et al 1993, Hesse et al 1994, Ratliff et al 1993, Wernig & Müller 1992). In particular, a recent review (Barbeau & Rossignol 1994) describes the development of the rationale for gait training with harness support, and provides a list of other research groups using similar or identical devices.

Apart from the harness support system, the changes in environmental demand that are possible with the present apparatus may allow for other treadmill-based strategies for gait rehabilitation. The differences in treadmill and overground contexts regarding the demands for propulsion and equilibrium control will doubtless limit the transfer of treadmill locomotor skills to functional overground locomotion. Nonetheless, altering the mechanical demands of the task alters the output required of the locomotor system, thus creating opportunities for training of specific components of gait. Further research is required to determine to what degree gait rehabilitation can be facilitated when such opportunities are created.

The treadmill apparatus was developed to provide conditions for locomotor evaluation and rehabilitation that are frequently impractical in an indoor overground situation and unavailable with many commercially available treadmills. It enables the study of locomotor pattern in people with severe gait disability, as well as the study of gait adaptability in normal and disabled subjects. It may thus assist both in the evaluation of interventions to improve gait pattern and in the process of rehabilitating patients with gait disabilities.

MANUSCRIPT #2: Effects of drugs on walking in SCI subjects

INTRODUCTION

It has long been understood that recovery from spinal cord injury is better when there has been partial preservation of neurological function caudal to the lesion. This is commonly referred to as an incomplete injury, indicating that the loss of sensory and/or motor function has been incomplete. The proportion of injuries that result in incomplete loss of motor and/or sensory function now form the majority of SCI cases in many countries (Dixon et al 1993, Knutsdottir 1993, Shingu et al 1995, Silberstein & Rabinovich 1995, Stover & Fine 1986, Tator et al 1993). The proportion of newly injured SCI patients who are capable of reciprocal gait by discharge from rehabilitation is approximately one-quarter to one-third (Knutsdottir 1993, Stover & Fine 1986) and may rise with improved management of acute injuries. However, many patients who are able to walk need assistive devices and do not use walking as their primary mode of locomotion.

A spinal cord injury interrupts or alters the function of systems that project to the spinal cord and thus changes the inputs to the neurons of the cord. There are alterations in voluntary movement patterns including walking patterns and, in many cases, signs of spasticity. In spinal cord injury and in other neurological disorders the clinical signs of abnormal gait and spasticity are often associated with one another, although the nature of their relationship is unclear (Conrad et al 1985, Dietz et al 1981, Fung & Barbeau 1989, Kerrigan et al 1991, Knutsson & Richards 1979). Spasticity has been found to be generally of greater severity among SCI patients with incomplete loss of motor and/or sensory function than among SCI patients with complete loss of sensory and motor function (Little et al 1989). It is thus unsurprising that antispastic treatment is frequently recommended to patients with incomplete injuries. In recent studies of standard clinical care, it was found that over one-third of SCI patients received medical or surgical treatment for spasticity within rehabilitation, including over half of those with severe incomplete injuries (Maynard et al 1990, 1995). Thus, therapeutic strategies for controlling spasticity are often applied to patients for whom substantial recovery of voluntary control, including walking, may be possible. Many of the therapeutic strategies

are directed at neurotransmitter systems that have been shown in animal models to play a role in the modulation of locomotion. It is thus important to examine these strategies in light of findings regarding locomotor control. For the purposes of this study, we have focussed on the roles of noradrenaline, serotonin and gamma amino-butyric acid (GABA) in the motor systems of the spinal cord.

Noradrenergic projections to the spinal cord have been implicated in the regulation of reflexes as well as the control of locomotion (Fung et al 1991, Jankowska 1992, Marshall 1983, Rossignol & Dubuc 1994). The effects of noradrenergic drugs on locomotion have been extensively studied in cats with low spinal transections. Following spinal transection at T13, an adult cat will regain the ability to perform hindlimb walking on a motorized treadmill with daily training for 1-3 months (Barbeau & Rossignol 1987, Lovely et al 1986). Similar recovery can be achieved in cats over a period of just 6-11 days after spinal cord transection with daily injections of clonidine, a noradrenergic alpha-2 agonist, in conjunction with daily locomotor training (Barbeau et al 1993a).

Serotonergic neurons projecting to the spinal cord have been hypothesized to be one of facilitating motor output, particularly rhythmic motor output (Jacobs & Fornal 1993, Wallis 1994). Specifically, they have been implicated in modulating the amplitude of reflexes (reviewed in Anderson 1983) as well as the amplitude of motor neuron or muscle activity during locomotion (reviewed in Grillner & Dubuc 1988). Barbeau and Rossignol (1990) reported the results of administering 5-hydroxytryptophan (the precursor of serotonin) or serotonergic agonists to the adult chronic spinal cat with a well-established treadmill locomotor pattern. The serotonergic activation resulted in increased electromyographic (EMG) amplitude of both flexor and extensor muscles in a pattern suggestive of human spasticity. These effects were blocked by cyproheptadine, a serotonergic antagonist, and the previous locomotor pattern was partially restored.

GABAergic neurons intrinsic to the spinal cord are located throughout the spinal grey matter, with a high concentration in the dorsal horn where GABAergic neurons play a role in presynaptic inhibition (Barber & McLaughlin 1980, Nistri 1983). The success of

baclofen, a $GABA_B$ agonist, in treating spasticity is attributed to its capacity to reduce the transmission from sensory afferents to motor neurons (Davidoff 1985, Milanov 1992). Baclofen has been in clinical use for spasticity in SCI patients for over twenty years in many countries (Birkmayer 1971, Feldman et al 1980) and has increasingly been used in an intrathecal application to reduce the central side effects (Broseta et al 1989, Lazorthes et al 1990, Penn et al 1989). Baclofen treatment, oral or intrathecal, has been associated with improvements in some aspects of motor function (Azouvi et al 1996, Parke et al 1989) but whether it has specific effects on recovery of walking has received little attention. In parallel with baclofen's use as an antispastic medication in SCI patients, GABAergic drugs have been studied for their effects on locomotion in animal models. As an inhibitory transmitter, it was hypothesized to play a role in inhibiting locomotion at a spinal level (Grillner & Dubuc 1988). More recent research has suggested that that hypothesis should be refined to reflect roles for spinal GABAergic neurons not only in "braking" locomotion (Cazalets et al 1994) but also in modulating the motor output of an ongoing locomotor pattern (Cazalets et al 1994, Tegner et al 1993). In light of these results, it is important to evaluate baclofen's effects on walking following spinal cord injury.

In contrast to baclofen, clonidine and cyproheptadine have both been studied for their effects on walking pattern in SCI humans (Fung et al 1990, Stewart et al 1991, Wainberg et al 1990). Clonidine did not affect locomotion in SCI subjects with functionally complete injuries (Dietz et al 1995, Stewart et al 1991), but was associated with improved walking in SCI subjects with incomplete injuries (Stewart et al 1991). Cyproheptadine has been associated with an improvement in walking pattern in subjects with spastic paresis (Fung et al 1990, Wainberg et al 1990). However, clonidine and cyproheptadine have not been compared to each other, and neither has been compared to baclofen. SCI subjects more than one year post-injury were recruited to participate, based on the observation that the majority of neurological recovery has taken place by the end of the first year (Ditunno et al 1992, Piepmeier & Jenkins 1988).

The purpose of the present study, therefore, was to compare the effects of clonidine, cyproheptadine and baclofen on the walking pattern of SCI subjects who had sustained incomplete lesions more than one year before entering the study. A repeated single-subject design was selected in order to maximize the number of subjects in whom the effects of the drugs could be studied. Preliminary results of this study have been reported previously (Norman & Barbeau 1992, 1993a,b).

METHODS:

Subjects:

Twelve subjects were recruited to participate in the study based on the following inclusion criteria: incomplete spinal cord injury more than 1 year previously, with motor sparing and hyperreflexia; no other neurological diagnoses or major orthopedic diagnoses; and not taking any drug known or suspected to alter muscle tone, other than the drugs under study. All subjects recruited had previously been inpatients in rehabilitation institutions within Québec and were currently living in the community, independently or with family. They ranged in age from 19 to 35 years old and were free of other medical problems except as noted (see Table 1, parts A, B, & C). All had sustained a traumatic spinal cord injury 1-6 years prior to entering the study. All subjects were men; none of the women referred to the laboratory during the study recruitment period were eligible to participate. Almost all subjects had some experience with drug for spasticity, and six were on current oral drug for spasticity at entry to the study. A description of the subjects can be found in Table 1, parts A, B & C. The information in Table 1, except for the determination of the neurological level of injury (NLI), was obtained from the referring physician as well as from the initial meeting with each subject to determine eligibility and willingness to participate. The NLI was obtained from a focussed clinical evaluation conducted by the experimenters based on the reported level of injury.

All subjects confirmed in writing their informed consent to participate to the protocol which had been approved by the ethics committee of the School of Physical &

TABLE 1: Subject characteristics

Part A: Subjects with no overground reciprocal locomotion[1]

	Age at entry	Years since injury at entry	NLI[2]	Activity when injury occurred	Primary mode of locomotion at entry	Able to rise from sitting?	Able to maintain standing?	Able to walk on level surfaces?	Past experience with antispastic drugs	Drugs at entry
H 1	32	1.2	C5	diving	manual wheelchair	with help	with forearm-support walker	No	baclofen	baclofen
H 2	27	1.6	T11	all-terrain vehicle riding	manual wheelchair	with walker	with walker	Limited swing-to with walker	diazepam, baclofen	none
H 3	33	2.3	C6	diving	manual wheelchair	No	No	No	clonidine, baclofen, diazepam	none
H 4	23	5.3	C5	diving	manual wheelchair	No	No	No	clonidine, baclofen, diazepam	none

Part B: Subjects with limited overground reciprocal locomotion[1]

W 1	29	3.5	C6	fall	manual wheelchair	with walker	with walker	with walker, supervision	none[3]	none[3]
W 2	35	4.8	C6	fall	manual wheelchair	with walker	with walker	with walker	baclofen	baclofen[4]
P 1	30	2.3	C4	diving	manual or motorized[5] wheelchair	with super-vision	with supervision	with supervision, assistance[5]	baclofen	none
C 1	19	1.1	C7	riding in car	manual wheelchair	with forearm crutches	with forearm crutches	with forearm crutches	baclofen	baclofen
C 2	28	1.3	C6	diving	manual wheelchair	with forearm crutches	with forearm crutches	with forearm crutches	clonidine	clonidine
C 3	22	2.2	T12	motor cycle riding	manual wheelchair	with forearm crutches	with forearm crutches	with forearm crutches	baclofen	baclofen

Part C: Subjects with functional overground reciprocal locomotion[1]

S 1	20	4.9	C6	riding in car	walking with 1 cane	without help or aid	without help or aid	without help or aid	baclofen[6]	baclofen
S 2	19	2.8	C6	diving	walking, 1 forearm crutch	without help or aid	without help or aid	with forearm crutch	baclofen	none

FOOTNOTES FOR TABLE 1

1. Within the Frankel classification (Frankel et al 1969), all of the subjects in Part A would be considered in category C: sparing of both sensory and motor function where the motor function is not functional. They were not evaluated according to the newer A.S.I.A./I.M.S.O.P. protocol, but would almost certainly all be in category C. All of the subjects in Part B would be considered in category D on the Frankel classification: sparing of both sensory and motor function where the motor function is functional. If they had been evaluated using the A.S.I.A./I.M.S.O.P. protocol, some would likely be in category C and others in category D. The subjects in Part C would be considered in category D of the Frankel classification, and almost certainly in category D of the A.S.I.A./I.M.S.O.P. protocol.
2. N.L.I. = neurological level of injury (A.S.I.A./I.M.S.O.P. [1992] classification system; lowest spinal level with normal sensory and motor function).
3. W1 had a lifelong history of epilepsy and was taking anticonvulsant medication (divalproex sodium: Epival®). He had also been taking an antidepressant (imipramine: Tofranil®) since his injury. Both medications were held at stable dosage throughout his participation in the study.
4. W2 had previously been prescribed an anxiolytic (bromazepam: Lectopam®) which he took occasionally to help him sleep. He reported that his pattern of usage of this medication did not change over the course of his participation in the study.
5. P1 generally used a motorized wheelchair when outdoors, and a manual wheelchair when indoors. He propelled the latter with his feet. Due to his high level of injury, he was unable to make use of walking aids and required supervision or standby assistance for overground walking.
6. S1 had received surgical treatments for spasticity in addition to the medication. He had undergone partial neurectomies for right gastrocnemius spasticity and right adductor spasticity. The surgeries took place 21 months and nine months, respectively, prior to entry to the study.

Occupational Therapy of McGill University as well as by the ethics committees of the rehabilitation institutions from which subjects were referred.

Four of the twelve subjects were incapable of walking at entry to the study and required the support of the harness system (Barbeau et al 1987b, Norman et al 1995) in order to be evaluated. They have been coded H1, H2, H3 and H4. The other eight subjects were able to walk at entry to the study, although six of those eight continued to use a wheelchair as the primary mode of locomotion. These six subjects have been coded according to the aids used for walking overground: W indicates that a four-point walker was used; P indicates that another person was required for minimal assistance; and C indicates that two forearm crutches were used. These six subjects were coded W1, W2, P1, C1, C2, and C3. The other two subjects had discontinued any use of a wheelchair and have been coded S1 and S2 because both used a single aid (cane or crutch) for walking overground.

Drugs:

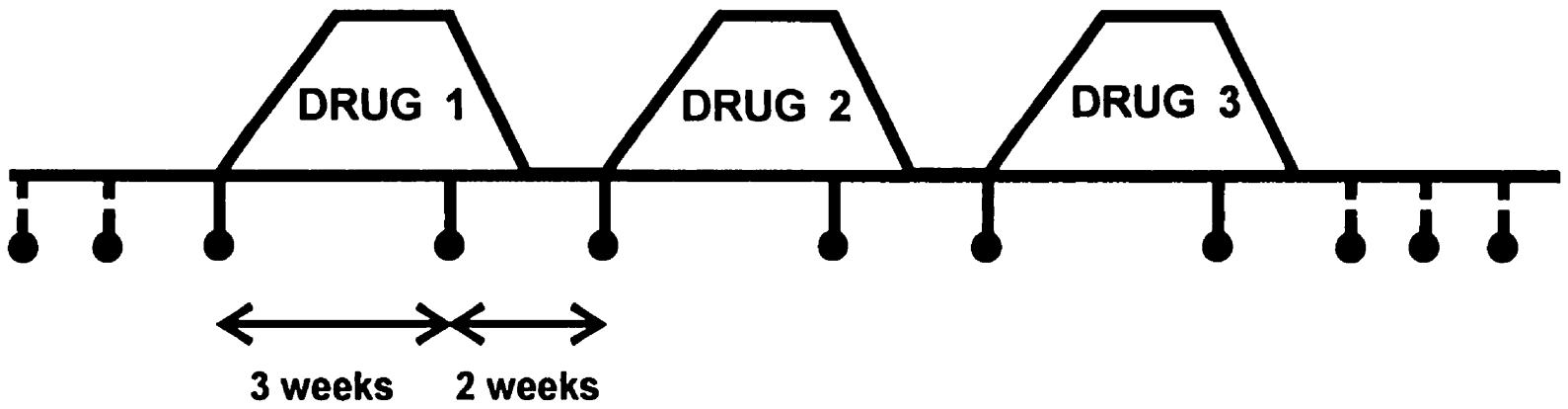
All drugs were preparations to be taken orally. A schematic version of the protocol can be found in Figure 1. For each drug there was a stage of increasing dosage followed by a stage of stable dosage, then a stage of tapering dosage, and finally a stage of no drug (washout). The stages of increasing dosage and stable dosage together took three weeks, and the tapering stage and washout together took two weeks. The maximum total daily doses were as follows: baclofen 80 mg, clonidine 0.25 mg, and cyproheptadine 24 mg. Table 2 shows the order of drugs and sequence of evaluations conducted for each subject in the study. Reasons for missing data sets are listed in the footnotes of Table 2. Since clonidine can have a hypotensive effect, each subject was followed by a nurse in his home community during the period of increasing dosage of clonidine for side effects that might suggest hypotension. Measurement of blood pressure was performed where symptoms indicated.

Since this was intended as an exploratory study, decisions regarding drug dosage, order and duration of drug period were taken with the intent of maximizing the subjects' motivation to continue in the study and minimizing the time that it took for each subject to

FIGURE 1

The study protocol is illustrated. Evaluations were conducted at the beginning of each drug period, at the end of a period of stable dosage, and at the end of each washout. Additional evaluations before any drugs, and after all three drugs were conducted where possible. The time from starting a drug to the evaluation for that drug was at least three weeks, and the washout period was at least two weeks.

Figure 1



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● EVALUATION

TABLE 2: Drug order and locomotor evaluations conducted

Each evaluation represented by (●)

	Pre-drugs	First drug [1]	Washout	Second drug [1]	Washout	Third drug [1]	Other(s)
H1		baclofen [2] (80) ●●	●	cyproheptadine (16) ●	●	clonidine (0.25) ●	
H2	●	cyproheptadine (18) ●	●	baclofen (80) ●	●	clonidine (0.25) ●	●[3]●
H3	●	clonidine (0.25) ●	●●	cyproheptadine[4]			
H4	●●●●	clonidine (0.25) ●	●	cyproheptadine[5]	●	baclofen[5]	●
W1	●	cyproheptadine (16) ●	●	baclofen (80) ●	●	clonidine (0.25) ●	
W2		baclofen[2] (0.20) ●	●●	clonidine (0.20) ●	●	cyproheptadine (16) ●	●
P1	●●●[6]●	clonidine (0.25) ●	●	cyproheptadine (24) ●	●	baclofen[5]	●
C1		baclofen[2] (40) ●	●	clonidine (0.25) ●	●	cyproheptadine (24) ●	
C2		clonidine[2] (0.30) ●●	●	cyproheptadine (16) ●	●	baclofen[5]	●
C3		baclofen[2] (50) ●●●	●	cyproheptadine (16) ●	●	clonidine (0.20) ●	●
S1		baclofen[2] (40) ●●	●	cyproheptadine (16) ●	●	clonidine (0.25) ●	
S2	●	clonidine (0.25) ●	●	cyproheptadine[5]	●[7]		

Footnotes

1. The dosage listed is the stable dosage achieved (in total mg daily) and maintained for at least eight days prior to evaluation.
2. The subject was taking this drug at the time of referral and entry to the study.
3. The final two evaluations for this subject were conducted while he was taking a combination of cyproheptadine and clonidine.
4. The subject dropped out at this point for personal reasons.
5. The subject could not continue this drug long enough for an evaluation, due to adverse effects.
6. The subject was taking a mixture of medications during the fourth evaluation.
7. The subject dropped out at this point, unwilling to risk further adverse effects.

complete the study. Thus, subjects who were referred while taking one of the three study drugs were evaluated first without any change in their drug [H1, W2, C1, C3, S1: baclofen; C2: clonidine]. It was intended that there be an equal number of subjects following each of the possible drug orders. However, the arrangements for the community nurse during the clonidine period sometimes altered the timing and thus the order of drugs. Further, neither the subjects nor the experimenters were blind to the drug order. A double-blind design would have necessitated an infrastructure that was not present in the context of this exploratory study. In view of the fact that these drugs are visibly different (produced by different pharmaceutical companies), and the fact that subjects resided as much as 500 km from the laboratory, attempts to keep the subjects blind to drug identity was deemed prohibitively difficult. To minimize the effect of expectation, the consent form listed the possible effects of the drugs together. Thus, the subjects were not led to expect specific effects from any one drug.

