Forces consistent with plateau-like behaviour of spinal neurons evoked in patients with spinal cord injuries

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Summary

Percutaneous electrical stimulation over tibialis anterior and triceps surae was performed in 14 patients with traumatic spinal cord injury (SCI) to look for evidence that 'extra contractions' can develop, beyond those due to activation of the motor axons beneath the stimulating electrodes. Criteria for the extra contractions included marked asymmetry of force with respect to stimulation, progressively rising force during stimulation of constant amplitude and frequency, and force remaining high after stimulation frequency had returned to the control level following a high-frequency burst. Twelve of the 14 patients showed evidence of such behaviour, more frequently in triceps surae than tibialis anterior. Force or electromyographic activity commonly outlasted the stimulation in these patients. There was no apparent correlation between the completeness or level of injury and the ability to induce the behaviour. Evidence of force potentiation and 'habituation' was also seen. Eleven of the 14 patients exhibited hyper-reflexia and reported spontaneous spasms, but there was no obvious association with the extra contractions. It is concluded that non-classical behaviour of neurons within the spinal cord can contribute to the extra contractions evoked by electrical stimulation over muscles in spinal cord-injured subjects. This central contribution is less easy to obtain than in intact healthy subjects, all of whom showed the phenomenon. These contractions are consistent with the activation of plateau potentials in spinal neurons and, if so, plateau potentials may contribute to a patient's clinical manifestations.

Introduction

The spinal cord contains complex machinery for the control of movement, and it is now realized that its neurons are involved in multiple functions that depend on circumstances and go far beyond the simple reflexes that were first thought to be the main providence of the cord (McCrea, 1992). Examples of some simple spinal cord reflexes that may be elicited by artificial stimulation of afferents are the H-reflex, the tonic electrical reflex, the tonic vibration reflex and the flexion reflex. Mechanical vibration applied to the tendon of a skeletal muscle in humans tends to induce an involuntary tonic reflex contraction of this muscle and reciprocal relaxation of its antagonists (De Gail *et al.*, 1966; Eklund and Hagbarth, 1966). Under some conditions, the muscle

contraction may continue for 30 s or more after the cessation of the vibration. Similar effects have been observed when electrical stimulation was applied over the tibial nerve in normal man (Lang and Vallbo, 1967). These phenomena are largely mediated by Ia afferents.

Strong stimulation can result in a nociceptive flexion reflex (Dimitrijević and Nathan, 1968). In the lower limbs, depending on the site of stimulation, the reflex results in either plantar or dorsiflexion of the toes, dorsiflexion of the ankle and flexion of the knee and hip on the ipsilateral side. There are two components to this response: an early response mediated by A fibres and a late response through C fibres. These reflexes are associated with the perception of pain in

Table 1 *Subjects' condition including ASIA scale, drug therapy and the presence of 'extra' contractions following electrical stimulation*

Patient	Age (years)	Gender	Level	Duration of injury (months)	Medication	Hyper-reflexia	Extra contractions	ASIA scale		PND
								TS	TA	
1	38	M	T12 complete	3	Unrecorded	N	TS	0	0	–
2	42	M	T8 incomplete	9	Oxybutynin	Y	TS	1	0	Y
3	36	M	L1 incomplete	3	Oxybutynin	N	TA	0	0	–
4	21	M	T6 incomplete	4	Baclofen, oxybutynin	Y	TS	0	0	–
5	25	F	T4 incomplete	24	Nil	Y	TS	0	0	Y
6	47	M	L4 incomplete	8	Nil	N	TS, TA	2	1	–
7a	33	M	T12 complete	4	Baclofen, oxybutynin	Y	N	0	0	–
8	17	M	C7 incomplete	7	Baclofen, oxybutynin	Y	TS, TA	0	0	Y
9	35	M	C5 complete	10	Baclofen, oxybutynin	Y	TS	0	0	Y
10	10	M	C1 complete	77	Oxybutynin	Y	TS	0	0	–
11	21	F	L1 incomplete	150	Nil	Y	TS, TA	2	1	N
12	41	M	C4 complete	152	Baclofen, oxybutynin	Y	N	0	0	–
13	33	M	T10 incomplete	12	Oxybutynin	Y	TS	0	0	N
14	49	F	C4 incomplete	3	Baclofen	Y	N	1	2	–
7b	34	M	T12 complete	9	Baclofen, oxybutynin	Y	TS, TA	0	0	–

PND = peripheral nerve dysfunction (see Methods); TS = triceps surae; TA = tibialis anterior; ASIA = American Spinal Injury Association; Y = yes; N = no; – = not done.

intact subjects. They are not stereotyped responses and may be modulated by the movement and position of the limbs (Rossi and Decchi, 1994). Below the pain threshold, cutaneous stimulation in the legs of humans may produce results different from those of stimulation above threshold, and these responses are also modulated by movement and position (e.g. Burke *et al*., 1991).

In these reflexes, motoneurons may discharge in a linear fashion, with firing frequency proportional to the integrated sum of their inputs (Eccles, 1957; Kernell, 1965; Granit *et al*., 1966), but, under some circumstances, they may also discharge for prolonged periods outlasting any excitatory inputs (Schwindt and Crill, 1980; for a review see Binder *et al*., 1993). The latter may occur after activation of muscle spindle afferents by vibration (Hagbarth and Eklund, 1966) or electrical stimulation (e.g. Granit *et al*., 1957; Hultborn *et al*., 1975; Wada *et al*., 1989; Collins *et al*., 2001). With the long delay between input and response, it was thought originally that polysynaptic reflexes were involved (De Gail *et al*., 1966; Lang and Vallbo, 1967). However, animal experiments have shown that direct stimulation of motoneurons with injected current can produce bursts of motoneuron action potentials. These discharges last much longer than the original stimulus input, and are superimposed on a long-lasting depolarizing shift in membrane potential termed a 'plateau potential' (Hultborn and Kiehn, 1992; Fraser and MacVicar, 1996; Heckman and Lee, 1999; Kiehn *et al*., 2000; Hultborn *et al*., 2003; for reviews see Perrier and Hounsgaard, 2000; Hornby *et al*., 2002; Hounsgaard, 2002). Plateau potentials can also be produced by the application of neurotransmitters or neuromodulators, or indirectly by afferent volleys evoked by vibration, muscle stretch or electrical stimulation in the same manner as the reflexes in humans described above (Bennett *et al*., 1998*a, b*; Gorassini *et al*., 1999). Furthermore, their initiation may take 1 s or more, indicating that a long latency does not necessarily imply transmission through polysynaptic circuits (Genet and Delord, 2002).