Evaluations:

Timing of evaluations

The initial protocol specified six evaluations: each subject was to be evaluated at entry, after the period of stable dosage of each drug, and after each washout period (See Figure 1). After several subjects had completed the protocol, it was decided that multiple baseline evaluations were more important than previously assumed. Whenever feasible, this was implemented for subsequent subjects.

Procedure for evaluations

At each visit to the laboratory, subjects were interviewed for their impressions of beneficial effects and side effects associated with the current drug or washout. Although they were not blind to drug identity, it was felt that their impressions would be useful for future clinical prescriptions of these drugs.

The instrumented gait evaluation yielded electromyography (EMG) and kinematic data. One side of the subject was evaluated in greater detail. It was the side that seemed to be more spastic during a clinical evaluation on the first visit. If both sides were essentially

equal, the choice was based on practical considerations (e.g. the usual location of a urine collection bag, if present).

Surface electrodes were taped to the skin over selected lower limb muscles: ipsilateral tibialis anterior (TA); soleus (SO); medial belly of gastrocnemius (GA); vastus lateralis (VL); and the medial hamstrings (MH). Each electrode set had a built-in differential pre-amplifier with a gain of 10. The signals were fed via a common cable to amplifiers in which there was a bandpass filter (10-1000 Hz) and a notch filter (60 Hz) and a further gain. The signals were then recorded on FM tape (Ampex Precision Magnetic Tape) using a Honeywell 101 tape recorder. The total gain of the EMG signals on tape was 1000 or 2000 X, depending on the amplitude of the signal.

Pressure-sensitive switches were taped to the soles of the subject's shoes: under the centre of the heel, under the head of the fifth metatarsal, and under the great toe. The foot-switch records were recorded on FM tape simultaneously with the EMG signals.

Kinematic data was obtained from digitization of video records. For visualization of joint positions, reflective markers were attached to the subject over the following anatomical landmarks: head of the fifth metatarsal, lateral aspect of the calcaneus, lateral malleolus, lateral joint line of the knee, greater trochanter of the femur, and greater tubercle of the humerus. Where markers were attached to a shoe or other clothing, every effort was made to reduce any movement of the article with respect to the anatomical landmark. For all markers, the background was made as dull and dark as possible to reduce error in subsequent digitizing. Angular data are reported using standard biomechanical convention: hip at 0° represents neutral position (0° flexion, 0° extension), knee at 0° represents full extension, ankle at 0° represents neutral position (shank and foot segments at 90° to one another).

Four of the twelve subjects (H1-4) required harness support to be evaluated on the treadmill. The harness has been more fully described elsewhere (Norman et al 1995). Essentially, it allows for the support of body weight via a pulley system over the treadmill.

Although it has been recognized that support levels above 50% of body weight are associated with abnormalities in walking patterns (Finch et al 1991), some subjects were incapable of producing any reciprocal leg movements unless greater support was provided. Support provided by the harness varied from 10 to 90% body weight support (BWS) depending upon the subject's posture and the extent to which he gained support from the parallel bars on the treadmill. Treadmill belt motion was started from a full stop, and increased slowly until the subject reported that it was at a comfortable speed for him to continue stepping. Subjects were assisted, if appropriate, in the movement of their legs by experimenters positioned adjacent to the treadmill. The assistance continued in the first evaluation for as long as the subject required it, and was repeated at any subsequent evaluation in which the subject was unable to perform stepping independently. If the subject was capable of taking steps independently, the treadmill belt movement was set at the speed at which he could best sustain continuous stepping. If the subject required assistance, the treadmill speed was generally 0.03 to 0.05m/s, depending upon the experimenters' difficulty in moving the subjects' legs. In such situations, however, a subject's maximal treadmill speed was classified as 0.0m/s, reflecting his inability to follow the treadmill unassisted. During each trial the treadmill belt movement continued at a steady speed for as long as the subject could continue to follow it without needing a rest, generally several minutes at a time. After several trials at the reported comfortable speed, trials were attempted at higher speeds if the subject could tolerate them. Before each successive trial, the harness height and attachments were adjusted if necessary for optimal performance of stepping.

For the other eight subjects, treadmill walking was evaluated without harness support. All subjects used the parallel bars on the treadmill as much as they wished. As with the harness-using subjects, the treadmill belt motion was started from a full stop, and increased slowly. For the slower subjects, a comfortable speed was reached quickly, generally ≤ 0.10m/s. For the subjects whose walking capacity was less limited, a longer habituation period of several minutes' duration was provided, so that subsequent decisions regarding comfortable and maximal speeds could be more certain.

For all subjects at each of their evaluations, trials were performed at the reported comfortable speed, as well as at higher speeds. When the comfortable speed at a given evaluation was higher than at previous evaluations, trials were performed at previously comfortable speeds to allow better comparison across evaluations. The subject rested between trials and the speed was re-increased slowly for re-starting the walking trials. For the trials at speeds exceeding the comfortable speed, the treadmill speed was increased by intervals of 0.05m/s (for slower subjects) or 0.10m/s until the subject was unable to complete a trial at a given speed, or he indicated that he did not wish to continue. A subject's maximal treadmill speed was considered the highest speed at which he could manage to continue walking for at least 10 gait cycles or one minute, whichever was shorter.

RESULTS

Completion of the protocol by subjects

The drug order and the timing of locomotion evaluations conducted for each subject are shown schematically in Table 2. Seven of the twelve subjects were able to undergo evaluations in association with all of the three drugs. For four of the other five subjects, adverse effects prevented the completion of one or more of the evaluations for drug effects. The adverse effects are summarized in Table 3, and will be discussed in a subsequent section. One subject (H3) dropped out for personal reasons.

Subjects with no overground reciprocal locomotion

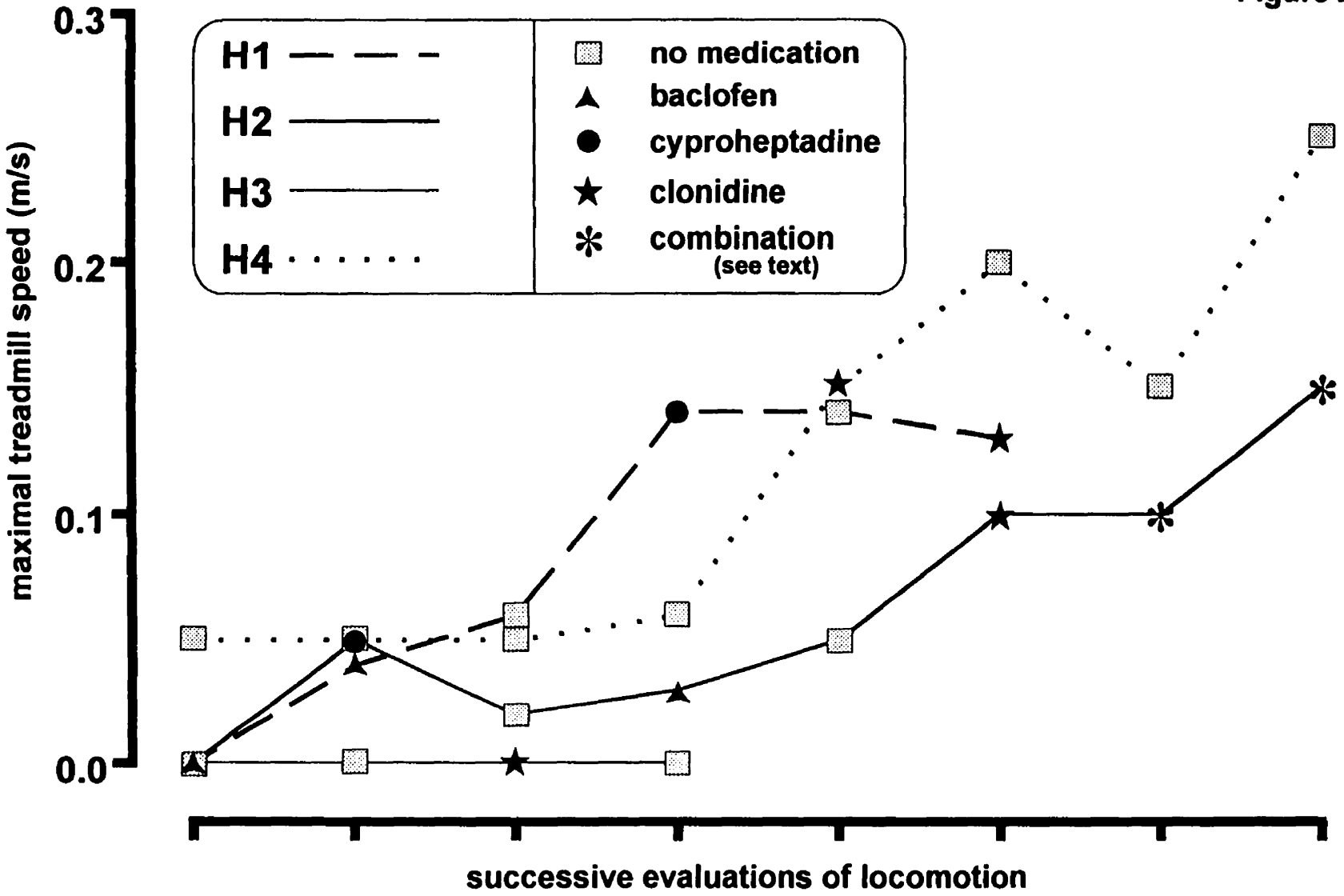
The most striking results were seen in the subjects who were incapable of overground locomotion at entry to the study. For all four of the subjects in this group, their changes in maximal treadmill speed (MTS) are shown in Figure 2.

All four of the subjects required manual assistance during every step cycle in their first attempt at harness-supported stepping on the treadmill. By the end of his initial evaluation, H1 had performed a few unassisted step cycles but never two consecutive cycles. H2 and H3 remained dependent for continuous manual assistance throughout their respective initial evaluations. For H1, H2 and H3, their initial MTS was therefore rated as 0.0m/s. In

FIGURE 2

Maximal treadmill speed (MTS) over successive evaluations of locomotion in H1, H2, H3 and H4. In all cases, the MTS was evaluated at whatever harness support level was optimal for highest speed. The initial zero values for H1 and H2 reflect the fact that neither could sustain stepping without manual assistance for at least one minute. Zero values for all evaluations for H3 reflect the fact that he was unable at any evaluation to perform stepping without manual assistance. (See Results section text for further explanation of how MTS was ascertained.) Drug status is reflected by the symbols as indicated in the legend. Each subject's values are linked by a different type of line (see legend).

Figure 2


0.3
0.2
0.1
0.0
maximal treadmill speed (m/s)
H1
H2
H3
H4
no medication
baclofen
cyproheptadine
clonidine
combination
(see text)
successive evaluations of locomotion

contrast to the other three subjects, H4 was able, after several sequences with assistance, to perform stepping without manual assistance in his first evaluation at a MTS of 0.05m/s. The MTS for H1 and H2 were rated above zero when they were able to perform at least one sequence with multiple consecutive step cycles without manual assistance, resulting in at least one minute of unassisted stepping. H3 continued to require manual assistance for every cycle throughout all of his evaluations.

Over successive evaluations, three subjects (H1, H2 and H4) showed changes in MTS. Cyproheptadine was associated with an increase in MTS from the immediately previous evaluation in two subjects (H1: 0.06m/s to 0.14m/s; H2: 0.00m/s to 0.05m/s). Clonidine was associated with an increase in two subjects (H2: 0.05m/s to 0.10m/s; H4: 0.06m/s to 0.15m/s). Overall, two subjects in this group - H1 and H2 - entered the study with a MTS of zero and were able to complete drug periods for all three of the study drugs and their results are described in detail. Although there were changes in MTS across evaluations for these subjects, the following comparisons of kinematic and electromyographic (EMG) data are of sequences at similar speeds.

H1 was referred to the study while taking baclofen and was evaluated twice with no change in drug status. He was subsequently evaluated during a washout period, a cyproheptadine period, another washout period and a clonidine period. Figures 3 and 4 show kinematic data and Figure 5 shows temporal and EMG data from evaluations of H1. Some kinematic data have been illustrated in both of Figures 3 and 4 to enable inter-drug comparisons and drug-washout comparisons. The stance-swing transition is indicated in these illustrations and is later in the cycle than is usually reported for human gait but represents an average value for H1. It is important to note that there is a generally inverse relationship between the gait speed and the proportion of the cycle taken up by stance phase (Pépin & Barbeau 1992).

During the first of H1's evaluations for baclofen, he required manual assistance from the experimenters to move his legs on the treadmill, despite the high degree of support provided by the harness (20-40% BWS) and his use of the parallel bars. A few times, he

was able to perform a single cycle without manual assistance from the experimenters at 0.04m/s. The hip, knee and ankle excursions from a single unassisted cycle are illustrated in solid lines in Figure 3A, B and C, and again in the bold lines of Figure 4A, B and C. The data are also shown in Figure 3D, illustrating the flexed posture that results from the flexion. Both the hip and the knee remain in flexion throughout the cycle, as is often seen when the BWS level is in or above the range of 20-40%. In addition, his ankle remains in dorsiflexion throughout most of stance, also reflecting the flexed posture (see Figure 3C), until he attempts to bring his foot forward resulting in large oscillations of ankle dorsiflexion and plantarflexion (see arrows in Figure 3C and 3D).

The changes seen in the kinematic records are paralleled by changes seen in the EMG records seen in Figure 5A. These EMG signals were obtained in the second baclofen evaluation (technical problems prevented the collection of valid EMG signals from the first baclofen evaluation). H1 still required manual assistance for most stepping, the longest interval of unassisted stepping being five cycles at 0.04m/s. The temporal data from these five cycles are shown in Figure 5A immediately above the raw EMG signals from three of these cycles. There was irregular activity of soleus throughout the cycle, with clonus in the third cycle accompanied by coactivation of tibialis anterior. The vastus lateralis record shows little cyclical modulation in activity. The medial hamstrings record shows some cyclical modulation with activity primarily during single limb support, in contrast to the usual pattern of activity for the hamstrings in which it is active mostly in double limb support prior to single limb support on the ipsilateral side (Winter 1983).

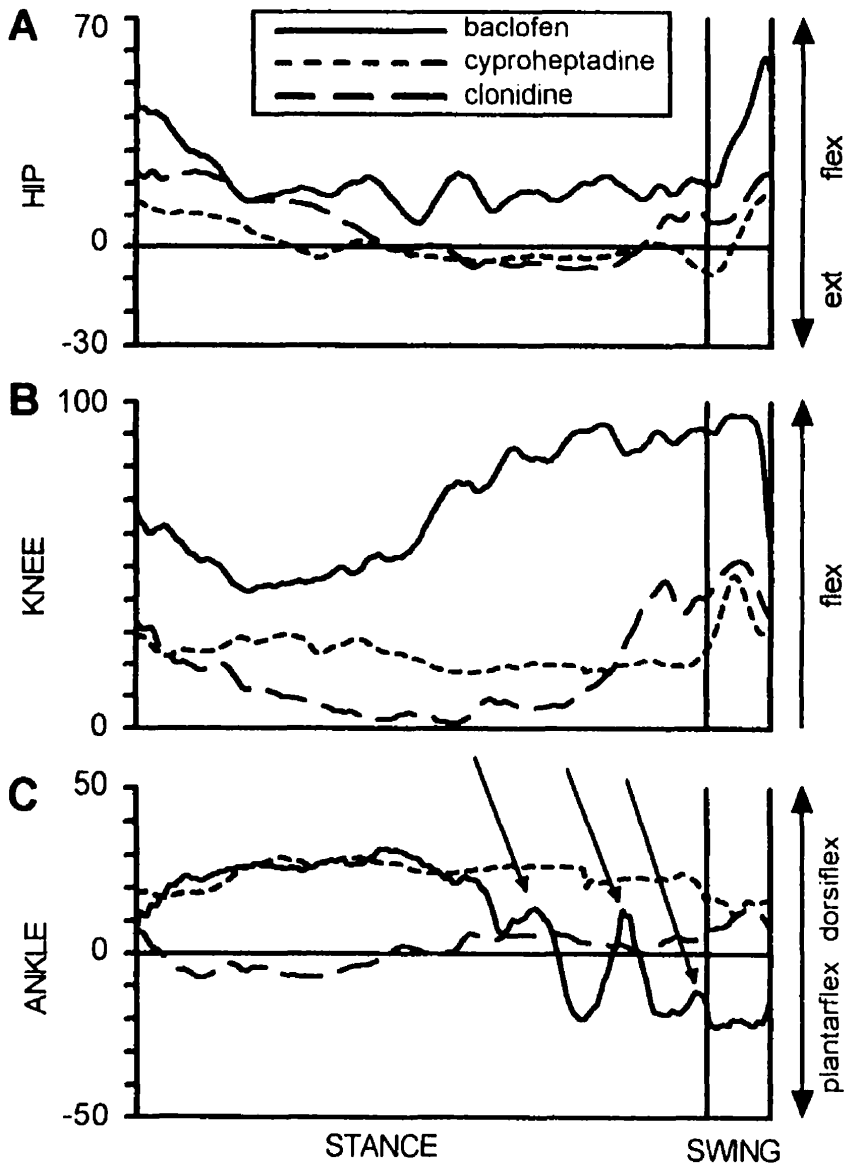
In the post-baclofen washout evaluation, H1 showed minor changes in kinematic patterns (Figure 4A-C) although more striking changes in EMG patterns (Figure 5B). Furthermore, he had become capable of nine consecutive unassisted cycles, up from five in the previous evaluation. The hip and ankle excursions show little change except for the lesser degree of hip flexion (Figure 4A) and of ankle plantarflexion (Figure 4C) in the latter part of the cycle. There is dorsiflexion in swing phase of the washout evaluation that was not present in the evaluation for baclofen. The knee excursions are also similar in profile, although there was a substantial reduction in flexion in late stance and swing in the

FIGURE 3

Normalized angular excursions of the left hip (A), knee (B) and ankle (C) of H1during treadmill stepping with harness support for each of baclofen (solid line), cyproheptadine (dotted line) and clonidine (dashed line) evaluations. In order to align the stance-swing transition from all displayed cycles, a stance proportion of 90% was chosen as being representative of all cycles. Arrows in the ankle excursion (C) in late stance phase indicate oscillations occurring during efforts to initiate forward movement of the foot, accomplished in the swing phase by dragging it along the treadmill belt.

Stick figure representations reconstructed from kinematic data for cycles during treadmill stepping in baclofen (D), cyproheptadine (E) and clonidine (F) evaluations. For stance phase, every tenth sample is illustrated such that between successive stick figures the time lapse is 0.167 seconds; for swing phase, every fifth sample is illustrated such that between successive stick figures the time lapse is 0.083 seconds. For the composite representations, the horizontal distance between stick figures was increased by .002 m over the distance actually moved (in direction of horizontal arrow) in order to improve the visibility of posture and joint angle excursions. The false impression of a long step length and a large backward translation of the trunk during stance is an artifact and should be disregarded. The diagonal arrows in D correspond to the ankle oscillations indicated by diagonal arrows in C.

Figure 3


A
70
HIP
0
-30
baclofen
cyproheptadine
clonidine
flex
ext
B
100
KNEE
0
flex
C
50
ANKLE
0
-50
dorsiflex
plantarflex
STANCE
SWING

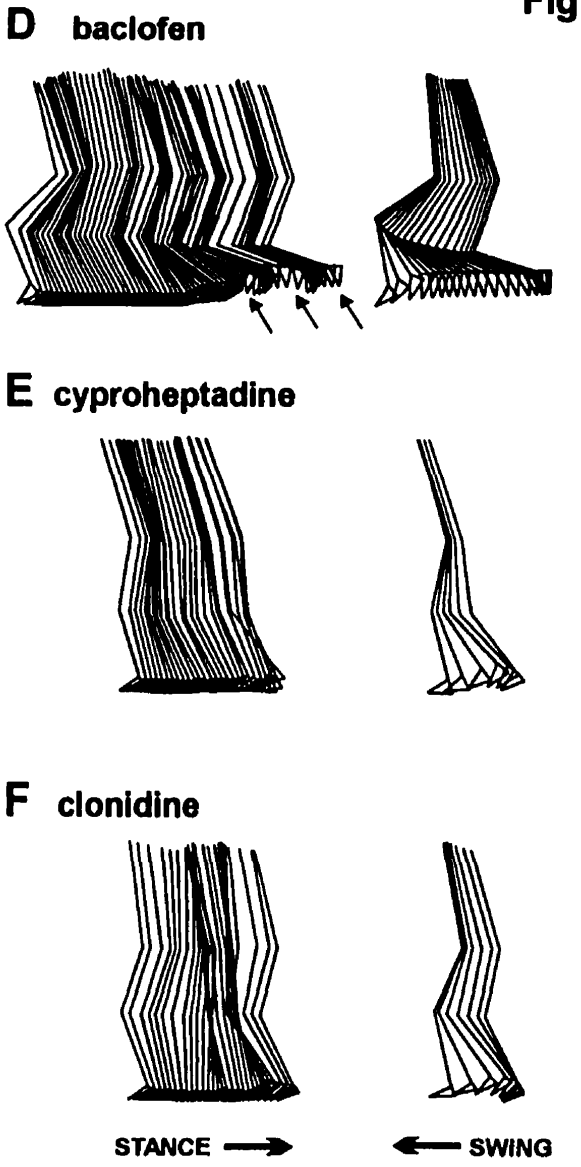

D baclofen
E cyproheptadine
F clonidine
STANCE
SWING

FIGURE 4

Normalized angular excursions of the left hip, knee and ankle of H1 during treadmill stepping with harness support: comparison of drug (bold line) and washout (fine line) evaluations. The stance-swing transition is normalized to 90% of cycle duration, representative of all cycles.

Left column: hip (A), knee (B) and ankle (C) angular excursions for baclofen (bold solid line) and the subsequent washout (fine solid line) evaluation.

Right column: hip (D), knee (E) and ankle (F) angular excursions for cyproheptadine (bold dotted line) and the subsequent washout (fine dotted line) evaluation.

Figure 4

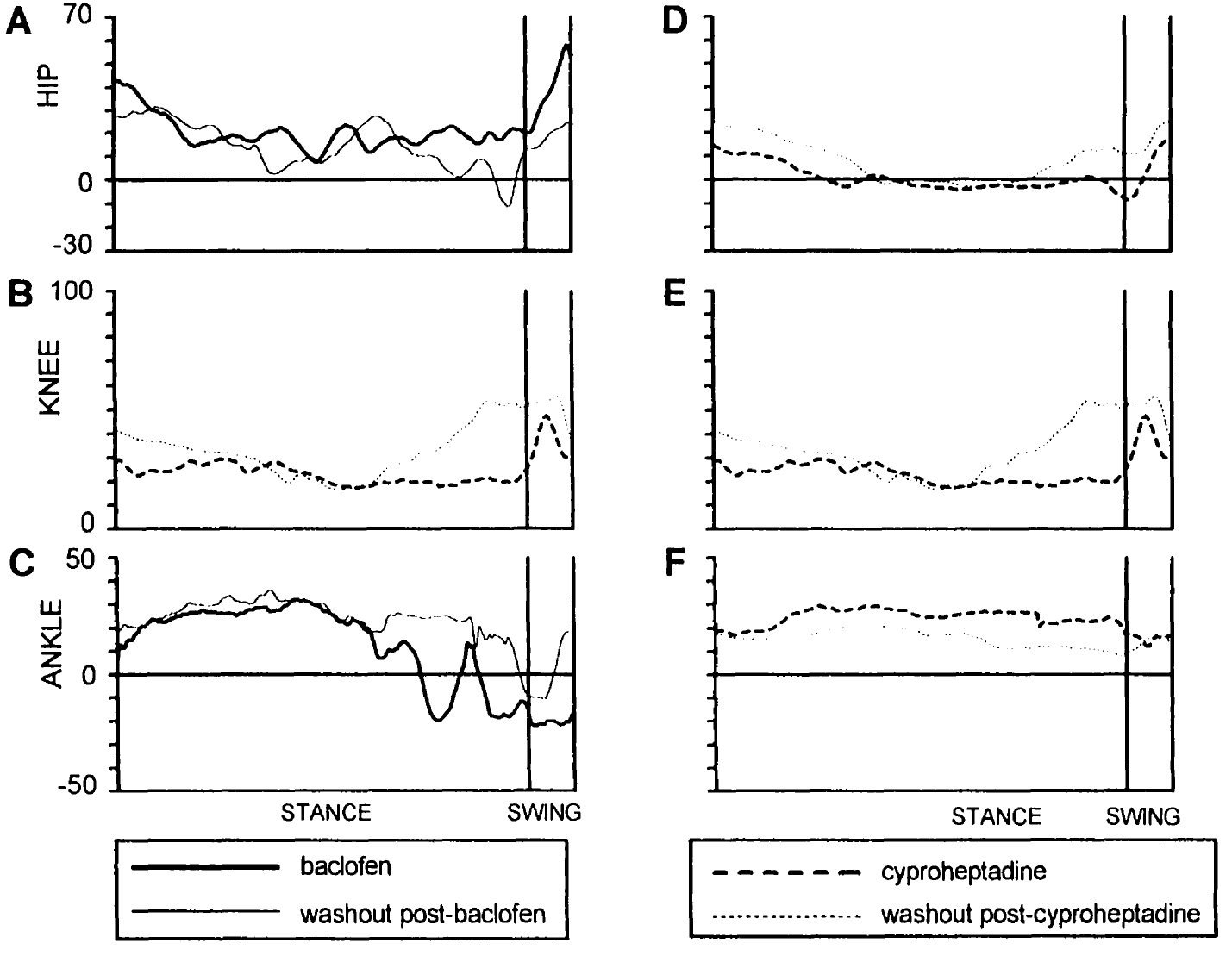

A
70
HIP
0
-30
B
100
KNEE
0
C
50
ANKLE
0
-50
STANCE
SWING
baclofen
washout post-baclofen
D
E
F
STANCE
SWING
cyproheptadine
washout post-cyproheptadine

FIGURE 5

Average temporal durations and raw EMG signals from the left leg of H1 during treadmill stepping with harness support. Bars at top of each of A, B, C & D indicate temporal data. EMG records are shown below each set of bars.

Upper unshaded bar indicates cycle duration, middle shaded bar indicates stance duration and lower unshaded bar indicates swing duration. Error bars indicate standard deviation, the number of cycles averaged is in parentheses.

TA = tibialis anterior; SO = soleus; VL = vastus lateralis; MH = medial hamstrings. Vertical lines indicate cycle boundaries (beginning of ipsilateral foot contact with the treadmill belt). Upward arrows at baseline indicate stance-swing transition.

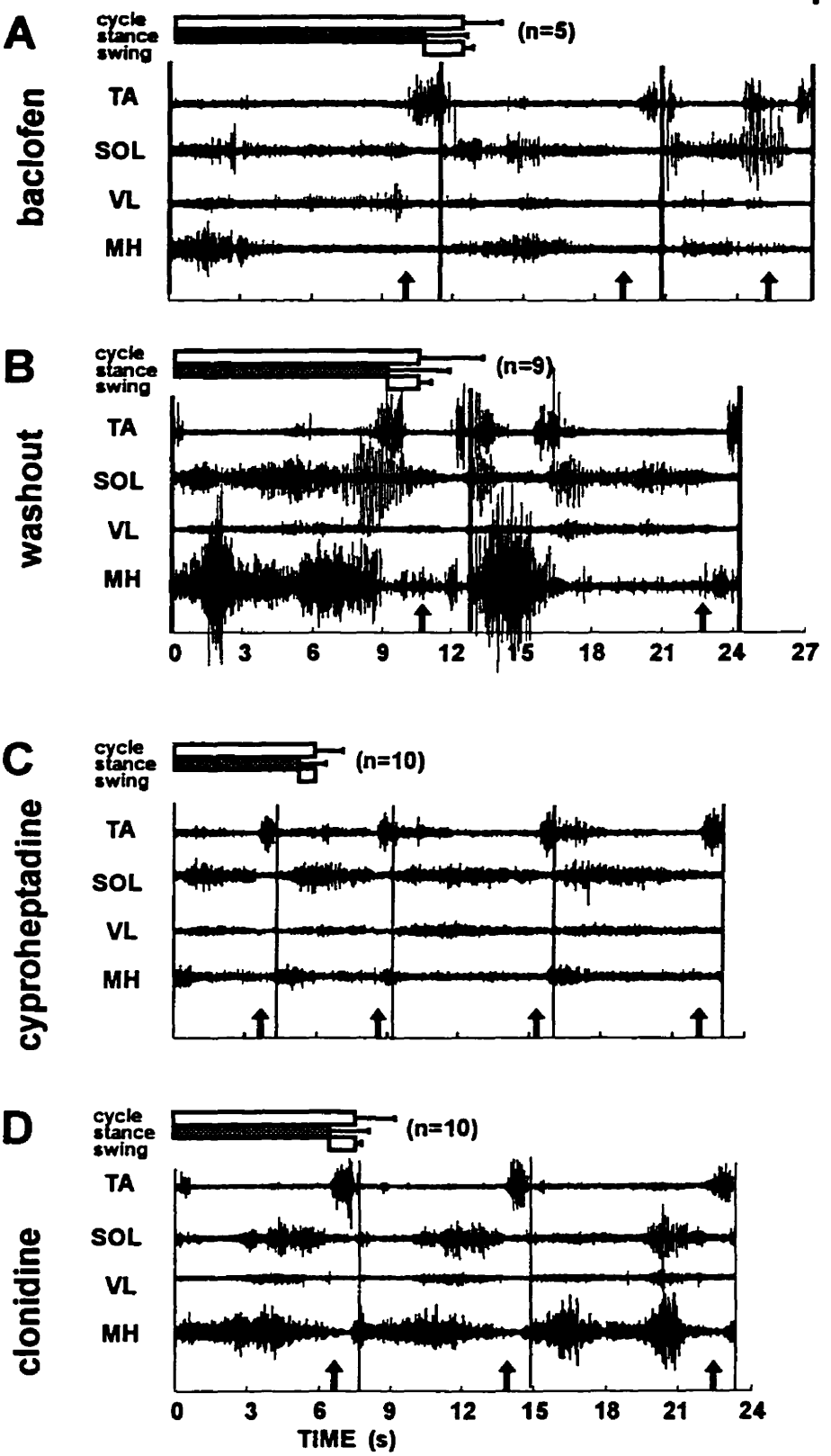
A. Second evaluation while taking baclofen.

B. Evaluation at the conclusion of washout period after baclofen.

C. Evaluation during cyproheptadine period.

D. Evaluation during clonidine period.

Figure 5


A
baclofen
cycle
stance
swing
(n=5)
TA
SOL
VL
MH
B
washout
cycle
stance
swing
(n=9)
TA
SOL
VL
MH
0
3
6
9
12
15
18
21
24
27
C
cyproheptadine
cycle
stance
swing
(n=10)
TA
SOL
VL
MH
D
clonidine
cycle
stance
swing
(n=10)
TA
SOL
VL
MH
0
3
6
9
12
15
18
21
24
TIME (s)

washout evaluation as compared to the baclofen evaluation. In Figure 5B, it can be seen that the cycle durations remain long and the muscle activity is generally higher than in the previous evaluation. In particular, there is greater evidence of ankle clonus in the soleus, visible in late stance in the first cycle, and in early and mid-stance in the second cycle, with a burst of tibalis anterior activity frequently in coactivation with soleus. There is also prolonged, high-amplitude activity in the medial hamstrings.

During his cyproheptadine evaluation, H1 was able to follow the treadmill for several minutes without assistance and with 20-40% BWS at a speed of 0.06m/s, and for at least a minute at 0.14m/s with similar BWS. The kinematic records from one cycle at 0.06m/s are illustrated in the dotted lines in Figure 3A-C, in the stick figure representations in Figure 3E, and in the bold dotted lines of Figure 4D-F. He achieved a more upright posture, as seen in the near-0° hip angle and in the reduced knee flexion in stance phase. The knee and hip also show a more coordinated flexion pattern during swing phase: both joints moved rapidly into flexion in early swing, and the knee moved back toward extension in late swing before the next foot contact. H1 also reduced the foot dragging that had been present in the baclofen evaluation. Abnormalities persist, however, in that the ankle remains dorsiflexed past neutral throughout stance phase, and he still required harness support for approximately the same BWS. Figure 5C shows temporal and EMG data from this evaluation. In marked contrast to the evaluation for the previous (post-baclofen) washout, H1 showed a regular pattern of muscle activity with cyproheptadine (Figure 5C). The soleus and tibialis anterior show a much more reciprocal pattern than previously seen. The soleus activity usually begins in early stance and diminishes in late stance at which point the tibialis anterior activity begins for its sharpest peak during the cycle. There is also some tibialis anterior activity seen in early stance, as is normal for weight acceptance. In addition, there is both a disappearance of clonus in soleus and a reduction in the prolonged high-amplitude EMG activity in the medial hamstrings.

In the post-cyproheptadine washout evaluation, H1 showed a retention of many of the kinematic patterns seen in the cyproheptadine evaluation with three notable differences, as

seen in Figure 4D-F. First, there is less extension at the hip and knee in early stance of the washout evaluation, suggestive of a slightly more flexed posture at foot contact without cyproheptadine. Second, there was a decrease in ankle dorsiflexion in mid-stance. Third, the coordinated flexion movement at the hip and knee in early swing in the cyproheptadine evaluation is absent in the washout evaluation, replaced by an earlier, less coordinated flexion of both joints that begins well before swing phase. Although some of the improvements seen in the cyproheptadine period disappeared in the washout period, it must be emphasized that the pattern did not revert to that seen in the washout evaluation that preceded cyproheptadine (i.e. the post-baclofen washout). In particular, the hip and knee remained less flexed in the post-cyproheptadine washout evaluation than in the washout evaluation that preceded cyproheptadine (compare the fine solid lines in Figure 4A & B with the fine dotted lines of Figure 4D and E). The EMG records (not illustrated) reflected that H1's walking pattern only partly reverted to its state before cyproheptadine. The abnormal timing seen in the post-baclofen washout did not return, but clonus in soleus did return.

During the clonidine evaluation, H1 remained similarly capable of independent gait cycles with 20-40% BWS, and the kinematic records from one cycle are illustrated in the dashed lines in Figure 3A-C and the stick figure representations in Figure 3F. There is little change in the hip angular excursion, in comparison with the cyproheptadine data, with a near-zero hip angle in stance reflecting an upright posture. The knee and ankle, however, show more noticeable differences. With clonidine, the knee remains in greater extension during stance phase and begins flexion earlier with respect to swing phase. The ankle remained near 0° during stance, associated with his more upright posture in this evaluation. A comparison of the kinematic data from the previous washout (i.e. post-cyproheptadine washout: Figure 4D-F, fine dotted lines) with those of the clonidine evaluation (Figure 3A-C, dashed lines) shows that the hip extension, knee extension and relative absence of ankle dorsiflexion are new changes with clonidine and had not been seen previously. In the stick figure representations in Figure 3F, the relative extension of

the hip and knee are reflected in the more vertical orientation of the thigh and lower leg segments in the mid- to late stance phase.

Temporal and EMG data from a sequence at 0.06m/s during H1's clonidine evaluation are shown in Figure 5D. Although there was a return of evidence of ankle clonus (most evident in the third cycle), the soleus also showed relatively greater activity in mid- to late stance in a reciprocal pattern with the tibialis anterior, reflecting a more normal recruitment pattern. The medial hamstrings record, however, showed a partial return of the prolonged, high-amplitude activation pattern that had been seen in washout evaluations.

In summary, H1 showed changes in walking ability at each successive evaluation with effects noted for all three drugs. From the baclofen evaluations to the subsequent washout evaluation, he showed a large increase in EMG activity and minor changes in kinematic pattern, including an increased dorsiflexion in swing phase. The greatest increase in stepping control and capacity was seen in the evaluation for cyproheptadine. Specifically, cyproheptadine was associated with a large increase in MTS, a more normal EMG pattern, reduced ankle clonus, a less flexed posture, and no further need for manual assistance with much longer sequences of stepping possible. Many of these improvements were retained in the subsequent washout period, although a slight deterioration can be seen in the kinematic pattern leading to a return to a more flexed posture. Clonidine was associated with a further improvement over the cyproheptadine period in the reciprocal activation of tibalis anterior and soleus, as well as in the less flexed posture.