In animal experiments, plateau potentials can be induced in spinal neurons by appropriate external stimulation and may occur during coordinated movements, such as walking (Eken and Kiehn, 1989; Brownstone *et al*., 1992). Plateau potentials in sacral motoneurons have been thought to underlie the spasms that occur with chronic spinal cord injuries (SCIs) in rats (Bennett *et al*., 2001*b*). However, there was no evidence of plateau potentials during the acute phase of SCI (Bennett *et al*., 2001*a*). Some indirect evidence suggests that plateau potentials may also be induced in able-bodied humans (Kiehn and Eken, 1997; Gorassini *et al*., 1998, 2002; Collins *et al*., 2001, 2002; Hornby *et al*., 2003; Nozaki *et al*., 2003) and it is thought that they contribute to muscle cramps (Baldissera *et al*., 1994). Although the mechanisms are not well understood, flexor spasms in patients with chronic SCI can be triggered by noxious and non-noxious skin stimuli, at a lower threshold than for intact subjects, and the reflex electromyographic activity (EMG) can persist after the initial stimulus (e.g. Dimitrijević and Nathan, 1967, 1968, 1970; Shahani and Young, 1971). Extremes of ankle movement have also been found to trigger flexor spasms in patients with SCI, presumably through group III and IV muscle afferents (Schmit *et al*., 2000).

The rationale for the present study was to look for evidence that extra contractions thought to be due to 'plateau-like' behaviour in spinal neurons can contribute to the contractions evoked by surface stimulation of muscle in patients with SCI,
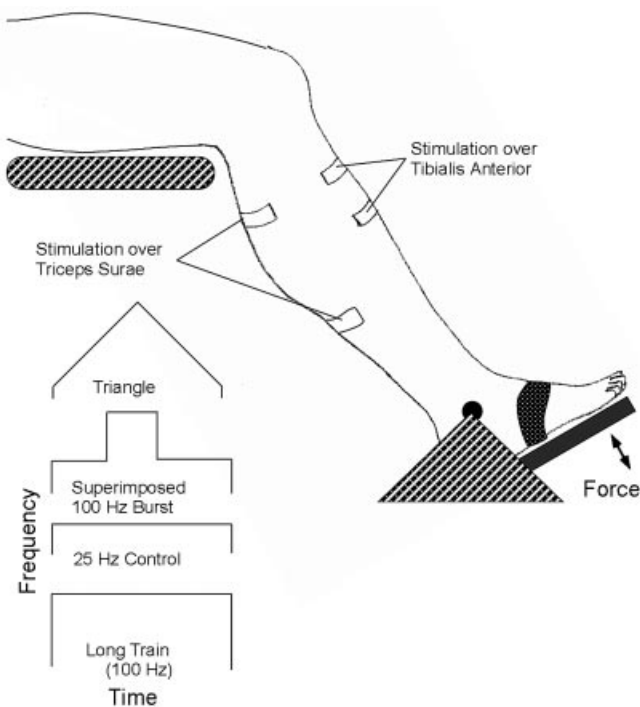
Fig. 1 Experimental method. Patients reclined in a comfortable chair with one foot strapped to a plate that was hinged co-axially with the ankle joint. A force transducer on the foot-plate recorded the resultant force produced by contraction of the triceps surae (TS) or tibialis anterior (TA) upon stimulation with rectangular current pulses of 1 ms duration. These groups of muscles were stimulated in separate sequences through surface electrodes, using the stimulation patterns in the bottom left of the diagram. In any one run, five or six test trains of a particular pattern (triangle, superimposed 100 Hz burst or long train of 100 Hz) were given to either TA or TS. The test trains were separated by intervals of 30–60 s.

and to assess whether these extra contractions are associated with the spasms and disturbance of tone typical of spinal spasticity.

Methods

The studies were performed on 14 patients (11 male, three female) with traumatic SCIs. Table 1 shows the clinical details for the patients. The study was repeated on one male after 5 months (patient 7). Five of the 14 patients were deemed to have complete cord sections on clinical grounds, i.e. as well as having no movement they had no residual sensory perception below the lesion. It is still possible to have functioning pathways between the brain and neurons below the lesion in clinically complete cord damage (Bunge *et al.*, 1993). Two of the incomplete patients were able to produce a force of level 2 on the American Spinal Injury Association scale with their triceps surae (TS) muscles, one incomplete patient produced a force of 1–2 in tibialis anterior (TA), the remainder produced voluntary force in the range 0–1 in the muscles tested. The procedures were approved by the local human research ethics committee, and were performed in accordance with the Declaration of Helsinki. All patients gave informed consent to participate in the study. Patients reclined in a comfortable chair with their hips, knees

and ankles flexed to between 90 and 110°. The right foot was strapped to a foot-plate hinged in the same axis as the ankle joint, constrained by a strain-gauge, designed to measure isometric torque developed by the muscles about the ankle joint (Fig. 1).

Electrical stimulation was applied over both the TS and TA of the right leg through pairs of flexible strip electrodes. For TS, the electrodes were 10–18 cm long and 3.5 cm wide and were positioned across the long axis of the muscle, ~10 cm apart, ~10 and 20 cm distal to the popliteal fossa. For TA, the electrodes were 5 cm long and 3.5 cm wide and were positioned at right angles to the long axis of TA, 2.5 cm apart, with the proximal electrode 3 cm distal to the tibial tuberosity (Fig. 1).