The results for H2 were similar to those for H1 in that both cyproheptadine and clonidine were associated with marked changes in kinematic patterns and in MTS. During the baclofen period, there was almost no change in comparison with the washout evaluations preceding and following baclofen. In order to explain most clearly the changes in H2's locomotion, the results will be described chronologically. Throughout the evaluations, the support level recorded was approximately 20% BWS, surprisingly low for the kinematic

patterns he exhibited. The discrepancy may be explained by his heavy reliance on the parallel bars observed during evaluations.

H2 was first evaluated while taking no medication. In this initial evaluation, H2 needed manual assistance for every step due to the strong extension and adduction that rendered his lower limbs virtually immobile. Kinematic data could not be obtained from this evaluation as a result of the assistance provided. Each foot had to be slid forward rather than lifted because his extensor tonus permitted little passive ankle dorsiflexion, knee flexion, or hip flexion. Ankle clonus was frequently visible. It is important to note that his passive range of motion had been much greater during the prior clinical evaluation: the hip could be moved to >90° flexion and into extension past neutral; the knee could be moved from full extension to full flexion; the ankle could moved from full plantarflexion to >10° dorsiflexion.

A remarkable change was apparent in H2's cyproheptadine evaluation. He was able to maintain a slightly flexed position with harness support and move his legs reciprocally at a treadmill speed of 0.05m/s for ≤3 minutes at a time with intermittent assistance, and ≤1 minute with no assistance. The kinematic records from one cycle from the cyproheptadine evaluation are illustrated in the dashed lines in Figure 6A, B & C, showing approximately 30-40° flexion throughout stance phase and additional hip flexion in swing phase (Figure 6A, dashed lines). The knee is also flexed, particularly in mid- to late stance phase with a kicking motion in swing phase (Figure 6B, dashed lines). The ankle remains near neutral except for plantarflexion in swing phase and early stance phase. Clonus is present in stance phase although of too small amplitude to be visible in the kinematic graphs. The ankle plantarflexion at foot contact is related to the harness support and the hip and knee flexion, wherein the forefoot must make contact with the treadmill belt because the heel cannot reach the treadmill belt until the foot is under the body. The stick figure representation shown in Figure 6D illustrates the maintained flexion of the hip and knee with near-neutral ankle position. The foot contact with the treadmill belt is made with the forefoot and the heel does not make contact. The EMG records (not shown) revealed a reduction in tonic activation from the previous evaluation.

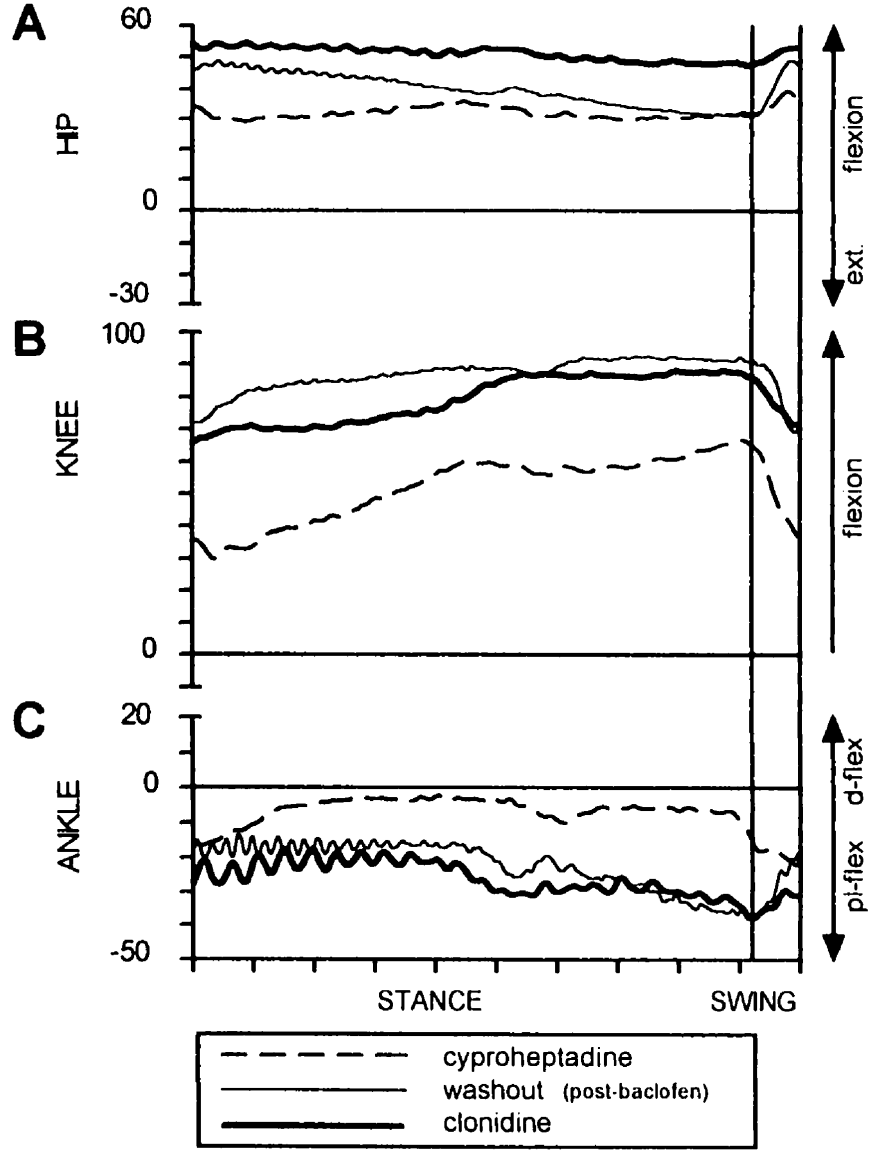
FIGURE 6

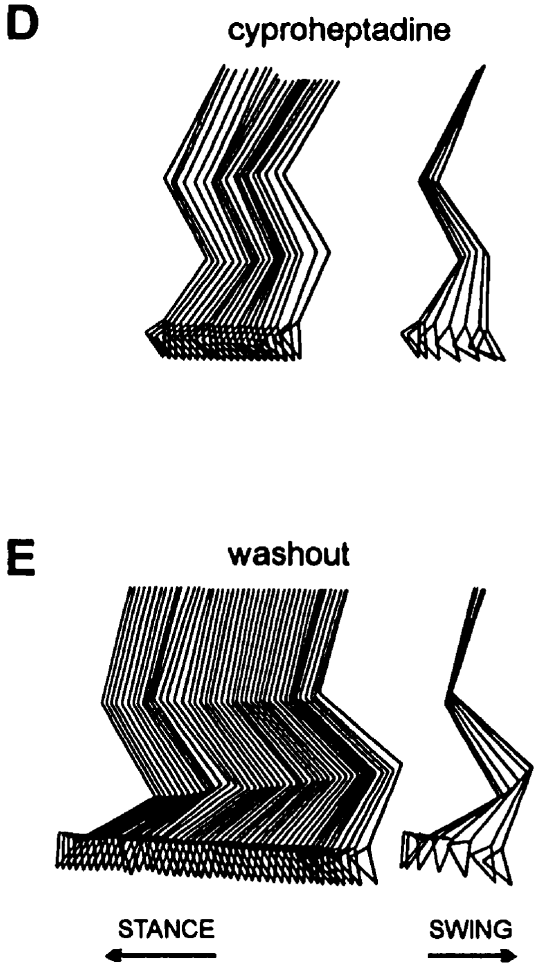
Normalized angular excursions of the right hip (A), knee (B) and ankle (C) of H2 during unassisted treadmill stepping with harness support: comparison of cyproheptadine (dashed lines), washout post-baclofen (dotted lines) and clonidine (solid lines) evaluations. In order to align the stance-swing transition from all displayed cycles, a stance proportion of 92% was used as representative of all cycles. For these sequences, H2 remained in a flexed position using parallel bars and harness for partial support of his body weight.

Sinusoid-type oscillations in the ankle excursion in the early stance phase from the washout and clonidine evaluations reflect ankle clonus. Low-amplitude oscillations in the hip records from the same evaluations arise from whole limb oscillation created by the ankle clonus. The clonus is of the same frequency on each occasion. The false impression of different frequencies of clonus in the normalized records is because the cycle durations are different in each evaluation.

Stick figure representations of H2 reconstructed from kinematic data in cyproheptadine (D), and post-baclofen washout (E) evaluations. For stance phase, every tenth sample is illustrated such that between successive stick figures the time lapse is 0.167 seconds; for swing phase, every fifth sample is illustrated such that between successive stick figures the time lapse is 0.083 seconds. For the composite representations, the horizontal distance between stick figures was increased by .002 m over the distance actually moved (in direction of arrow) in order to improve the visibility of posture and joint angle excursions. The false impression of a long step length and a large backward translation of the trunk during stance is an artifact and should be disregarded.

Figure 6


A
60
HP
0
-30
flexion
ext.
B
100
KNEE
0
flexion
C
20
0
ANKLE
-50
d-flex
pl-flex
STANCE
SWING
cyproheptadine
washout (post-baclofen)
clonidine


D
cyproheptadine
E
washout
STANCE
SWING

The kinematic and EMG records for the next three evaluations were very similar: washout post-cyproheptadine, baclofen, and washout post-baclofen. In these evaluations, H2 displayed a limited ability to perform independent stepping while supported by the harness in a flexed position. He could sustain this movement pattern for ≤2 minutes with intermittent assistance before his legs assumed a position of extension and adduction similar to the posture in the first evaluation previously described. Unassisted stepping was then no longer possible. The dotted lines in Figure 6A-C and the stick figure representations in 6E show kinematic data from the third of these three evaluations. The hip is more flexed in early to mid-stance phase. The knee excursion in Figure 6B shows a similar profile to the profile in the cyproheptadine evaluation, but at an angle of 20-30° additional flexion. The ankle excursion in Figure 6C shows a similar angle at foot contact to that seen in the cyproheptadine evaluation followed by a striking difference in profile throughout the cycle. Instead of moving toward dorsiflexion, the ankle immediately begins an oscillating pattern reflective of clonus. The clonus is of high enough amplitude to move the whole leg up and down, causing oscillations in the early stance portion of the hip excursion (Figure 6A). The greater flexion of the hip and knee in this evaluation is related to the appearance of movement toward dorsiflexion where it had not previously been seen. That is, a reduced degree of plantarflexion is required to achieve toe clearance during swing, whereas previously toe clearance was fully accomplished by flexion of the hip when the subject was in a less flexed posture (see Figure 6E). The more flexed posture of the hip and knee resulted in the foot travelling farther behind him and led to a reduction in ankle plantarflexion to achieve forward movement of the foot.

H2's stepping pattern in the flexed posture remained similar with clonidine. Angular excursions from a cycle in the clonidine evaluation are shown in solid lines in Figure 6A-C. The hip and knee show little change in overall profile, although some change in the amount of flexion (see Figure 6A,B). The ankle excursion is similar to the previous washout evaluation, with clonus throughout the stance phase, oscillating enough to cause fluctuations in the hip excursion. However, H2 was able to maintain this pattern at a

treadmill speed that was twice as high with a more rapid cadence (see Figure 2, bold solid line).

In addition, clonidine was associated with an improvement in H2's ability to sustain reciprocal stepping with his legs nearly straight. He performed this stepping at a treadmill speed of 0.03m/s with the harness system registering low amounts of support (< 10% BWS). His legs continued to display a tendency for involuntary adduction, and he required intermittent assistance to prevent both lower limbs from advancing while trying to advance only one. For a brief period of two cycles, he was able to advance his legs without any manual assistance.

At the conclusion of the clonidine period, H2 elected to try a combination of clonidine and cyproheptadine to find out if he could experience further improvement from a combination. Although this period of combined cyproheptadine and clonidine did not form part of the experimental protocol, the results are reported here because of the changes that were seen. H2 continued to be capable of stepping in a flexed, harness-supported position at a MTS of 0.10m/s. More importantly, he also became capable of independent stepping in an upright position with the harness system registering little support (<10% BWS) whereas previously he had always required assistance for more than two cycles when his legs were in this extended, adducted posture. He maintained this pattern at a treadmill speed of 0.05m/s without assistance for sequences of at least a minute at a time. In a subsequent evaluation while still taking a combination of clonidine and cyproheptadine, he continued to increase his MTS at stepping in a flexed position to 0.15m/s (see Figure 2). His maximal speed for unassisted upright stepping rose to 0.07m/s. The improvement permitted him later to attempt reciprocal stepping overground with a walker and thus to participate in a subsequent study of overground walking training.

In summary, H2 showed changes in his walking ability over the course of successive evaluations, with the greatest changes taking place during his cyproheptadine and his clonidine periods. Cyproheptadine was associated with a transformation from a posture with rigidly extended lower limbs requiring extensive manual assistance for even a few

small steps to a state of independent stepping with only mechanical BWS for several minutes at a time. Following washout of cyproheptadine, he remained able to perform independent stepping, but with an altered kinematic pattern with more clonus and for more limited periods. The sequences of independent stepping in these evaluations were terminated when his posture reverted involuntarily to that of rigid extension and adduction of the lower limbs, an effect that had not been seen in the evaluation for cyproheptadine. This profile continued across three evaluations, baclofen appearing to have no effect on his abilities. He showed minor increases in MTS across these evaluations. Clonidine was also associated with more important changes in his abilities. H2 doubled his MTS in the stepping sequences with his hips and knees flexed, similar to the posture of his previous independent sequences. He also began to show signs of becoming independent at a stepping pattern with the hip and knee near extension in stance phase, performing only two cycles independently. He achieved independence at this stepping pattern in subsequent evaluations while he was taking a combination of cyproheptadine and clonidine.

H3 did not show changes as striking as those seen in H1 and H2. He did not become capable of taking independent steps during any of his evaluations. His participation in the study was terminated early, at his request. In contrast, H4 showed considerable change in his stepping ability over the course of the study, as seen in his changes in MTS (see Figure 2). He showed a sharp improvement in MTS in the clonidine evaluation, but changes in stepping pattern for same-speed comparisons were minimal and he remained highly dependent on the harness for support. His inability to tolerate sufficiently long periods of cyproheptadine or baclofen meant that he could not be evaluated during these drug periods and therefore inter-drug comparisons of drug effect on stepping pattern cannot be made for H4.

Subjects with limited overground reciprocal locomotion

Results in this group of subjects were generally less striking than those seen in the group described above. All six of them were able to walk on the treadmill for several minutes at a time with no harness support or manual assistance throughout the study. All of them

increased their MTS over the course of their participation in the study, illustrated in Figure 7. Four subjects in this group were able to undergo evaluations for all three drugs and one of these four subjects experienced sharp increases in MTS in association with two of the three drugs. The results for this subject, C3, are described in detail.

C3 was referred to the study while taking baclofen and was evaluated three times with no change in his drug status. He showed an increase in MTS from his first evaluation (0.22m/s) to his second evaluation (0.30m/s) as seen in the symbols connected by a solid bold line in Figure 7. His MTS remained stable from the second to the third evaluation and then increased following washout of baclofen to 0.34m/s, and increased again to 0.44m/s during the evaluation for cyproheptadine. His MTS decreased to 0.30m/s following washout of cyproheptadine, but increased again to 0.45m/s during the evaluation for clonidine. Unlike the post-cyproheptadine washout, his post-clonidine washout evaluation showed no change in MTS from the previous evaluation.

Figure 8 shows EMG data from six evaluations of C3 and Figure 9 shows averaged kinematic data from sequences at 0.20m/s from the same six evaluations. The principal differences noted were in the the EMG amplitude of TA, the ankle excursion in swing phase, and the clonus visible in the soleus record in stance phase.

The EMG records for TA are illustrated in the top traces of Figures 8A-F, inclusive. In the evaluation for baclofen (Figure 8A), the TA amplitude in swing is comparable to its amplitude in stance phase, with no burst of activity. In contrast, in the post-baclofen washout evaluation (Figure 8B) there is a burst of activity in the swing phase in TA. This swing phase EMG burst in TA remains evident in subsequent evaluations (Figures 8C-F). The duration of this TA burst is reduced during the evaluation for clonidine (Figure 8E). The significance of these changes in TA activity for the ankle excursion can be seen in the averaged ankle excursion records for swing in Figure 9F. During the evaluation for baclofen the swing phase ankle excursion is much more plantarflexed than in any other evaluation, >20° more plantarflexed than in any of the washout evaluations. In the

FIGURE 7

MTS over successive evaluations of locomotion in W1, W2, P1, C1, C2 and C3. Drug status is reflected by the symbols as indicated in the legend. Each subject's values are linked by a different type of line (see legend). Note that the scale is different from that used in figure 2.

Figure 7

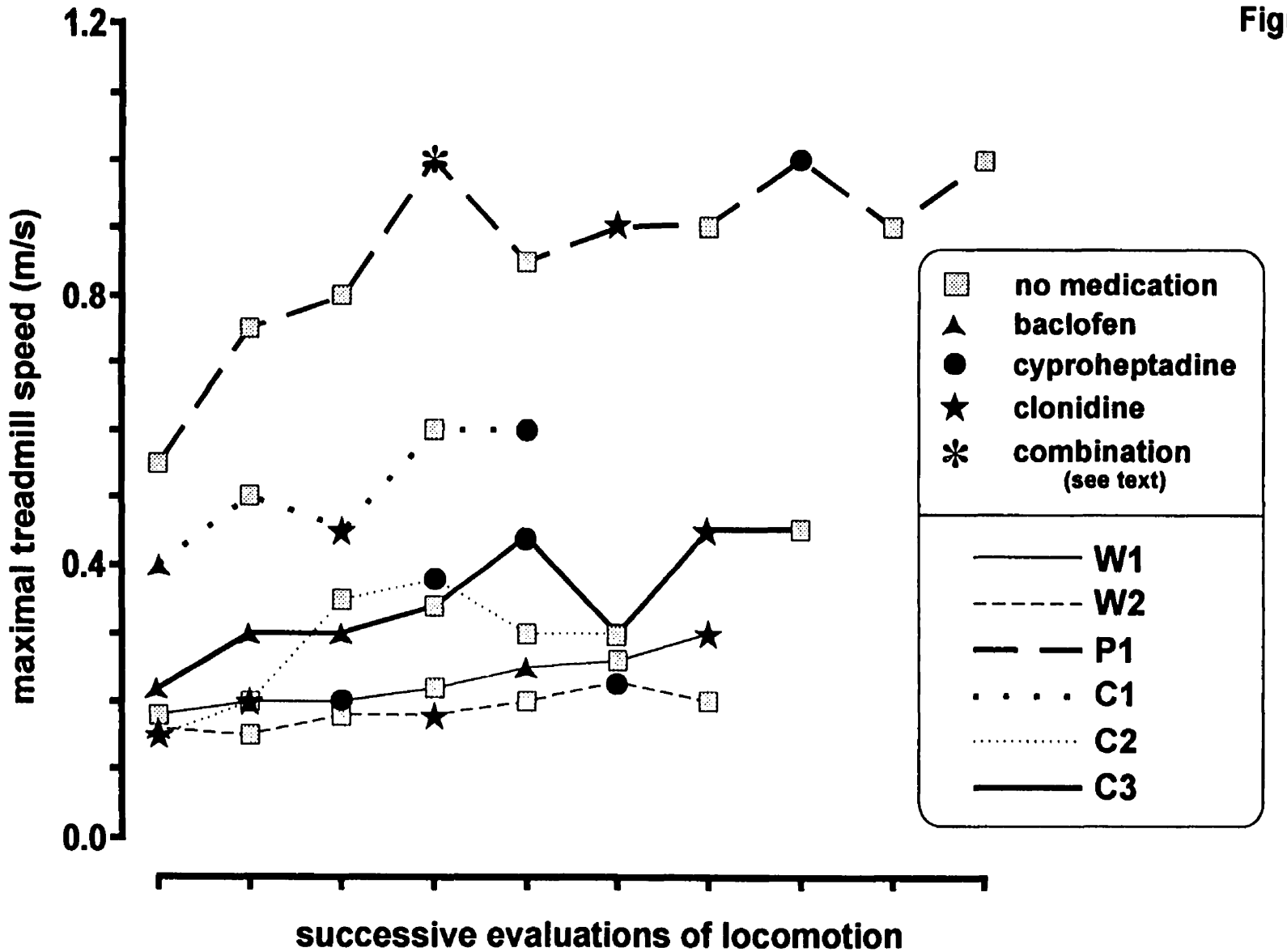

1.2
0.8
0.4
0.0
maximal treadmill speed (m/s)
successive evaluations of locomotion
no medication
baclofen
cyproheptadine
clonidine
combination
(see text)
W1
W2
P1
C1
C2
C3

FIGURE 8

A-F: Rectified, averaged EMG signal from muscles of the right leg of C3 during 10 cycles of treadmill walking. TA = tibialis anterior; SO = soleus; VL = vastus lateralis; MH = medial hamstrings. Vertical lines indicate stance-swing transition. Averaging was performed separately across stance and swing phases from EMG records from 10 consecutive cycles which had been digitized, full-wave rectified and smoothed. The two averages were placed side by side, and their lengths adjusted to reflect the average length of the 10 stance and swing phases. The average absolute cycle duration is noted in the figure for each evaluation. All data displayed were gathered during sequences at a treadmill speed of 0.20 m/s.

G-L: Rectified, smoothed EMG signals from the right soleus muscle in C3 during stance period of 5 of the ten cycles illustrated in A-F, respectively.

A,G. Third evaluation while taking baclofen.

B,H. Evaluation at the conclusion of washout period after baclofen.

C,I. Evaluation during cyproheptadine period.

D,J.Evaluation at the conclusion of washout period after cyproheptadine.

E,K. Evaluation during clonidine period.

F,L. Evaluation at the conclusion of washout period after clonidine.

Figure 8

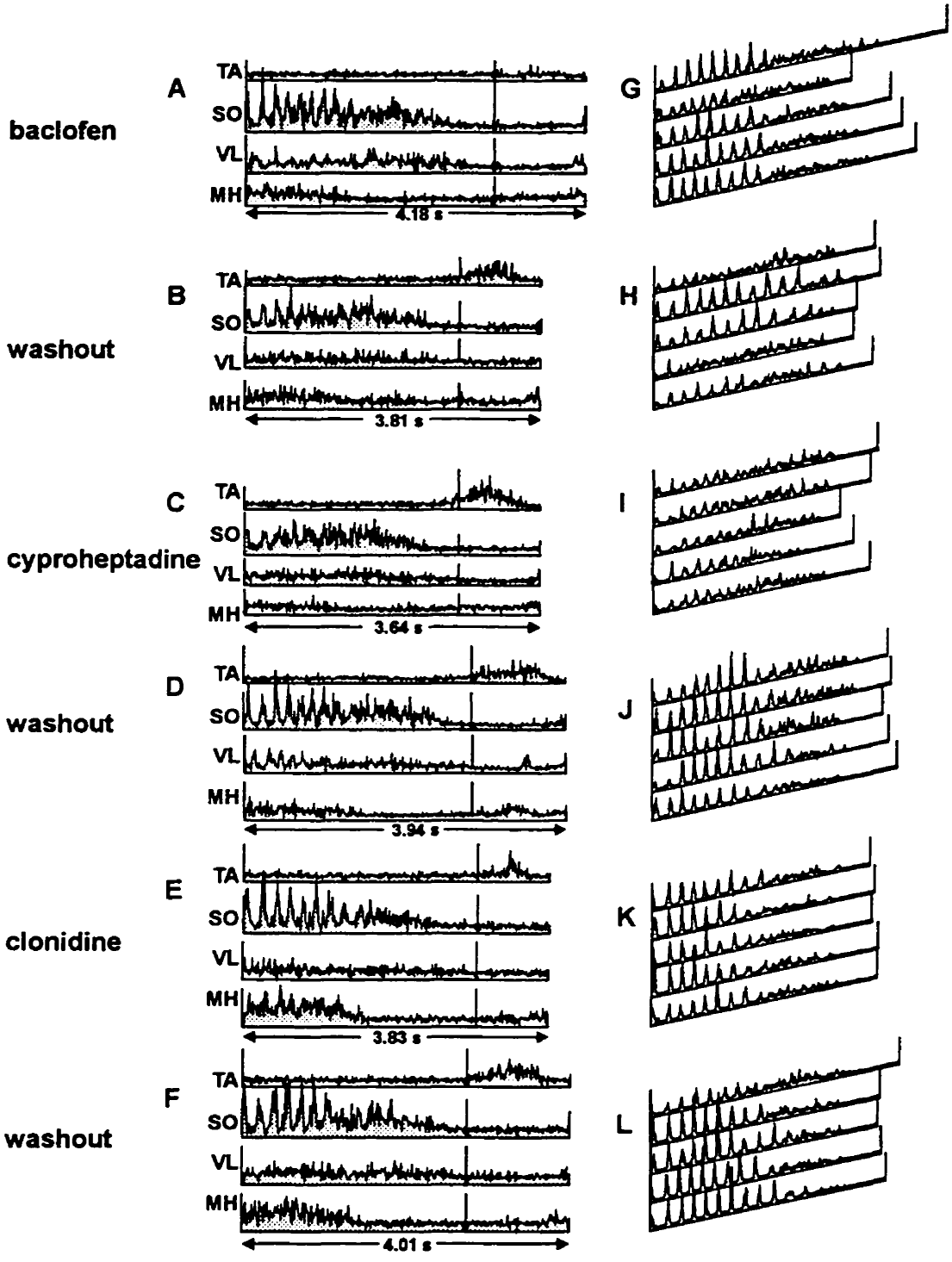
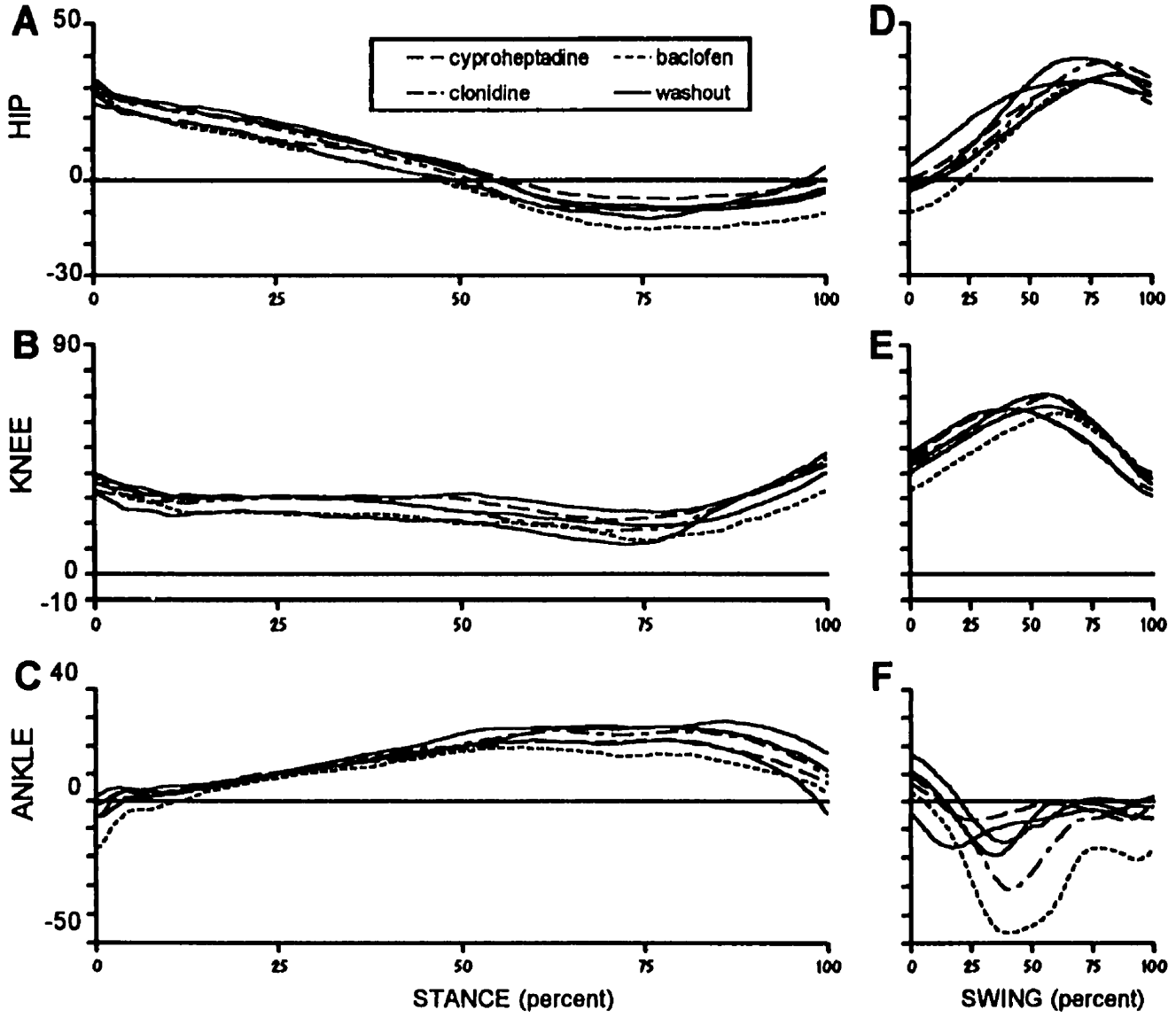

baclofen
A
TA
SO
VL
MH
4.18 s
G
washout
B
3.81 s
H
cyproheptadine
C
3.64 s
I
washout
D
3.94 s
J
clonidine
E
3.83 s
K
washout
F
4.01 s
L

FIGURE 9

Averaged angular excursions of the right hip (A,D), knee (B,E) and ankle (C,F) of C3 for stance (A,B,C) and swing (D,E,F) phases during treadmill walking. Averaging was performed across separately across 6 stance periods and 6 swing periods (except for cyproheptadine evaluation and subsequent washout evaluation, 10 stance and swing periods used). The widths of the graphs are proportional to the average stance and swing proportions across all cycles analysed. Solid lines indicate averaged traces for washout evaluations. Broken lines indicated averaged traces for evaluations during drug periods (baclofen: dotted line; cyproheptadine: dashed line; clonidine: dashed-dotted line).

Figure 9


A
B
C
D
E
F
HIP
KNEE
ANKLE
50
0
-30
90
0
-10
40
0
-50
cyproheptadine
baclofen
clonidine
washout
0
25
50
75
100
STANCE (percent)
SWING (percent)

evaluation for clonidine, the ankle excursion reverts part way to a more plantarflexed pattern, related to the shorter burst of TA activity in this evaluation.

The other important difference across evaluations for C3 was in the EMG activity related to ankle clonus. In order to obtain better visualization of EMG activity related to clonus, unaveraged soleus records were used. Figures 8G-L shows soleus records from five consecutive cycles of the ten that were used to form the averages shown in Figures 8A-F. The individual soleus EMG records for the evaluation for cyproheptadine displayed in Figure 8I show that activity related to ankle clonus was diminished in comparison with the soleus EMG from all other evaluations (Figures 8G,H,J-L) but not entirely eliminated.

In summary, C3 showed changes associated with all three drugs. From the evaluations for baclofen to the subsequent washout evaluation, he showed an improved pattern of ankle excursion and tibialis anterior EMG activation. There was, however, no change in MTS apart from his previously established trend of modest increase. Cyproheptadine was associated with a sharp increase in MTS as well as a reduction in ankle clonus; neither effect was maintained in the subsequent washout period. Clonidine was also associated with a sharp increase in MTS that was maintained in the subsequent washout, and with a change in ankle excursion and tibialis anterior EMG activation that was not maintained.

Three other subjects in this group also experienced a reduction in ankle clonus associated with cyproheptadine. W1 had a reduction in clonus activity in soleus with cyproheptadine. Similar to the effect seen in C3, the reduction in clonus was not seen in evaluations for either of the other drugs or in washout evaluations. W2 and C1 reported a similar effect of reduced ankle clonus in other activities, such as performing transfers and descending stairs.

For the other five subjects in this group, changes in MTS were less clearly suggestive of beneficial effects associated with any of the drugs. Two subjects, W1 and W2, the slowest-walking subjects of the group, increased their MTS in an almost linear manner across consecutive evaluations, as seen in the fine solid line and the fine dashed line,

respectively, in Figure 7. In two other subjects, C1 and C2, the greatest change in MTS occurred following washout of one of the drugs. The two increases in MTS for C1 occurred during washout periods, with a decline in MTS during the clonidine period, and no change in MTS during the cyproheptadine period, seen in the bold dotted line in Figure 7. Nonetheless, C1 reported subjective benefit during the cyproheptadine period. The greatest increase in MTS for C2 occurred following washout of clonidine, with a smaller increase seen during the evaluation for cyproheptadine, seen in the symbols linked by the fine dotted line in Figure 7. The other subject in this group, P1, showed increases in MTS, both at some drug evaluations and at some washout evaluations (bold dashed line in Figure 7).

Subjects with functional overground reciprocal locomotion

In subjects who entered the study with functional overground reciprocal locomotion, S1 and S2, there were no consistent differences in EMG patterns, kinematic patterns or gait speed in association with changes in drug status. The data for MTS for these subjects is illustrated in Figure 10. It can be seen that S1's MTS was greater at his second baclofen evaluation than at his first baclofen evaluation, and that there were no other changes. It can also be seen that both of these subjects were capable of treadmill speeds that were substantially higher than the other subjects in the study.

Summary of speed changes and secondary drug effects

Speed changes

In Figure 11, the change in MTS has been plotted as a function of the subject's initial MTS for H1, H2, H4 and all six of the subjects in the second group. Cyproheptadine (Figure 11A) was associated with an increase (H1, H2, W2, C2, C3, P1) or no change (W1, C1) in MTS. Several of the increases with cyproheptadine represented a large change as a proportion of their initial MTS (H1, H2, C3). Clonidine (Figure 11C) was also associated with increases in MTS (H2, H4, W1, C3, P1) some of which were large proportional increases (H2, H4, C3). However, clonidine was associated in other subjects with no

FIGURE 10

MTS over successive evaluations of locomotion in S1 and S2. Drug status is reflected by the symbols as indicated in the legend. Each subject's values are linked by a different type of line (see legend). Note that the scale is different from those used in figures 2 and 7.

Figure 10

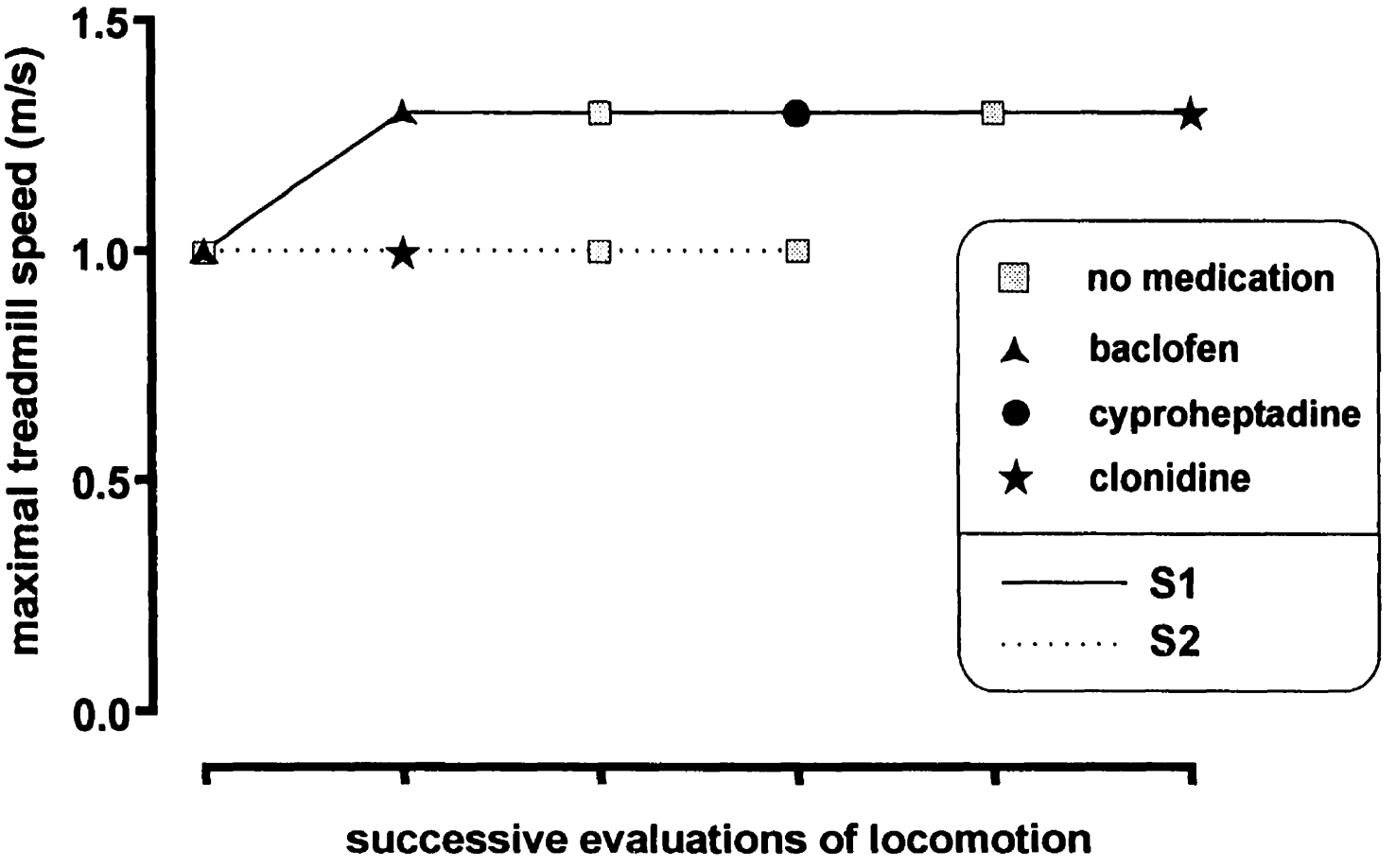

1.5
1.0
0.5
0.0
maximal treadmill speed (m/s)
no medication
baclofen
cyproheptadine
clonidine
S1
S2
successive evaluations of locomotion

FIGURE 11

The change in absolute value of MTS is plotted as a function of the subject's initial MTS. In each graph, each vertical dotted line represents a single subject except for the left-most dotted line which represents H1 and H2 who both had an initial (unassisted) MTS of zero. See legend for different drug symbols. Data from H4, S1 and S2 have been omitted because they showed no MTS changes in association with change in drug status.