Trains of five or six pulses, each of 1 ms duration and constant amplitude, were delivered to TA and TS on separate occasions at a rate of 100 Hz by a stimulator (Digitimer DS7), while the force recorded by the strain-gauge attached to the foot-plate was noted. The trains were repeated with increasing stimulus amplitudes until there was no further increase in force. Stimulus amplitude was then adjusted until either the force was 6–10% of the maximal stimulated contraction force for the muscle, or the signal-to-noise ratio of the force was 15 dB (i.e. peak force ~6 times the peak noise), whichever was the greater. This stimulus level was similar to that used previously in normal subjects (Collins *et al.*, 2001, 2002) and was chosen to avoid stimulating nociceptors, although the level may have been below that required to produce extra contractions in some patients. If a signal-to-noise ratio of at least 15 dB could not be maintained, further experiments on that muscle were stopped. This occurred for TS in one patient (no. 3). Two additional patients could not be studied because, in spite of stimulus intensities >100 mA for both TS and TA, the forces produced were too small to be distinguishable from the noise. Hyper-reflexia was noted as being present if the patient reported regular spasms at least once per week, if spasms were observed in the patients' muscles or recorded on the force or EMG traces, or if it was found to be present on clinical examination (Table 1).

Having set stimulus strength as described above, four patterns of stimulation were delivered to each muscle in turn, controlled by a computer using Spike2 software and a '1401 plus' data acquisition interface (Cambridge Electronic Design). All pulses were of 1 ms duration. This pulse width is optimal for 'central' contributions to the force generated by repetitive submaximal stimulation (Collins *et al.*, 2002). The four patterns of stimulation (see Fig. 1) were a control train at 25 Hz for 7 s and three patterns of test stimuli. The first test pattern consisted of pulses at frequencies increasing linearly from ~4 to 100 Hz over 3 s and then decreasing from 100 Hz to ~4 Hz over 3 s (a triangular pattern of stimulation frequency, referred to as 'triangle' stimulation). The second test pattern was of 7 s duration and consisted of stimulation at 25 Hz for 2 s, then 100 Hz for 2 s, then 25 Hz for 3 s (referred to as 'superimposed 100 Hz burst'). The third test pattern consisted of a stimulus train at 100 Hz of variable duration but typically >7 s (referred to as 'long trains'). Usually five test trains were delivered during each experimental run, with 30–60 s between trains. At the beginning and end of the run, brief trains (5–6 pulses at 100 Hz) were given five times to check the consistency of the patient's response to stimulation. In some experiments, EMG from TA and TS was recorded using surface electrodes positioned adjacent to those used for stimulation.

Based on previous studies using similar methods, the following criteria were used to indicate that extra, centrally generated contractions had occurred with stimulation (Collins *et al.*, 2001, 2002). With triangle stimulation, there was marked asymmetry in the
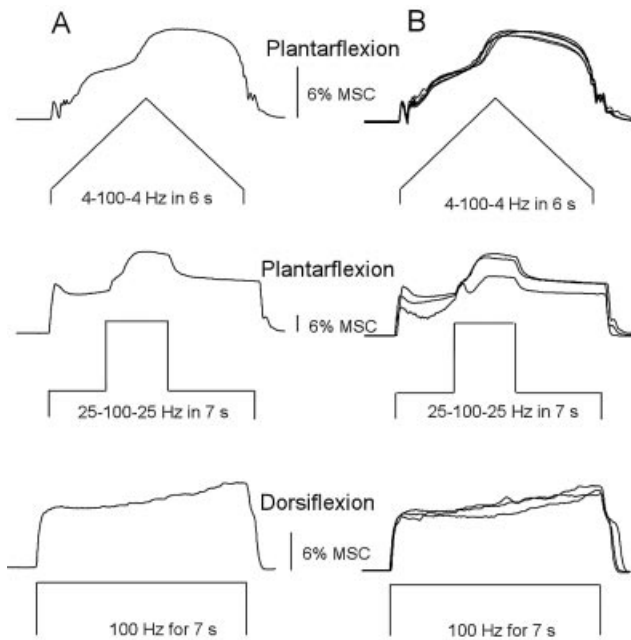
Fig. 2 Reproducibility of extra contractions in a patient (5) with incomplete spinal cord injury. The top trace in **A** is the force generated by TS as a result of triangle stimulation, with frequency increasing from 4 to 100 Hz and then decreasing again to 4 Hz, as shown in the second trace. The force generated was asymmetrical, with a major component produced as the stimulating frequency approached 100 Hz and then decreased. In **B**, the top set of traces shows the five superimposed force traces from one run. The middle set of traces in **A** shows the force developed by TS during a 25–100–25Hz stimulation pattern. The middle set of traces in **B** shows superimposed forces in three successive stimulations. The force in the second 25 Hz stimulating segment was higher than in the first 25 Hz segment. The bottom set of traces shows the responses of TA to a 7 s burst at 100 Hz in three successive trials. The force increased with time during the stimulation. Note the persistence of the force after cessation of stimulation. Vertical scales represent 6% of the maximal stimulated contraction (MSC) force.

evoked force such that the forces were relatively larger when stimulus frequency was declining. With the superimposed 100 Hz burst during the 25 Hz train, the force was higher after the 100 Hz burst when compared with the responses evoked by control trains of 25 Hz (of the same duration). In addition, the force was higher after the 100 Hz period than before it. In long trains, force rose after the first 1 s of the tetanus. Force and EMG persisted long (>1 s) after the stimulus trains had been turned off. Each criterion was assessed as being either present or absent, and only one was required for extra contractions to be considered present.

It is known that peripheral nerve dysfunction external to the spinal cord can occur in SCI patients (Nemchausky and Ubilluz, 1995; Rutz *et al.*, 2000). Six patients had motor and sensory studies performed on the median and peroneal nerves. These consisted of conventional nerve conduction studies and needle electromyography, as well as specialized microneurographic and other assessments of nerve excitability and conduction.