A, B: cyproheptadine/washout

C, D: clonidine/washout

E, F: baclofen/washout

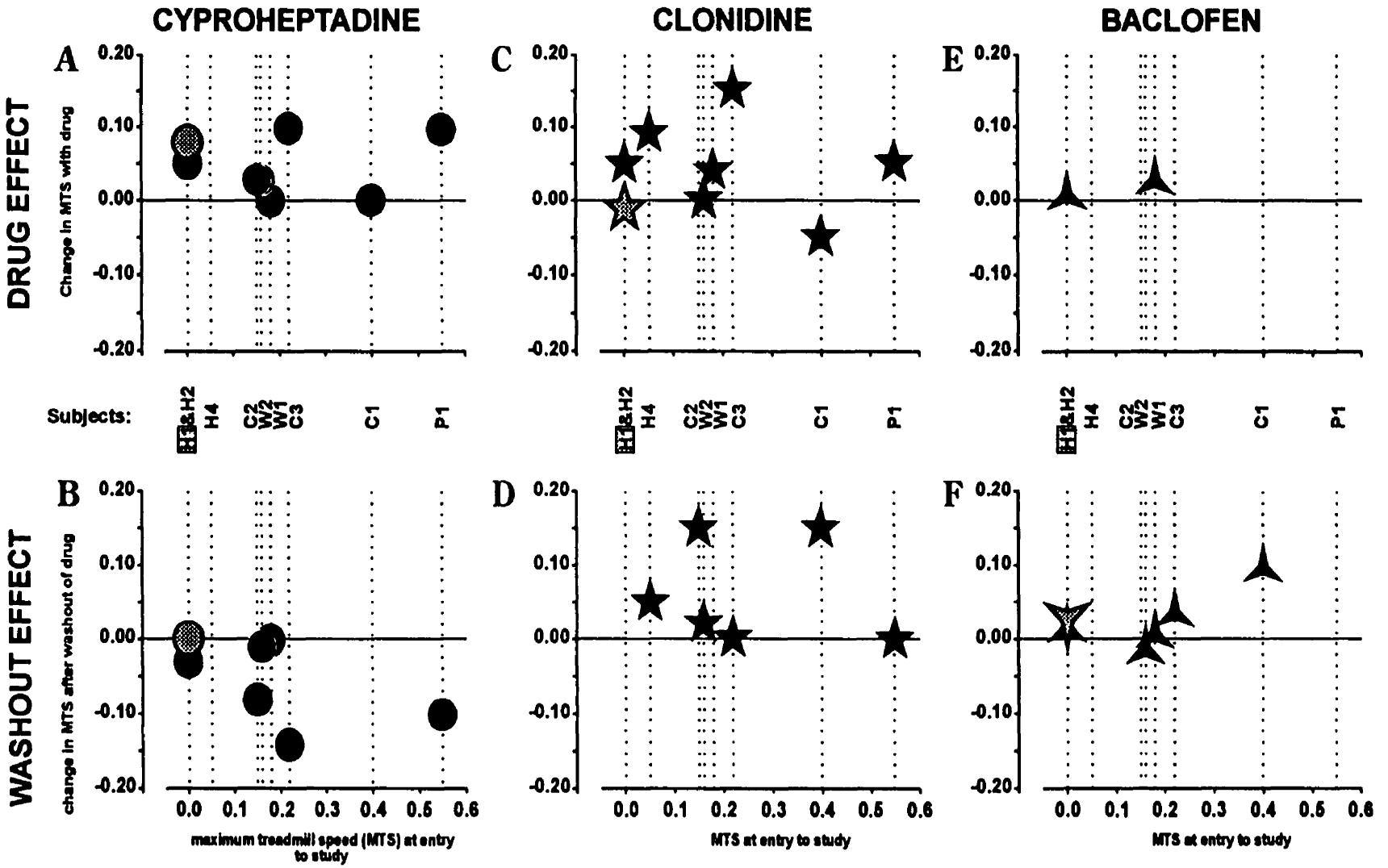
A, C, E: The change value for each drug has been calculated as the subject's MTS during a drug period minus his MTS during the immediately previous period of no medication.

Missing values are due to subjects' being unable to complete a drug evaluation (cyproheptadine: H3, H4; baclofen: H3, H4, P1, C2) or to subjects' entering the study while taking a drug (baclofen: H1, W2, C1, and C3; clonidine: C2).

B, D, F: The change value for each drug has been calculated as the subject's MTS during a drug period minus his MTS during the immediately subsequent period of no medication.

Missing values are due to subjects' being unable to complete a drug evaluation (cyproheptadine: H3, H4; baclofen: H3, H4, P1, C2) or to subjects' discontinuing the study without completing a final washout evaluation (cyproheptadine: C1; clonidine: H1, H2, W1).

Figure 11


CYPROHEPTADINE
CLONIDINE
BACLOFEN
A
B
C
D
E
F
DRUG EFFECT
WASHOUT EFFECT
Change in MTS with drug
change in MTS after washout of drug
0.20
0.10
0.00
-0.10
-0.20
Subjects:
H3&H2
H4
C2
W2
W1
C3
C1
P1
0.0
0.1
0.2
0.3
0.4
0.5
0.6
maximum treadmill speed (MTS) at entry to study
MTS at entry to study

change (W2) or a decrease (H1, C1) in MTS. Baclofen (Figure 11E) was associated with a small increase (W1) or no change (H2) in MTS.

The data regarding change in MTS following washout of each drug are equally interesting. Cessation of cyproheptadine was never associated with an increase in MTS, but rather with no change (H1, W1) or a decrease (H2, W2, C2, C3, P1) in MTS (see Figure 11B). In contrast, cessation of clonidine (Figure 11D) or baclofen (Figure 11F) were often associated with an increase in MTS (clonidine: H4, W2, C1, C2; baclofen: H1, H2, C1, C3) and other times with no change (clonidine: C3, P1) or a minimal decrease (baclofen: W2) in MTS.

Secondary effects

The side effects reported by the subjects are summarized in Table 3. The list of effects was compiled from effects attributed to the drugs by the subjects, reported either during a drug period or after the subsequent washout.

Clonidine was associated with side effects more often than the other two drugs, in particular the effect of dry mouth which was reported by over half the subjects. Cyproheptadine was commonly associated with an increase in appetite, unsurprisingly because it has been prescribed in other populations as an appetite stimulant (Kardinal et al 1990, Saleh et al 1979). The most commonly reported side effect during the baclofen period, among those who completed this drug period, was a feeling of drowsiness or somnolence, consistent with other reports in the literature (reviewed in Whyte & Robinson 1990, Young & Delwaide 1981) The side effects of drowsiness and fatiguability with any of the drugs were not visible to the experimenters, nor did they interfere with completion of evaluations, except where noted below (also see Table 3).

The side effects associated with clonidine were not deleterious enough in any subject to result in drop-out or missing an evaluation. In contrast, cyproheptadine and baclofen were both intolerable to one or more subjects: cyproheptadine principally because of the side effect of headache and nausea, baclofen principally because of a feeling of fatiguability and

TABLE 3: Side effects

clonidine	Subjects reporting
dry mouth	H1, H2, W2, P1, C3, S1, S2
↑ urinary frequency	W1, C2, S1, S2
fatiguability / ↓ energy	C1, W2, P1, S2
constipation	C2, S1, S2
light-headedness / dizziness	W2, C1, C3, S2
↓ urinary urgency[1]	H3, P1
↑ appetite	C1, S2
numbness	P1
altered sexual function[2]	C2
nausea	C3

cyproheptadine	Subjects reporting
↑ appetite	H2, W1, C1, C3, S1
↑ urinary frequency	C2
fatiguability / ↓ energy	C3, S1
subjective ↓ in strength	W1
headache / nausea[3]	H4, S2
skin rash[3]	H4

baclofen	Subjects reporting
fatiguability / ↓ energy / ↓ concentration[3]	H4, P1, C2
subjective ↓ in strength	H1, C3
drowsiness / somnolence	W1, P1, C3
subjective ↓ in sensation	C3
↑ spasms[3]	H4, P1

[1] regarded as a benefit by subjects
[2] real incidence may be higher because subjects may be reluctant to discuss
[3] cited as (one of) reason(s) for discontinuing drug early and/or dropping out of the study

inability to concentrate. In two subjects, baclofen was associated with a increased occurrence and/or severity of spasms. Both had had experience with baclofen prior to entering the study: H4 had experienced the same effect at that time, although it had not been as severe; P1 had not experienced this effect in his prior therapy with baclofen.

Many subjects elected to continue one or more of the drugs following their participation in the study, despite the occurrence of side effects in some cases. Both H1 and H2 chose to continue a combination of cyproheptadine and clonidine at the conclusion of the study. In particular, they were pleased with cyproheptadine: H1 because he was able to walk overground for short distances using a rolling walker with forearm supports; and H2 because he had a marked reduction in night spasms that had been interrupting his sleep. W1 reinstated a low dose of cyproheptadine in order to control ankle clonus. W2 started a combination of cyproheptadine and baclofen to reduce stiffness and spasms. C1 continued cyproheptadine because of the benefit of reduced stiffness and spasms. C3 chose to try a combination of cyproheptadine and clonidine because he had experienced benefit during both of those periods. S1 reported that during the clonidine period he was able to attempt jogging and jumping. He chose to continue clonidine at the conclusion of his participation in the study.

In summary, only one subject (W2) elected to continue baclofen after participating in the study, in combination with cyproheptadine. Six subjects elected to continue cyproheptadine, alone or in combination with another drug, and four subjects elected to continue clonidine, alone or in combination with another drug. In all cases of continuing drug therapy, the subjects continued them for at least several months and in some cases for over a year. Three subjects (H2, W1 & W2) subsequently entered a study of the effects of functional electrical stimulation (FES) and training on walking, and they continued a stable dose of drug(s) from the present study into the FES study. It is believed that H2 would not have been able to participate in the FES study, and that the other two would have had more difficulty participating, without the continuing drug therapy.

DISCUSSION

This study is the first comparison of cyproheptadine, clonidine and baclofen on walking pattern in human subjects, specifically SCI subjects with partial loss of motor function. The results show that cyproheptadine and clonidine have different and sometimes powerful effects on the walking pattern of such subjects whereas baclofen has less evident effects. The changes in walking pattern were most noticeable in subjects who were among the most disabled. The finding that severely disabled subjects benefit most from cyproheptadine and clonidine is consistent with previous studies (Fung et al 1990, Stewart et al 1991, Wainberg et al 1990) and important for rehabilitation because this is a large and growing subset of the SCI population (see Introduction). In addition, the findings from repeated evaluations of chronic incomplete SCI subjects provide increased understanding of the potential for recovery of walking more than a year post-spinal cord injury and suggest directions for further research.

The two largest transformations in walking pattern in the study occurred in two of the most disabled subjects when each was taking cyproheptadine following a period without drugs (i.e. entry to study or washout). The changes in each of H1 and H2 in the cyproheptadine evaluation as compared to the previous evaluation resemble observations in chronic spinal cats in some respects. In such animals, a coordinated hindlimb stepping pattern on a treadmill can be achieved with regular training (Barbeau & Rossignol 1987, Belanger et al 1988, Lovely et al 1986, reviewed in Edgerton et al 1992, Hodgson et al 1994, Rossignol & Barbeau 1993). Administration of a serotonergic precursor or agonist resulted in a marked increase in EMG amplitude, including some flexor-extensor coactivation as well as some patterns resembling clonus and spasms. The subsequent administration of cyproheptadine blocked these effects (Barbeau & Rossignol 1990). The reduction in clonus and coactivation in H1 and the reduction in strong extension in H2 with cyproheptadine bear some similarity to the latter findings in animals. In addition, in both H1 and H2, cyproheptadine was associated with an emergence of sustained reciprocal stepping previously unseen, a finding that is not directly comparable to the findings in chronic spinal cats.

Cyproheptadine was associated with other, more modest effects in some subjects. As noted for C3, cyproheptadine was associated with an increase in MTS that was not retained in a subsequent washout period. The reduction in MTS may have been partially due to the re-appearance of frequent episodes of ankle clonus which had been greatly diminished during the cyproheptadine period. Overall, cyproheptadine was frequently associated with a reduced incidence of ankle clonus, similar to findings in other studies in humans of these drugs (Barbeau H et al 1982, Wainberg et al 1990). Clonus is a self-sustaining oscillation that depends principally upon the monosynaptic reflex loop. High reflex gain is thought to be responsible for clonus being more commonly visible in patients with neurological disease than in normal subjects (Rack et al 1984, Rossi et al 1990). The role of cyproheptadine in reducing clonus may be hypothesized from findings regarding the role of serotonin in motor output. It has been proposed elsewhere that the serotonergic system plays a role in modulating the gain of motor output across many species and many behaviours (for review, see Jacobs & Fornal 1993). The findings that cyproheptadine was associated with an emergence of unassisted stepping and that it was the most effective among the three drugs at reducing clonus implies altered functioning of the serotonergic pathways and/or receptors in incomplete SCI subjects.

Like cyproheptadine, clonidine was also associated with changes particularly in harness-using subjects. It is important to note that, among the literature for the three drugs compared in the present study, the evidence for clonidine is especially compelling as an agent to improve the recovery of walking following a lesion of the spinal cord. In chronic spinal cats who have been trained to walk on a treadmill, an injection of clonidine leads to a stepping pattern with longer cycle durations in conjunction with longer bursts of flexor muscles (Barbeau et al 1987a). Among such cats that had developed a poor locomotor pattern, clonidine injection led to an improvement (Rossignol et al 1996).

The changes in the cats are similar to some of the findings in the subjects in the present study, specifically the longer cycles and improved reciprocal activation of ankle muscles of H1, the increased MTS of H2, H4, C3, and the more upright posture of H2. H2 showed a shorter cycle duration, in contrast to the findings in cats, but this may be related to the use

of the harness for BWS. BWS has been associated with lowered values of hip flexion compared with sequences at similar speeds without the use of the harness (Finch et al 1991). In addition, the finding in the present study of retained gain in MTS or further increase in MTS following washout of clonidine has interesting implications for the mechanism of clonidine's effects on walking. It may act to create a permissive situation: that is, a condition in which improvement is more easily permitted that is then retained after clonidine is no longer present.

The finding that clonidine's effect on walking ability is greater in subjects with greater disability is consistent with a previous comparison of clonidine to placebo in spastic paretic subjects (Stewart et al 1991). In the latter study there was one subject comparable to the four harness-using subjects in the present study, and he showed a large improvement in stepping pattern following four weeks of clonidine. The two subjects in that study who had already regained functional overground walking showed little effect of clonidine. The six other SCI subjects in the study had clinically complete injuries, and they required continuous assistance for harness-supported stepping during the evaluations. Dietz and colleagues (1995) reported similar findings to the latter with intrathecal clonidine in two SCI subjects with clinically complete injuries: that is, reduced EMG activity consistent with clonidine's role as an antispastic drug but no initiation of independent stepping. Thus, the clonidine-induced initiation of walking in spinal cats has yet to be replicated in human SCI subjects. These findings regarding subjects with clinically complete injuries imply that the beneficial effects of clonidine on walking in incomplete SCI subjects are unlikely to be entirely due to its action on postsynaptic receptors, as has been demonstrated for spinal cats (Barbeau et al 1987). Further research will be required to explore the relative contribution of presynaptic and postsynaptic effects in the changes associated with clonidine in subjects with incomplete spinal cord injury.

There are few other reports of clonidine's effects on SCI subjects in the literature -- some case reports (Nance et al 1985, Rosenblum 1993, Tuckman et al 1982, Yablon & Sipski 1993) and a few studies (Donovan et al 1988, Maynard 1986, Weingarden & Belen 1992).

All used oral or transdermal clonidine to reduce spasticity and none of these studies reported measuring or observing changes in walking or pre-gait activities.

Recently, a preliminary report was published regarding the effects of intrathecal clonidine injections in incomplete SCI subjects (Rémy-Neris et al 1996). Intrathecal injections of clonidine were associated with rapid improvement in maximal overground walking speed between parallel bars. Subjects continued to show improvements in maximal overground walking speed for up to six hours following intrathecal injection of clonidine. The increases in maximal speed were associated with increased step length and the walking changes coincided with reduced reflex responses to cutaneous stimulation and reduced resistance to passive movement in clinical examination (i.e. Ashworth scale). The changes in walking and in spasticity were generally reproducible across days of intrathecal injection of clonidine, and were significantly different from outcomes on the same measures on the days when placebo injections were given (Rémy-Neris et al 1996). Taken together, the findings for clonidine in SCI subjects suggest that it is particularly important to pursue the study of this drug to assist in the recovery of walking in SCI subjects with severe but not complete loss of motor function.

The study of pharmacological control of locomotion has largely focussed on the role of excitatory amino acid systems and monoaminergic systems (for reviews, see Grillner 1986, Grillner & Dubuc 1988, Rossignol & Dubuc 1994). The role of spinal GABAergic neurons in locomotion was not well-studied until comparatively recently and the findings suggest that they function primarily to modulate or reduce locomotion. Cazalets and colleagues (1994) induced fictive locomotor activity through pharmacological activation of NMDA receptors in an *in vitro* preparation of isolated newborn rat brainstem-spinal cord. Addition of GABA or GABAergic agonists to the preparation led to a lengthening of the period of the locomotor pattern or a complete cessation of the activity. In other experiments, GABAergic antagonists were able to induce a stable rhythmic activity in a preparation in which the prior stimulation was sub-threshold for a locomotor pattern. The authors proposed that GABAergic neurons function as an "inactivatory" pathway that controls locomotion, either by modifying it or by stopping it altogether. Tegner and

colleagues (1993) concluded that GABAergic systems normally function to modulate fictive locomotor output in the lamprey spinal cord, with greater GABAergic activity leading to reduced output. They noted that baclofen was associated with both a decrease in locomotor related synaptic drive as well as to a depression of the AHP, suggesting that it acts both presynaptically and postsynaptically, respectively. The findings in fictive locomotion have been supported by findings in treadmill locomotion in chronic spinal-transected cats. Chau and colleagues found that the injection of baclofen disrupted a well-established locomotor pattern particularly by inducing paw drag, reduced weight support and other deficits. With higher doses of baclofen, the locomotor pattern could be arrested altogether (Chau et al 1995).