Statistical comparisons, between subsets of the patients' clinical status, and between the responses of patients to different forms of stimulation, were made using either χ^2 tests (Fisher's exact test
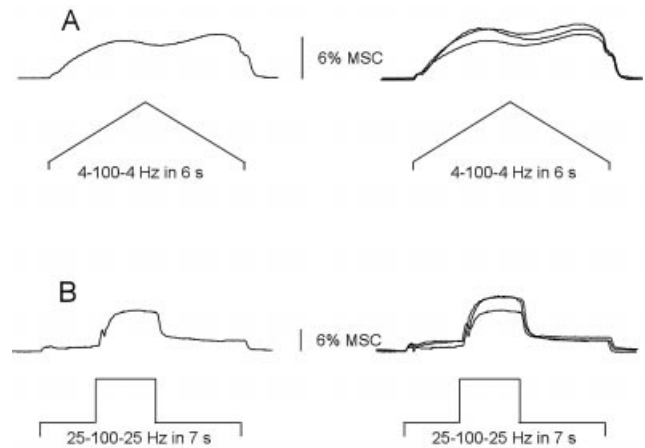

Fig. 3 Extra contractions in patients with complete spinal cord injury. The top trace in **A** is the force produced by TS in patient 1 as a result of triangle stimulation, with frequency increasing from 4 to 100 Hz and then decreasing again to 4 Hz, as shown in the second trace. The force was asymmetrical, with the larger component produced as the stimulating frequency decreased from 100 Hz. The consistency of the response can be seen in the three successive force traces from repeated triangle stimulation at 30 s intervals in the right panel in **A**. The left pair of traces in **B** shows the force developed by TS in patient 10 during a 25–100–25 Hz stimulation pattern. The force during the second 25 Hz stimulating segment was higher than during the first 25 Hz segment. The right traces demonstrate the consistency of the response to successive stimulations for this patient. Vertical scales represent 6% of the maximal stimulated contraction (MSC) force.

where appropriate) or Student's *t* tests. Student's *t* test was performed between patients exhibiting extra contractions and those without to see if there was any relationship to the level of SCI or the time since injury. The significance level was set at 0.05.

Results
It was possible to induce extra contractions (i.e. contractions in addition to those thought to be generated by direct stimulation of the motor axons) in the majority of patients (12 out of 14) with stimulus strengths greater than or equal to that required to produce 6% of the maximal stimulated contraction force. In such cases, the pattern of evoked force was qualitatively similar to that seen in able-bodied subjects (Collins *et al.*, 2001, 2002).

Extra contractions
Typical responses of patients with incomplete injuries to stimulation are shown in Fig. 2 (patient 5). The left panels (Fig. 2A) show three patterns of stimulation versus time, with the evoked muscle force above. With 'triangle' stimulation (top panel), there was an asymmetry of the force, with greater force as stimulus frequency was decreasing than when it was increasing. With the 'superimposed 100 Hz burst' stimulation (middle panels), the force was greater after the 100 Hz burst than before it, even though the stimulus frequency was 25 Hz
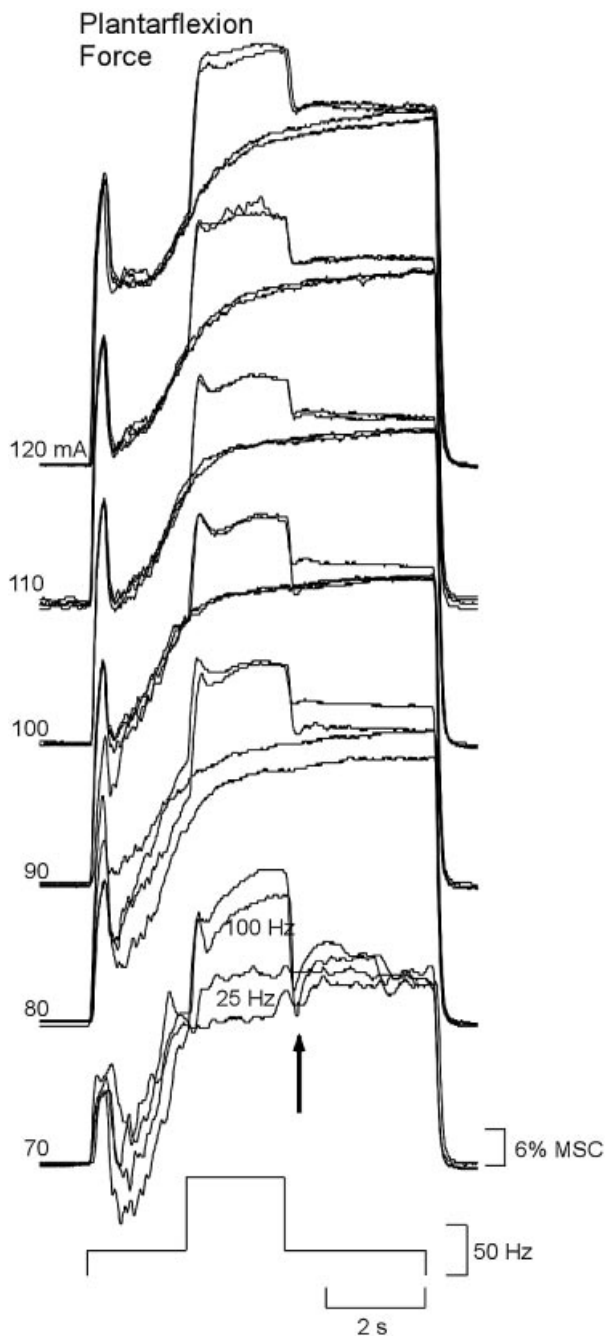
Fig. 4 Successive runs with increasing stimulation current (patient 13). Forces due to superimposed 100 Hz bursts are shown for different stimulation intensities. At each intensity, there were two sets of 25 Hz control stimulation for 7 s followed by a test superimposed 100 Hz burst. The intervals between each stimulation train ranged from 30 to 60 s. For the 70 mA stimulating current, there was no difference between test (100 Hz burst) and control (25 Hz) at the time indicated by the vertical arrow. As the current increased, the force outlasting the 100 Hz burst stimulation exceeded the control force. At currents of 110 and 120 mA, the force increment outlasting the 100 Hz burst was smaller than following 90 and 100 mA.

before and after the burst. The bottom traces show that, during a 7 s train at 100 Hz, the force continued to increase throughout the stimulation. The right panels (Fig. 2B) show

Table 2 *Frequency of extra contractions in relation to muscle group*

	Extra contraction	No extra contraction	Total
TS	68	83	151
TA	12	31	43
Total	80	114	194

$\chi^2 = 4.008$; $P = 0.019$ (Fisher's exact test); TS = triceps surae; TA = tibialis anterior.

the consistency of the response with successive stimuli. The bottom right panels show the forces persisting beyond the end of stimulation.