The clinical use of baclofen as an antispastic agent arose from research that pre-dates the study of GABA's role in locomotion. Baclofen came to be considered the drug of choice for spasticity of spinal origin (for review, see Burke 1975, Young & Delwaide 1981). The rationale was based on findings that baclofen was able to depress polysynaptic and monosynaptic excitatory post-synaptic potentials (Pierau & Zimmermann 1973), with no change found in motoneuronal excitability (Davidoff & Sears 1974), thus affirming that baclofen's primary role is to enhance presynaptic inhibition, in doses comparable to those given to humans for spasticity. Subsequent work by Wang & Dun (1990) confirmed these findings, but also found that in higher doses baclofen was also able to produce a hyperpolarization of the motoneuronal membrane, suggesting dual sites of action with greater doses, corresponding to the reports of baclofen's effect on fictive locomotion in the lamprey (Tegner et al 1993).

Although oral baclofen was and remains commonly used to treat spasticity due to spinal lesion, most recently published reports of baclofen's effects on spasticity are in regards to intrathecal baclofen. In measuring the effects of intrathecal baclofen, as in measuring the effects of oral baclofen, outcomes related to walking have generally not been evaluated, presumably because the treatment approach of intrathecal baclofen was initially applied to patients whose disability is severe and whose residual motor function is poor. In most studies of intrathecal baclofen's effects that report changes in locomotion, the changes

were reported as comments and not systematically quantified. There are reports of subjects' experiencing deterioration in walking as well as reports of subjects' experiencing improvement in association with intrathecal baclofen (Abel & Smith 1994, Broseta et al 1989, Latash et al 1990, Lazorthes et al 1990, Loubser et al 1991, Meythaler et al 1992b, Ochs 1993, Penn 1988, Sahuquillo et al 1991, Saltuari et al 1992; for review, see Campbell et al 1995). Azouvi and colleagues (1996) quantified changes in locomotion with intrathecal baclofen, but the time span was six months and the measurement was an ordinal scale based primarily on need for aids or assistance. Only seven of twelve SCI subjects in their report showed locomotor improvement, two of whom were rated higher because of better wheelchair locomotion.

Corston and colleagues (1981) reported on a comparison of oral baclofen and DS103-282 (tizanidine) on the walking pattern of spastic paretic subjects. They reported greater mean ankle dorsiflexion during baclofen than during tizanidine. However, the pattern during baclofen was not significantly different from the pattern before treatment or during placebo treatment. They concluded that only minimal objective and subjective changes in gait were found with baclofen or tizanidine. Their conclusions regarding baclofen seem generally borne out by our findings. In contrast to the other two drugs, baclofen was associated with little effect on walking pattern in any of the subjects, regardless of the extent of disability. H1 showed an increase in tonic muscle activity following washout of baclofen that is consistent with baclofen's well-documented effectiveness as an antispastic medication for the SCI population (Duncan et al 1976, Sachais et al 1977; for reviews see Campbell et al 1995, Lewis & Mueller 1993, Whyte & Robinson 1990, Young & Delwaide 1981). However, there was no associated deterioration in H1's walking pattern in terms of speed or of need for support or assistance. Similarly, another subject (C3) showed no deterioration in walking performance following washout of baclofen. Rather, he showed improved activation of tibialis anterior during swing phase with a concomitant reduction in the plantarflexion, opposite to the previously reported findings (Corston et al 1981). However, the results in C3 are consistent with the finding of increased paw drag in chronic spinal cats with baclofen (Chau et al 1995).

Thus, we observed neither the reduction or deterioration in locomotion seen in the animal models, nor the more normal walking that would be expected if it were always true that treatment to reduce spasticity will lead to improved voluntary motor control. There are several possible reasons for observing little effect. First, it is possible that there was a selection bias against baclofen among these subjects. That is to say, SCI subjects who agree to participate in a drug study are more likely to have been non-responders to standard therapy, a factor which would bias against baclofen more than the other two drugs. Second, although we employed higher doses than those employed by Corston et al (1981) [generally 80 mg versus 15-60 mg], we cannot rule out that our doses were still insufficient for any effect. Certainly, the differences in doses delivered to the lumbar spinal cord in an oral drug study as compared to an intrathecal drug study are sufficient to explain the differences observed in effect on clonus. That is, we observed little effect of baclofen on clonus whereas several authors (notably Latash et al 1989, Pirotte et al 1995) have observed a large reduction in clonus with intrathecal baclofen. Intrathecal application leads to sufficiently high doses of baclofen delivered to lumbar motoneurons that a post-synaptic effect may be present (Azouvi et al 1993, Dressnandt et al 1995) and this post-synaptic effect may then be responsible for the reduction in clonus.

Although this study was designed to permit comparison of the three drugs, the results also permit us to make observations regarding the progressive changes possible in the walking abilities of chronic incomplete SCI subjects. Subjects often retained in successive evaluations the gains made in previous evaluations, often in the washout period following a drug period in which they had greatly improved. Essentially, a return to baseline following a drug period was the exception rather than the rule. These observations are encouraging for clinical rehabilitation but they also lead us to examine the issues in having a well-controlled study of drug effects on walking.

SCI subjects with an incomplete loss of motor function clearly are not functionally stable well after the first year post-injury, and repeated measurement of walking, even as infrequently as every 2-3 weeks, permits improvement in walking regardless of changes in drug status. The retention of effects was particularly striking in the subjects who required

harness support. The three subjects who acquired the ability to perform stepping without manual assistance were repeatedly, and without exception, able at subsequent evaluations to perform at least short sequences of unassisted stepping. In the second group of subjects, retention of improvement is most evident in the speed data (see Figure 7). W1 and W2, for example, successively increased their MTS in an almost linear fashion. Subjects entered into the study later, such as P1 and C3, were repeatedly evaluated at first without changing their drug status. Repeated increases in MTS are visible in each of their first three evaluations. Part of the improvement that we observed may be due to a reversal of some of the disuse changes, such as muscle atrophy and fatiguability, that would particularly affect the subjects who used a wheelchair as their primary mode of locomotion. Furthermore, the improvements are consistent with studies of improved walking with treadmill training, including the use of body weight support where required (Barbeau & Blunt 1991, Barbeau et al 1993b, Dobkin et al 1992, Fung et al 1990, Hesse et al 1994, Visintin & Barbeau 1989, 1994, Wernig & Müller 1992, reviewed in Barbeau & Rossignol 1994). The surprising finding was that evaluations as far apart as two to three weeks permitted improvement. If the chronicity of the lesion does not assure a stable baseline from which to measure changes, then other steps are required for well-controlled studies, such as more frequent re-measuring of subject status or a more controlled walking task.

In subjects who showed large changes in response to one or more of the drugs, it was evident that washout of the drug was not equivalent to a return to baseline in walking status, particularly for clonidine. The results suggest the possibility that the drugs, when effective for a subject, create a permissive condition in which the subject may change his walking ability. When the drug is withdrawn, some of the changes in walking may persist. These findings suggest several avenues of further research regarding the mechanism of the ongoing change as well as the time course of the change in walking ability in drug and washout periods.

It is striking that, of the six subjects who were referred to the study having been taking one of the drugs for at least several months, four increased their MTS upon washout of

the drug (H1, C1, C2 & C3) and the other two showed a minor decrease (W2) or no change (S1). In considering the long-term benefits ascribed to drug therapy (e.g. Azouvi et al 1996), it would be interesting to know whether the functional gains depend on ongoing drug treatment, or whether benefit would be retained upon withdrawal, such as has been shown for withdrawal of intrathecal baclofen (Becker et al 1995, Dressnandt & Conrad 1996).

Some of the questions regarding the time course of change in walking may be addressed with acute doses of the drugs. The method of bolus intrathecal injection of baclofen has been useful in determining whether further intrathecal baclofen is appropriate to control spasticity. The same method may be appropriate in evaluating the acute effects of a drug in improving walking function. The aforementioned report of the acute effects of intrathecal clonidine on walking suggests that this method may allow an interesting examination of the relationship among aspects of walking and aspects of spasticity. The observation that changes in walking and changes in measures of spasticity occurred contemporaneously is of great interest, although not entirely surprising because clonidine has been previously shown to have a clinically useful effect on both. However, it is not at all clear whether other treatments, pharmacological or otherwise, are able to have such a contemporaneously beneficial effect. Further studies patterned after this study of intrathecal clonidine's effects, as well as after those in spinal cats of daily drug administration with training, will provide us with greater understanding of the role of pharmacological treatment in the recovery of walking.

All three of cyproheptadine, clonidine and baclofen have been in use for many years for a number of clinical problems, and the side effects reported by the subjects in this study were not dissimilar to those reported elsewhere. A few points are worth additional emphasis. In the doses used in this study, adverse side effects were relatively benign. Any side effects that were more troublesome were reduced by diminishing dosage and stopping the drug. The doses of clonidine used were at the low end of the range of doses used in previous studies of clonidine in spastic paretic subjects and much lower than the doses generally used for antihypertension (Atkin et al 1992, Materson et al 1993) or other

disorders (Rauck et al 1993, Singer et al 1995). Cyproheptadine and baclofen were generally associated with fewer side effects than was clonidine, although paradoxically each proved intolerable to some subjects. It is important to note that the severity of side effects seems to have no relationship with the severity of functional deficit (compare Table 1 with Table 3) while bearing in mind that all subjects had sustained traumatic spinal cord injury and the same may not be true of other spastic paretic populations. It is also important to note that subjects who elected to continue one or more of the drugs at the conclusion of their participation chose a dose that was less than or equal to, never greater than, the dose used in the study.

In conclusion, in the doses used in the present study, clonidine and cyproheptadine were each able to lead to improved walking in SCI subjects with incomplete loss of motor function, whereas baclofen did not lead to improved walking. The improvements associated with clonidine and cyproheptadine were variable in their nature and extent although generally greater in subjects with greater motor disability -- that is, SCI subjects who would usually be considered clinically to have no useful motor function caudal to the lesion level. Moreover, this comparison has shown differences among the drugs, particularly with respect to the effect on clonus and to the duration of effects. The findings regarding these drugs are consistent with the understanding of the roles of noradrenaline, serotonin and GABA in the modulation of locomotion in spinal animal models. Furthermore, the differences among the results support that it is important to evaluate the effects on walking of any treatment to affect spasticity if they interact with the neurotransmitter systems implicated in locomotion. We also conclude that there is a tendency for gains in walking ability in chronic SCI subjects, whether achieved during a drug period or not, to be retained in subsequent evaluations. Many studies have shown that drug therapy can be associated with improved clinical status. In contrast, this study has shown that additional clinical improvement may sometimes be obtained with reduction or withdrawal of the drug treatment, if the task (in this case, walking) continues to be demanded of the subjects. This has important implications for designing studies of therapeutic benefit of drug treatments, not merely in controlling for this effect, but also in

exploiting it for the maximum rehabilitation benefit with the least exposure to risk of adverse effects.

SUMMARY AND CONCLUSIONS

The recovery of walking ability has always been a goal for many individuals following spinal cord injury. As a result of changes in the spinal-cord-injured (SCI) population and progress in understanding the control of walking and in developing methods of rehabilitation, the goal of walking is becoming achievable for an increasing proportion of the SCI population. Based on the findings in animals and on the trials with human subjects, noradrenergic and serotonergic drugs may have a role to play in the recovery of walking in SCI subjects and warrant further study. The extensive use of baclofen for spasticity in the SCI population warrants a similarly close examination of its effects on walking. The main experimental study of this thesis was designed to compare the effects of cyproheptadine, clonidine and baclofen on the walking pattern of subjects who had sustained spinal cord injury with incomplete loss of motor function. This study showed differences in the effects of these drugs on walking that had not been compared in human subjects before. It confirmed some of the previous findings regarding cyproheptadine and clonidine and raised questions regarding the possible role of baclofen in the rehabilitation of walking in SCI subjects.

A summary of these drugs' effects on reflexes and locomotion can be found in the Table. There is evidence from multiple sources regarding several species that all three of these drugs are able to reduce spinal reflexes. Their mechanisms for producing such changes are different and thus they have differing profiles of effects across specific evaluations of reflexes from largely monosynaptic (e.g. H-reflex) to more complex polysynaptic reflexes. Nonetheless, all three drugs are able to produce clinically useful reductions in the signs and symptoms of spasticity in SCI subjects, and the selection of one over the others may be guided by the extent of troublesome side effects produced by action at the many receptors for each drug throughout the body. It is important to note, however, that the evidence in animal models does not suggest that a decrease in spinal reflexes will have a directly causal effect on locomotion. Although the decrease in spinal reflexes and the modulation of locomotion occur contemporaneously, it is far from clear whether one or the other is causal in this relationship. Furthermore, the effects on locomotion of

Table for Summary and Conclusions

Drug -> principal action in the spinal cord	Effects in animal models		Effects in human SCI subjects	
	Spinal reflexes	Locomotor output	Signs of spasticity & reflexes	Walking performance
clonidine -> stimulates noradrenergic α_2 receptors	decreases reflex responses, especially polysynaptic reflexes	Acute: "releases a spinal neuronal network generating locomotion" (Forssberg & Grillner, 1973, p. 186) Chronic: increases flexor bursts and step length in a well-performing cat; improves performance in a cat with previous deterioration	diminishes signs of spasticity with less effect on measures of monosynaptic reflexes (e.g. H-reflex, clonus) and more effect on presumed polysynaptic reflexes	improves performance in subjects with very little ability to walk causes little or no change in subjects who have already recovered substantial ability to walk
cyproheptadine -> blocks 5-HT receptors, principally 5-HT_2 receptors	decreases reflex responses blocks muscle activity that arises after application of 5-HT agonists or precursor	Chronic: reduces amplitude of muscle bursts with little effect on underlying pattern, by presumed effect at output of pattern generating circuitry rather than within circuitry itself	diminishes signs of spasticity, both monosynaptic (e.g. clonus) and polysynaptic	improves performance in subjects with very little ability to walk, especially reducing extraneous muscle activity such as clonus causes little or no change in subjects who have already recovered substantial ability to walk
baclofen -> stimulates $GABA_B$ receptors	decreases reflex responses, both monosynaptic (through presynaptic inhibition) and polysynaptic pathways [at high doses comparable to intrathecal application, induces motor neuron membrane changes]	Isolated spinal cord fictive output: reduces or blocks locomotor output Chronic: induces deficits in previously established pattern, and blocks walking at higher doses	diminishes signs of spasticity, both monosynaptic and polysynaptic [intrathecal doses can virtually or completely abolish reflex responses]	anecdotal reports of improved or deteriorated walking no reports of clinically important improvements in walking demonstrated by changes in muscle activity or angular excursion patterns

clonidine, cyproheptadine and baclofen are quite different, in contrast to their generally equivalent effect on reflexes. Clonidine, or other means of stimulating alpha-2-noradrenergic receptors, has triggered locomotor patterns in the hindlimbs of acutely spinalized cats, among other effects, and is believed to participate in stimulating the pattern-generating circuits themselves. Serotonergic drugs are believed to exert their effects on locomotion principally at the level of the output of pattern-generating circuits on motor neurons. Cyproheptadine may block the effect of excessive stimulation of serotonergic receptors that would otherwise result in overactivity of motor neurons during locomotion but with minimal interference in the expression of pattern-generating circuits at low doses. Baclofen has led to dose-dependent decreases in fictive and real locomotor output and the stimulation of GABA receptors is believed to be a means of down-regulating locomotion. In light of these differences, we turn to the results from the present doctoral thesis study.

Cyproheptadine and clonidine were associated with the greatest change in walking performance among subjects initially unable to walk without assistance. In this study, four such Frankel C subjects were recruited, all of whom were evaluated at each session with the use of the harness support system. Two of these four showed marked changes in walking status in association with both of cyproheptadine and clonidine and another showed a large relative increase in maximal treadmill speed in association with clonidine. There were eight subjects who entered the study already able to walk to some extent. Among these subjects, the effects of cyproheptadine and clonidine were less marked, although the speed changes in association with one or the other drug and the changes in ankle clonus associated with cyproheptadine suggest that the drugs had beneficial effects on the subjects' walking performance. The speed and clonus changes, and the finding that five of these eight subjects elected to continue one or more of these drugs at the conclusion of their participation, suggests that there were important benefits to the drugs. The benefits may have included the reduction of discomfort or other symptoms associated with spasticity, but they equally may have included an improvement in walking that is not well captured by the evaluation of brief sequences of walking pattern on a treadmill.

There are differences noted among the effects of the three drugs. The most obvious is that baclofen was not associated with marked improvements in the walking performance of severely disabled subjects as were the other two drugs. However, one of these four subjects entered the study already taking baclofen, and only one of the other three was able to complete a baclofen period during the study. Similar problems limited the conclusions for baclofen among the other eight subjects.

The differences between effects associated with cyproheptadine and those associated with clonidine were not as clear as has been found in the experiments in spinal cats. Both drugs were associated with modulation of the walking pattern in human SCI subjects as in chronic spinal cats, but the clear distinction between noradrenergic and serotonergic effects on relative timing and amplitude of muscle bursts was not seen in the humans. The one notable difference between the drugs' effects was that cyproheptadine was more commonly associated with a reduction in ankle clonus, similar to the cyproheptadine-associated reduction in brisk, spasm-like movements seen in spinal cats brought about by administration of serotonergic drugs. The reduced distinction between the effects of cyproheptadine and clonidine in human SCI subjects may be attributed to a combination of factors that were different in the cat experiments as compared to this and most other trials in humans. One factor is that the experiments in cats were of acute effects of injected doses, unlike the experiments in humans who took oral doses for several weeks and thus had time to make adaptations to any changes in motor function. A second factor is that the cats had undergone complete transection of the spinal cord, unlike the partial injury sustained by all of the human subjects. The state of the descending pathways is doubtless different, although to what extent is unknown. The discrepancies in methods and in findings between studies in animal models and studies in human SCI subjects limit the analysis of the mechanism of the drugs' effects in humans.

The experimental design of having multiple evaluations across several periods of drug intervention and washout gave rise to the finding of a greater adaptability in walking performance than had been expected in chronic SCI subjects not undergoing intensive training. Among all twelve subjects, there were seven instances of increased speed across

evaluations with no change in drug status. Moreover, ten of the twelve subjects left the study able to walk faster than they had at entry. The most likely explanation is that repeated evaluations, even as infrequently as every two to three weeks, creates a training effect which allows cumulative improvement. The mechanism of the improvement may involve several factors. There may be a reduction in disuse changes, such as muscle atrophy, that have occurred over time since the injury. There may also be other training effects such as the beneficial effect of practicing the same task repetitively at successive evaluations. Although the mechanisms of the improvement remain speculative, there are several clear implications for further research in the recovery of walking.