Similar responses were also seen in patients with complete injuries (Fig. 3). The top panels (Fig. 3A) show the response by patient 1 to 'triangle' stimulation, showing a similar asymmetry in the force trace to that for the incomplete patients. The bottom panels (Fig. 3B) show the response to 'superimposed 100 Hz burst' stimulation for patient 10, with the force after the 100 Hz burst being greater than before it. The right panels again show the consistency of the response with successive stimuli.

In one patient (subject 13), successive control trains at 25 Hz for 7 s were followed by 25 Hz stimulation with superimposed bursts at 100 Hz (see Fig. 4). Two control and two test trains were given in each experimental run. Six runs were performed, with the stimulus intensity increasing from 70 mA in the first run, in 10 mA steps to 120 mA in the sixth run. The force immediately after the 100 Hz burst (arrow) differed little from control sequences at 70 mA, but became increasingly greater than control values with higher test currents. This difference reached a maximum with test train currents of 100 mA.

Correlation with clinical status

In 12 of the 14 patients, it was possible to induce extra contractions, as defined, using the criteria given in the Methods. Six patients had studies on both TA and TS, seven on TS only, and one on TA only. In seven patients, extra contractions occurred only with TS, in one patient only with TA, and in four patients with both muscle groups. Overall, extra contractions were evoked in 11 out of 13 patients during stimulation over TS and five out of seven during stimulation over TA. In six experiments on the five patients with clinically complete lesions, the incidence of extra contractions showed no relationship to the level of the SCI (Fisher's exact test, $P > 0.05$). Similarly there was no significant relationship between the number of patients exhibiting extra contractions and the level of the injury. The stimuli resulted in extra contractions in TS more frequently than in TA ($P < 0.05$, Table 2, Fisher's exact test). In all, the 14 patients received 75 triangle stimulations, 54 long train stimulations and 59 superimposed 100 Hz stimulations. No one stimulus pattern was more efficacious, i.e. the type of stimulation did not influence the likelihood of inducing extra contractions.
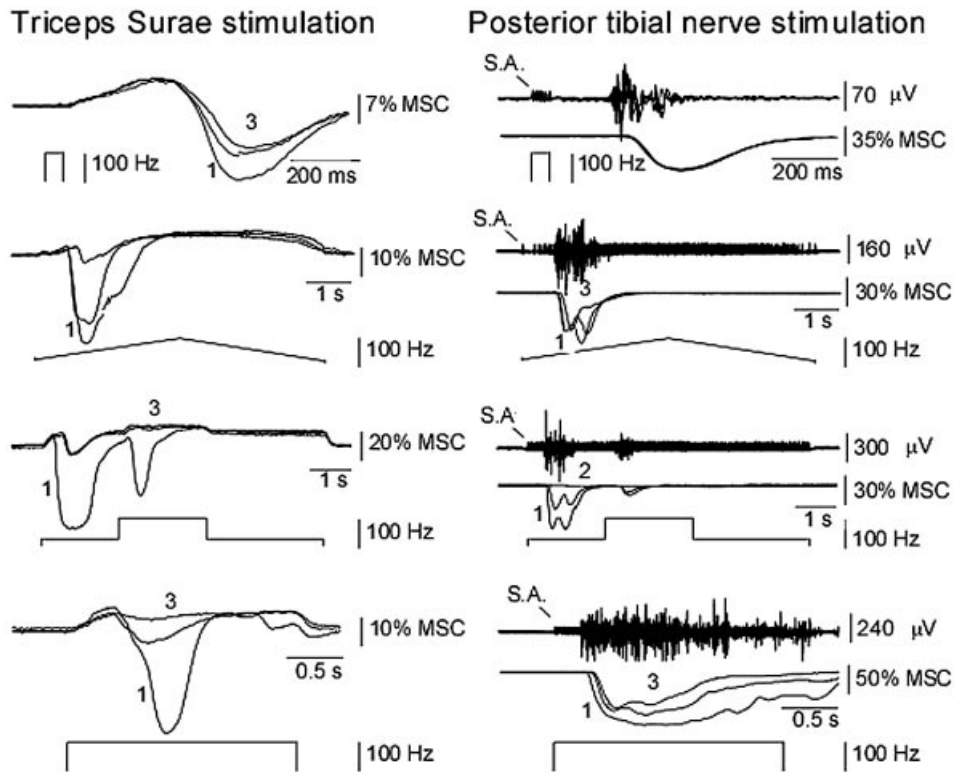
Triceps Surae stimulation

Posterior tibial nerve stimulation

Fig. 5 Flexion reflex accounts for antagonist activation in patient 7a. The panels show ankle torque during TS muscle stimulation (left panels), and ankle torque and TA EMG during post-tibial nerve stimulation at the ankle (right panels) using the same stimulus patterns. All panels show superimposed responses to three consecutive stimulus trains at 30–40 s intervals. Note the phasic nature of the contractions in both panels. Numbers next to the force data indicate the responses to the corresponding stimulus trains, showing that habituation occurred for both TS and tibial nerve stimulation. Stimulus artefacts are labelled S.A. MSC = maximal stimulated contraction.

Spasms and extra contractions

Eleven of the 14 patients showed symptoms or signs of hyper-reflexia below the level of injury (Table 1). They reported spontaneous spasms prior to the study, and six were on baclofen to control spasm. There was no significant correl-ation between hyper-reflexia and the ability to induce extra contractions for either the incomplete or the complete patients, as shown by Fisher's exact test. During stimulation over TS, some patients developed overt phasic contractions in the antagonist muscle (TA), resulting in the brief dorsiflexion torques shown in Figs 4, 5 and 6. In Fig. 6A (patient 7b), the onset of TS contraction was rapidly followed by a short period of over-riding antagonist contraction (a transient spasm in TA, see also Fig. 5) before the development of the extra contractions in TS. The 'two-humped' force profile shown in Fig. 6B (patient 9) evoked during triangular stimulation was typical and probably due to activation of the antagonist in a spasm as the stimulus frequency approached 100 Hz. Alternatively, or in addition, the second 'hump' may have been due to a spasm in the agonist.