An effect of retained increase in speed and independence was particularly pronounced in three of the four harness-using subjects, particularly in washout evaluations. That is to say, all three showed a sharp increase in speed with cyproheptadine or clonidine with an incomplete return to baseline in the washout period. In addition to the general training effect discussed above, it is suggested that each of cyproheptadine and clonidine may act to permit greater training in some subjects who then retain the increase in walking status following washout of the drug. If this finding is replicated, it has important implications for the clinical usage of these drugs.

An important inference from these findings is that the disability levels of at least some individuals with incomplete spinal cord injury remain adaptable more than one year post-injury. While the reports of longitudinal change in neurological impairment following spinal cord injury have concluded that there is generally little or no change after the first year, it now seems clear that there is not a strong correlation between impairment and disability in some incomplete SCI subjects more than one year post-injury. To clarify the difference, we will use the definitions put forth by the the World Health Organization (WHO, 1980). Impairment was defined as "any loss or abnormality of psychological, physiological or anatomical structure or function," and disability was defined as "any restriction or lack (resulting from an impairment) of the ability to perform an activity in the manner or within the range considered normal for a human being." The reports that SCI subjects show little change after the first year post-injury are based on ratings of

impairment, specifically using instruments such as the ASIA neurological classification. The observation that disability may be modifiable for much longer is exciting for rehabilitation possibilities, and has implications for the design of intervention studies.

In addition to the ongoing improvement seen in some subjects without changes in drug status, there were other unexpected effects regarding the time course of change in walking performance. Many subjects retained benefits from drugs into the washout period. This was observed for cyproheptadine in two of the more disabled subjects and observed for clonidine in three subjects across the groups. The increase in treadmill speed, for example, was greater in the drug period than would be expected from a training effect alone and a drug effect was thus inferred. The retention of at least some of the increase in speed implies that a drug's overall benefit for walking behaviour lasts beyond the period in which it is present in sufficient concentrations to stimulate the receptors in the spinal cord and that implication poses interesting questions regarding the mechanisms of drug effects on walking. In particular, it suggests that the time course of drug effects on walking, over a period of drug administration and beyond it, is worth exploring. It may be that at least some of the drugs' effects result because they create a permissive situation in which the subject is better able to benefit from walking experience.

From these findings, several recommendations may be made for further research regarding pharmacological intervention for recovery of walking after spinal cord injury. The first is that Frankel C (or ASIA C) subjects continue to be targeted for participation in drug trials because important gains in walking ability may be demonstrated in such subjects. As discussed in the section describing the harness and treadmill, the use of such a system permits participation of subjects who would otherwise be excluded from studies of walking. The second recommendation is that walking performance should be evaluated differently in less disabled subjects. Among the subjects who had limited overground walking ability, maximal treadmill speed was somewhat responsive to change as an outcome variable. However, other variables should be explored that may better reflect the drugs' effects. The preferences of some subjects to continue the drugs after completing the study may imply a greater ease of walking that might be reflected in walking tasks that

better evaluate the control of walking: for example, overground walking on uneven surfaces or with different walking aids. For the two subjects with functional overground walking ability (that is, clearly Frankel or ASIA D level), the variable of maximal treadmill speed was not responsive to change. In such subjects, it is even more important to quantify more challenging locomotor tasks than treadmill walking. Alternatively, it may prove to be true that the drugs are simply not effective for SCI subjects who have already experienced substantial recovery of walking ability. We are unable at this time to distinguish between an unresponsive outcome measure and a true lack of effect, and further research is required.

In order to identify optimal strategies for recovery of walking following spinal cord injury, it is important to seek an understanding of the differences among drugs' effects. However, issues regarding the time course of change in walking performance have confounded a comparative analysis of the drugs' effects, and these issues regarding time course should be clarified before further comparative studies in human subjects may be successfully designed.

Several strategies may be employed to investigate these issues regarding the time course of changes in walking performance. When speed or other functional indicators are to be used in studying drug effects on walking, one of the possible strategies is to evaluate subjects on several occasions after each change in drug status. Such a design would permit an estimate of the rate of change that is occurring as a result of training or practice, and drug effects or washout effects would be inferred from an increase or decrease in the rate of change. A strategy such as this would be particularly important for harness-using subjects because they have less opportunity to improve their walking performance outside of sessions with the harness and treadmill than do subjects with greater functional walking ability.

An experimental design with multiple evaluations may be used to examine acute effects, such as in the study of the effects of a bolus dose of intrathecal clonidine (Rémy-Neris et al 1996), or to examine effects that occur over a longer time period. We will consider first

the investigation of acute effects. Further investigation of intrathecal clonidine is important because of the interesting results briefly reported thus far, specifically the rapid increase in overground speed with a bolus does of intrathecal clonidine that was absent when placebo injections were substituted. For example, it would be very interesting to know, if placebo doses are omitted and clonidine doses administered consecutively, whether a cumulative improvement effect may be seen as was found in spinal cats. A similar protocol could readily be implemented in trials of intrathecal baclofen because bolus intrathecal doses of baclofen are already usually used as a screening procedure prior to making a decision about pump implantation. A similar research design could also be used for serotonergic drugs such as cyproheptadine, although there currently seem to be no developments toward intrathecal administration of serotonergic drugs.

It is also important to consider the effects of drugs on a time scale longer than that of the acute intrathecal injections, similar to the time scale of the main study of this thesis. As discussed above, a strategy of multiple evaluations during each drug and washout period would allow a better estimate of the background rate of change -- a presumed training effect from ongoing walking evaluations -- and any effects associated with changing drug dose could be more readily determined. It is particularly important to incorporate into any study design a period of reducing drug dose even when the drug is apparently beneficial. The findings of Becker and colleagues (1995) and of Dressnandt and Conrad (1996) that there was little drop in functional status following reduction or elimination of long-term intrathecal baclofen are interesting in this regard. The findings in the main study of this thesis that washout of baclofen or clonidine often led to an increase in walking speed suggest that reductions or cessations of drug dose should be incorporated into the design of any study of the drugs' effects. It is not necessarily true that improvement in functional status following reduction in drug dosage means that the drug had a negative effect on the functional status. Rather, it may be that periodic changes in drug status, among other variables that can be changed, are necessary to provide a stimulus for adaptation.

A full understanding of the drugs' effects will certainly remain elusive until their time course is better understood. However, as stated above, their mechanism for stimulating a

change in the walking patterns of human SCI subjects is partly obscured because such subjects have incomplete cord injuries and most of the basic research has been performed in animal models with complete spinal cord transections (SCTs). Athough there has been some research using animal models with spinal cord damage that is more analogous to the typical injuries sustained by humans, the majority of the latter literature is in regard to anatomy and pathophysiology of spinal cord lesions and not in regard to motor behaviour. If we are to understand the mechanisms of these drugs' effects on individuals with incomplete spinal cord injury, there needs to be study of the pharmacology of locomotion in animals with similar lesions. For example, the effects of clonidine on walking pattern in cats with SCT was found to be blocked by yohimbine, thus confirming an alpha-2-adrenergic effect. In cats with partial spinal cord lesions, it is important to know, first, how the effects of clonidine are similar to the effects seen in the cats with complete SCT, and second, how locomotion may be changed by administration of other alpha-adrenergic drugs.

Despite the questions that remain to be answered regarding the effects of cyproheptadine, clonidine and baclofen, there are several positive and useful implications from the findings for clinical rehabilitation. First, partial recovery of walking ability may take place for much longer after incomplete spinal cord injury than the changes in neurological impairment might imply. It is only relatively recently in some areas that a large proportion of newly injured SCI patients have had partial sparing of sensory and/or motor function. Thus, the process of recovery of abilities, walking among them, in a population of SCI individuals with less severe impairment has not been well mapped out. It is exciting to consider the possibilities implied by a long-lasting adaptability in movement ability, although there is a great deal still to be learned about the extent of the adaptability and what may limit it.

It is also positive for clinical rehabilitation that there are means to develop walking ability in Frankel C SCI patients who are unable to participate in most forms of conventional gait training. The harness and treadmill system has led us to understand that some elements of walking may be expressed by some of these patients, and they may participate in walking evaluation and training as a result. Furthermore, the use of clonidine and cyproheptadine

in oral doses with relatively benign side effects may lead to marked increases in walking performance. It remains to be determined whether baclofen may also create such a permissive situation.

In contrast with the possibility of a drug-related permissive situation for training, however, is the finding in other instances of greater walking ability without drugs than with them. For example, six subjects entered the study having been taking one of the three drugs for at least several months to control spasticity. Five of the six subjects were able to increase their treadmill speed following washout of the drug. In the analysis of the findings, we are limited by not knowing what their treadmill speed would have been had their first evaluation been conducted without drugs, and our interpretation must be cautious in light of the probable training effects seen throughout the study. Nonetheless, the implication for rehabilitation is that conventional thinking about duration of treatment may need re-examination. For example, a 1986 review of treatment for spasticity in SCI patients stated that drug therapy "will presumably [be required] for the remainder of a patient's lifetime." (Young & Shahani 1986). To be fair to the authors of the review, they are making this point as part of their argument in favour of the necessity of objectifying any beneficial effect to drug therapy. Many findings since the writing of the review, including the findings of the main study of this thesis, suggest that we should examine whether short-term treatment and frequent changes in treatment lead to a better outcome than ongoing treatment without any modification.

In conclusion, the recovery of walking is becoming possible for an increasing proportion of those who sustain traumatic spinal cord injury. In order to maximize the recovery of walking in this population, we are developing therapeutic strategies from our understanding of the control of locomotion. Noradrenergic drugs, such as clonidine, and serotonergic drugs, such as cyproheptadine, have roles to play in the recovery of walking especially for those with severe impairment of motor function. As this study has shown, the effects of these drugs are different. However, both clonidine and cyproheptadine appear to be able to bring about a permissive situation in which important clinical improvements in aspects of walking may be attained and then retained in the subsequent

absence of the drug. Baclofen's effects were found to be different from those of the other two drugs and it remains unclear whether it may also have a permissive effect on walking, perhaps on a different time-scale from the other drugs. These drug therapies may be combined with other therapies, especially training that incorporates devices such as harness support or electrical stimulation, to maximize the recovery of walking. In so doing, the possibility for ongoing rehabilitation of walking after spinal cord injury may be greater and more long-lasting than previously thought possible.

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APPENDIX 1

CONSENT FORM

(English version)

SCHOOL OF PHYSICAL AND OCCUPATIONAL THERAPY

McGILL UNIVERSITY

Consent to participate in a research project on the effects of cyproheptadine, clonidine and baclofen on locomotor pattern, functional mobility and the modulation of the H-reflex

I, _____, consent to participate in a research study designed to evaluate the effects of cyproheptadine, clonidine and baclofen on locomotor pattern, functional mobility and the modulation of the H-reflex.

a) Purpose and protocol of the study

The purpose of the study is to examine if cyproheptadine, clonidine and baclofen can improve walking pattern or functional mobility, or change the modulation of the soleus H-reflex.
I accept to receive each of the three medications in progressively increasing doses for a week and a half, followed by a period of stable dosage for a week and a half, then a decreasing dosage for a week. There will then be a week of receiving none of the three medications. My total participation will last 14 weeks.
I accept to remain uninformed until the end of the study as to the order in which I take the medications.
I accept to be evaluated at the Human Gait Laboratory at McGill University every 2-3 weeks, according to the schedule of medications.
I accept to inform the researchers of all medications that I take during the study period, including the dosages.

b) Evaluation procedures

The walking pattern and the soleus H-reflex (when necessary) will be evaluated at the Human Gait Laboratory of the School of Physical & Occupational Therapy of McGill University.
(1) The walking pattern will be evaluated on the treadmill and/or on the floor.
(2) The activity of the certain lower limb muscles will be recorded using surface electrodes.
(3) The kinematic pattern will be recorded on videocassettes with the help of reflective markers. There will also be switches placed on the shoes.
(4) When necessary, the H-reflex of the soleus muscle (one of the calf muscles) will be obtained using electrical stimulation by means of a surface electrode on the back of the knee.
I understand that the treadmill is equipped with parallel bars and a harness, for my security.
The functional mobility will be evaluated by a physiotherapist in the laboratory.

c) Disadvantages of participation in this study

The principal disadvantage of participating in this study is that I may feel adverse effects ("side effects") from the medications, such as drowsiness, fatigue, dry mouth, increased appetite (with possible consequence of weight gain), constipation, nausea and decreased blood pressure. The adverse effects are more frequent during periods of increasing dosage and generally disappear with stable dosage. The most serious adverse effect is a possible decrease in blood pressure. I understand that the adverse effects will be measured by a nurse.
The other disadvantage is that I will be evaluated on specified occasions, and I must travel to the Laboratory for evaluations (transportation costs paid). The evaluations may be tiring but I will be given rest breaks as often as I need them.

d) Advantages of participation this study

The three medications may possibly improve my ability to walk and may also decrease my spasticity. After I complete my participation in the study, the results will be available to me, as well as to my doctor. I may continue taking one or more of the medications, if they improve my condition.

e) Effects of participation in this study

Treatment that I am receiving or that I will receive will not in any way be affected by my decision to partipate or not in this study.
The evaluations performed over the course of this study do not constitute a modality of treatment.

f) Information concerning the study

I understand that all supplementary information that I would like to obtain concerning this study will be provided to me. I understand that certain information will form some of the content of scientific publications; however, my anonymity will be respected at all times.

g) Withdrawal from the study

I understand that my participation in this study is voluntary and that I can withdraw at any time without prejudice.

I, undersigned, understand the procedures, disadvantages, advantages, and effects of my participation or of my withdrawal with respect to this study, and I know that the researchers will answer my questions, and **I consent to participate in this study.**

_____

Signature of the participant

_____

Signature of witness

_____

Date

I certify that I have fully explained to the participant identified above the nature of the study, its risks, and the fact that (s)he has the right to withdraw from the study at any time, without prejudice.

_____

Signature of researcher

_____

Date

Information:

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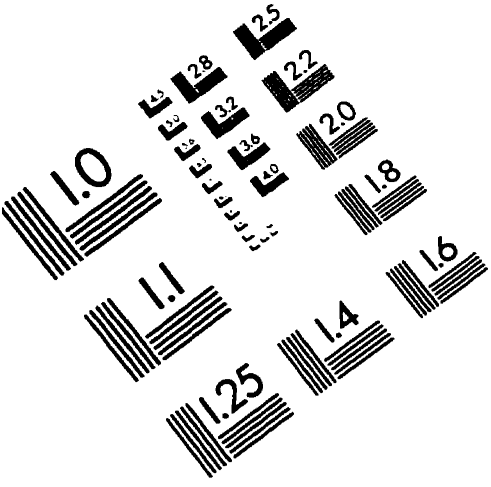
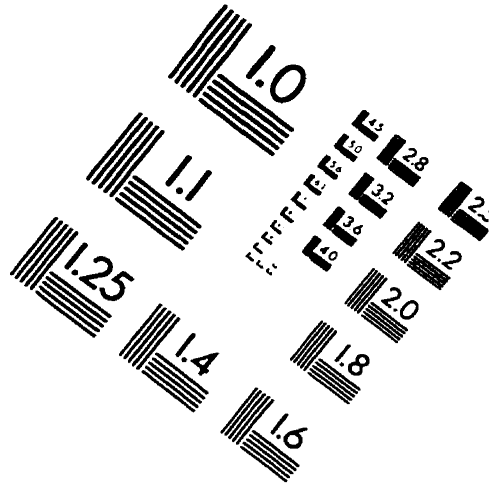
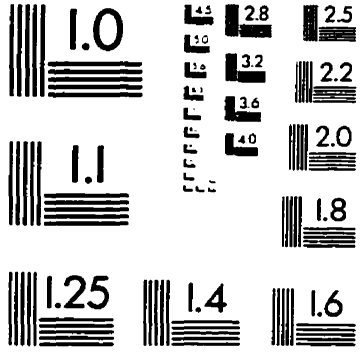
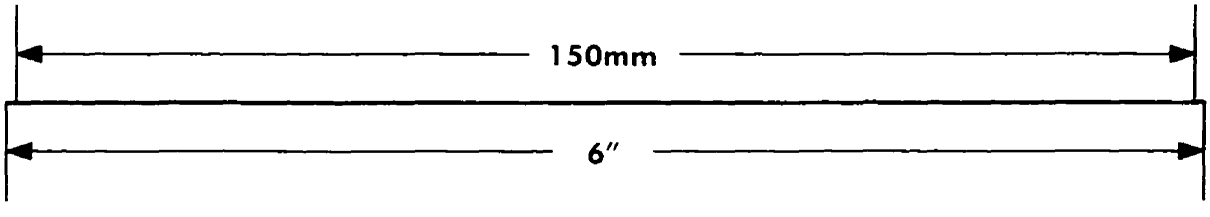
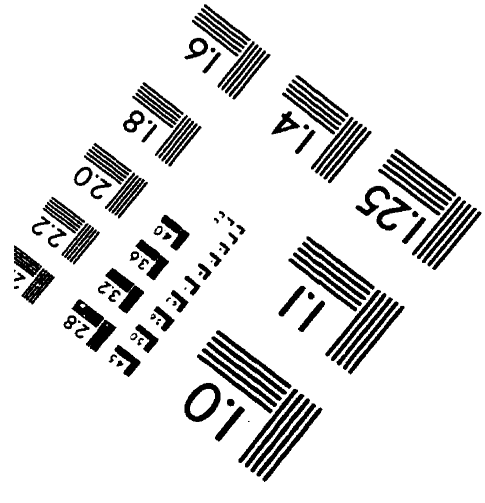
IMAGE EVALUATION
TEST TARGET (QA-3)

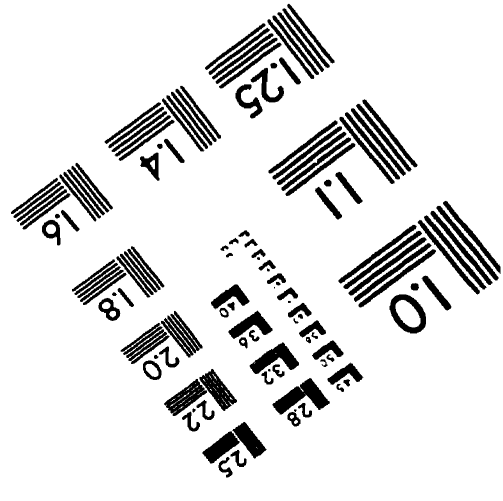












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