Data from one of the three patients who showed no signs of extra contractions, but suffered flexor spasms and had an exaggerated flexion reflex, are shown in Fig. 5 (patient 7a). In this subject, stimulation over both TS (left panels Fig. 5) and TA (not shown) triggered brief spasms in TA. During TS

stimulation, as shown in the left panels of Fig. 5, these spasms produced dorsiflexion force (downward deflection) superim-posed on plantarflexion force (upward deflection) due to direct TS activation. Panels on the right of Fig. 5 show EMG and force recorded during stimulation of the posterior tibial nerve at the ankle using the same stimulation patterns as used for the TS stimulation. Whether the trains were brief, triangular, superimposed 100 Hz bursts or long trains (successive panels in Fig. 5), posterior tibial stimulation evoked reflex spasms in TA, with dorsiflexion torque profiles similar to those during TS stimulation. Tibial nerve stimu-lation with six pulses at 100 Hz (top right panel) evoked a TA contraction at a latency of 230 $\pm$ 5 ms (SEM $n = 7$), 180 ms after the last pulse in the train. Figure 5 shows the superimposed force responses to three consecutive stimulus trains. The largest dorsiflexion responses were typically generated by the first in a series of stimulus trains, and successive responses became progressively smaller (i.e. there was habituation, see below).

Figure 6 also shows examples of a potentiation in force (a progressive increase in force with trains repeated at short intervals) and possible 'habituation' (Dimitrijević and Nathan, 1970). The potentation in force bears some similarity to the phenomenon of 'wind-up' except that the time constant of action is longer (1–3 min) than in the conventionally
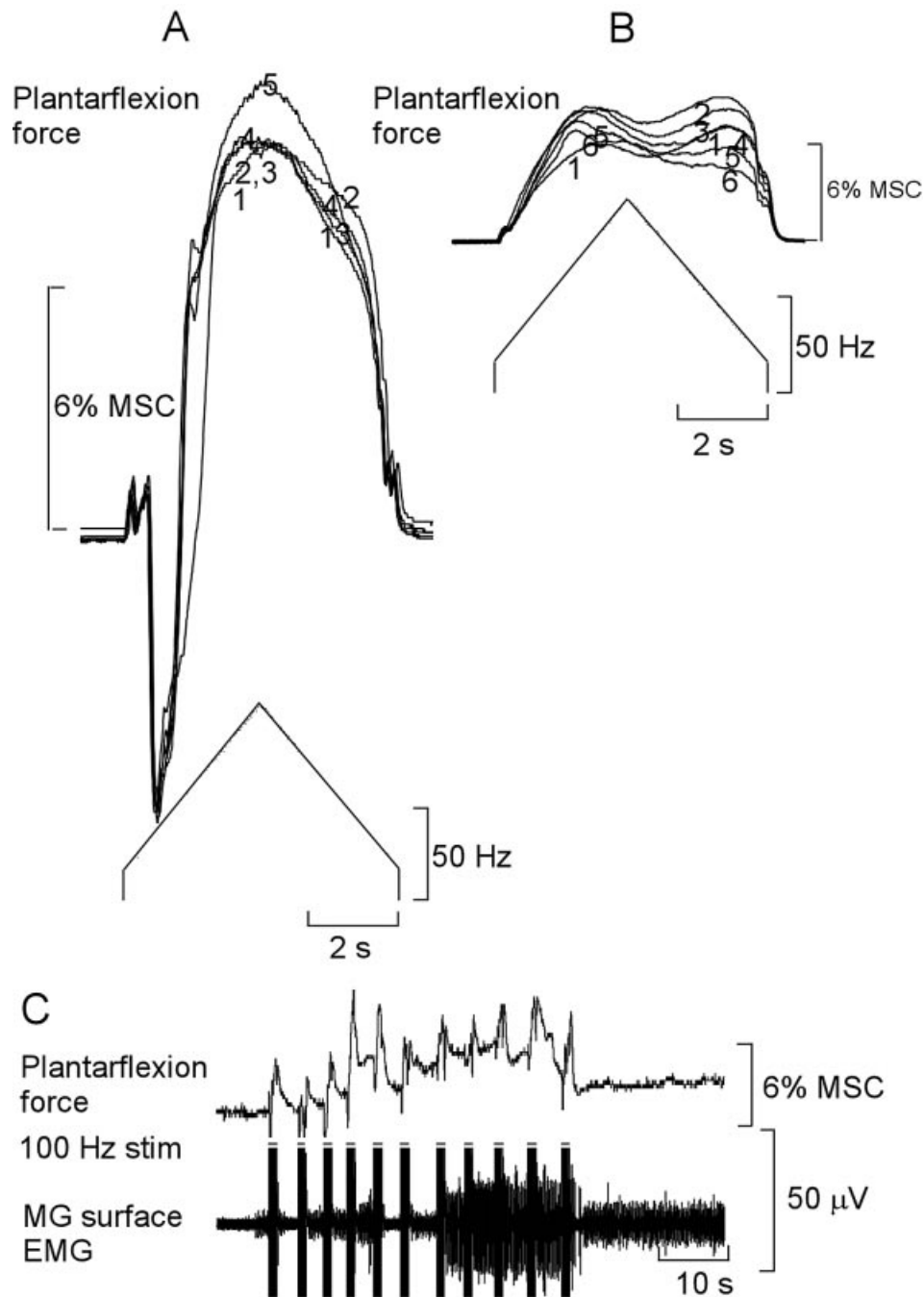
Fig. 6 Extra contractions, antagonist contraction, wind-up and habituation. (**A**) Examples of initial antagonist activity and then of extra contractions in patient 7b in trials at 30 s intervals due to triangle-type stimulation over TS. The force increases in successive runs 1–5. (**B**) For patient 9, the force initially increases, from 1 to 2, then progressively decreases in six successive trials. (**C**) Torque increments (upper trace) and MG EMG (lower trace) in response to multiple 2 s bursts of stimulation in patient 6. There was an initial phasic dorsiflexion with each burst, superimposed on a steadily increasing plantarflexion force. The phasic dorsiflexion becomes attenuated across the 11 bursts.

defined 'wind-up' occurring over 1–2 s (Herrero *et al.*, 2000; see also Gorassini *et al.*, 2002). Figure 6A illustrates responses to five successive triangle trains, separated by intervals of 30–60 s. The force increased with time. In another patient (Fig. 6B; patient 9), force increased from train 1 to 2, but then decreased over the subsequent trains. All patients showed a mixture of habituation and potentiation of their

responses. Habituation and potentiation commonly appeared to oscillate during an experimental run, with an approximate period of the oscillation ranging from 80 to 230 s. Overall habituation predominated over potentiation, with the mean drop in peak force being 11.7%, but the standard deviation was large (65.9%). The progressive torque increments in Fig. 6C (patient 6) evoked by consecutive 2 s bursts of 100 Hz
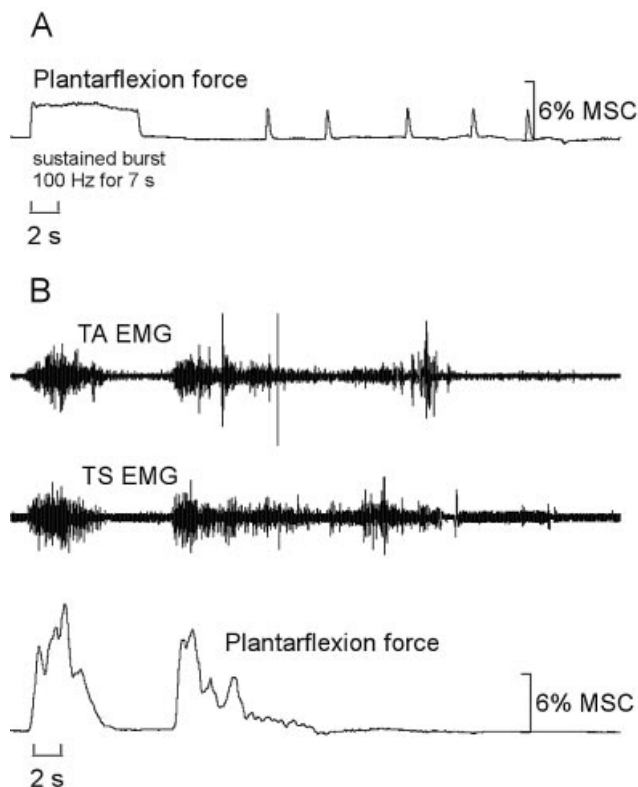
Fig. 7 Involuntary muscle contractions in patient 2. (**A**) Force during a 7 s burst of stimulation at 100 Hz, followed by five bursts of five pulses at 100 Hz (the brief trains given by percutaneous electrical stimulation through the same electrodes as the test trains and used before and after test trains to ensure that conditions remained comparable). The 7 s burst did not produce an extra contraction. (**B**) A spontaneous flexor spasm in TA and TS. The traces show, respectively, TA and TS EMG and force during the spasm, which had been preceded 45 s earlier by the stimulation of TS with the 7 s burst of 100 Hz stimulation illustrated in **A**.

stimulation were accompanied by increased EMG in all three components of TS (shown for MG) which continued in LG and MG for ~40 s after the final train. The EMG shows two runs of activity during the period of stimulation and a long third run after stimulation ceased, demonstrating that motoneuron firing continued beyond the end of stimulation, as is also clear in the force record. It is possible that one or more of these could have been due to spasm, though the limb was not postured to favour the development of extensor spasms (and spasms would have produced a more phasic EMG pattern). Persistent force or EMG after stimulus trains occurred in 12 of the 14 patients.

Figure 7 shows a recording of a spontaneous spasm in TS and TA in patient 2. It occurred 45 s after a stimulation of TS that did not produce extra contractions (Fig. 7A). Four of the 14 patients had spontaneous spasms during the experiments. χ^2 analysis revealed no relationship between the presence of spontaneous spasms during the study and extra contractions.

Four of the six patients who had peripheral nerve studies had evidence of lower motoneuron or peripheral nerve

dysfunction (Table 1). This was evident in those nerves arising below the cord lesion. It was characterized by decreased potentials and high thresholds for excitation, as well as some denervation. When corrected for temperature, there were no significant changes in conduction velocities (V. G. Macefield and M. Kiernan, personal communication). There were no significant correlations with the presence of extra contractions or clinical phenomena.

Discussion

This study confirms the anecdotal report of Collins *et al.* (2001) that, following trains of high-frequency stimuli, extra contractions may be evoked in patients with SCI. These involuntary contractions develop in addition to those due to direct activation of motor axons. The present results show that the magnitude of these extra contractions varies between patients with SCI and that this variability does not depend on whether the lesion is clinically complete or incomplete. Commonly force or EMG persisted after the cessation of stimulation in most patients. Although it is difficult to be certain that a lesion is truly complete on clinical grounds, so that some descending pathways between the brain and spinal cord may still be present in apparently complete SCI, the fact that extra contractions and persistent post-stimulus EMG activity were seen in patients with apparently complete SCI argues against the brain playing an essential role in the generation of these phenomena. There is also evidence that the excitability of the primary motor cortex decreases in normal subjects during sustained muscle contractions, that may be maintained by autonomous activity, thought to be due to plateau-like behaviour of neurons in the human spinal cord (Nozaki *et al.*, 2003).

A possible explanation for the extra contractions is as follows: stimulation over the motor axons causes an initial muscle contraction and activates muscle spindles which initiate action potentials in afferents. The stimulation also directly induces action potentials in afferent fibres. The afferent signals recruit other motoneurons directly and through interneurons and other spinal neurons. This enhances the muscle contraction and gives rise to further feedback to spinal neurons. Initially, the motoneurons would be generating action potentials in a conventional manner, dependent on the sum of their excitatory and inhibitory synaptic inputs. In between action potentials, they would revert to their resting state after the afterhyperpolarization. As the integrated excitatory synaptic input increased, an increasing number of spinal neurons would be driven from their resting state to a plateau-potential state (Genet and Delord, 2002; Hultborn *et al.*, 2003). With further synaptic input, these neurons would respond with sustained burst firing, so further enhancing the muscle contraction. This feedback would continue, with the motoneurons continuing to increase their output even as the stimulation decreased and in some cases continuing to fire after stimulation had ceased. Eventually the neurons would spontaneously revert from their plateau state to their resting

state or be driven back to the resting state by inhibitory synaptic input.

In normal healthy people and the incomplete SCI patients, some of the synaptic input giving rise to the plateau state will be from higher centres (Kiehn and Eken, 1997; Gorassini et al., 1998, 2002; Hounsgaard, 2002; for a review see Hornby et al., 2002). The role for plateau potentials is being increasingly recognized in a range of studies in animals and reduced preparations (for reviews see Hounsgaard et al., 1986; Hultborn and Kiehn, 1992; Hornby et al., 2002), and they are likely to be involved in the present findings.

It was possible to evoke these extra contractions in most of the SCI patients (12 out of 14 patients). The stimulation levels may have been too low to evoke the extra contractions in the two patients in whom the phenomenon was not observed. In addition, the presence of peripheral nerve dysfunction could have reduced the phenomenon in some patients. Two additional patients with SCI could not be studied because insufficient force was generated by stimulation over their leg muscles at >100 mA. In contrast, using similar testing methods, all able-bodied subjects examined by Collins et al. (2001, 2002) showed the phenomenon for both TA and TS stimulation. Six patients were tested electrophysiologically for peripheral neuropathy in their lower limbs, as may occur in SCI (Nemchausky and Ubilluz, 1995; Rutz et al., 2000). Evidence for peripheral nerve dysfunction was found in four. Six of the patients were on baclofen at doses designed to reduce spasms, and this drug may have reduced the magnitude and incidence of the extra contractions found in this study. Because of the drug therapy, peripheral neuropathy, the occurrence of spasms in patients, the time-dependent effects produced by stimulation (e.g. habituation) and the difficulty of ensuring identical levels of both afferent and efferent stimulation, it is injudicious to compare directly the amount of torque generated by the central mechanism in able-bodied subjects and those with SCI. However, the results in Figs 2 and 3, for patients with clinically incomplete and complete SCI, bear a qualitative resemblance to those reported in normal subjects (Collins et al., 2002). The size of the force increments was probably less in the patients for the different stimulus trains, though precise comparisons are difficult (see below). In contrast, in chronically spinalized animals, plateau potentials (and presumably the forces they generate) are more common than in intact animals (Bennett et al., 2001a, b). Presumably the difference between the results in spinal animals and humans is due in part to the baclofen therapy and the incidence of peripheral neuropathy (which would reduce afferent input into the cord and motoneuron output). Other causes may be the complete nature of the SCI in animal experiments, compared with the more usual partial injury in humans. This may lead to differences in cord plasticity, synaptic drive to motoneurons and possible effects from partially intact descending spinal cord pathways.

Harnessing this central mechanism to generate extra force by functional electrical stimulation of muscle may afford several advantages over more conventional stimulation techniques that initiate contractions primarily by the synchronous activation of the largest motor axons beneath the stimulating electrodes. The central mechanism activates muscle fibres asynchronously, with the smallest, motor units recruited first (see Collins et al., 2001), and thus, theoretically, the evoked contractions should be more fatigue resistant. It may be easier to evoke contractions of graded strength, and less battery power should be needed. Also, recruitment of muscle fibres that are not normally activated by electrical stimulation may help obviate the muscle atrophy that accompanies chronic SCI. Habituation in this study only caused an 11.7% decrease in force on average, so should not interfere unduly with any clinical application.

In this study, there was a significantly higher incidence of the extra contractions in TS than TA. This may be due to the higher proportion of small motoneurons innervating TS (associated with type I muscle fibres), particularly soleus. These motoneurons have a greater susceptibility to develop plateau-like behaviour (Lee and Heckman, 1998, 2000). However such a difference was not apparent in able-bodied subjects (Collins et al., 2002). It is possible that disruption of descending systems is more pronounced for flexor than extensor muscles after SCI. Such a loss could reduce the total excitatory synaptic input to the motoneurons, thus rendering them less likely to be driven into a plateau state.

In the present study, the level and completeness of the lesion and the time since injury had no significant effect on the incidence of the extra contractions. This could reflect the relatively small study population. We estimate that a sample size in excess of 50 may be required to assess these correlations with more certainty. It is difficult to evoke the tonic vibration reflex in patients with spinal cord lesions (Hagbarth and Eklund, 1968; Burke et al., 1972), a finding which suggests that the central mechanism for generation of extra forces is less obvious in these patients. All patients in this study sustained their injury at least 3 months prior to undergoing their study. Plateau-like phenomena are seen in chronic but not acute spinal rats (Bennett et al., 2001b). A factor complicating the interpretation of clinical data is medication. Extra forces induced by stimulation could not be demonstrated in patients 7a, 12 and 14 who were all on routine medication, including baclofen, but were clinically hyper-reflexic despite this medication.

Figure 6 illustrates other effects that have been reported previously for normal subjects and patients with SCI. In addition to the extra contractions, force potentiation and habituation were also seen (see also Fig. 5). Extra contractions are qualitatively similar to the 'wind-up' of force observed over a few seconds that is a feature of plateau potentials in motoneurons studied in animal preparations (Bennett et al., 1998b; Herrero et al., 2000; see also Hornby et al., 2003). However, the force potentiation occurred over a period of minutes, rather than seconds. Due to the long duration of the stimulation trains used in this study (6–7 s), any such wind-up during a stimulation train would contribute

to the extra contractions. Other factors with a longer time course may also be involved. The force potentiation over a longer period than that of wind-up, demonstrated in this study, could be due to integration with a longer time constant of excitatory effects in spinal circuits.

Stimulation of the posterior tibial nerve resulted in a flexion reflex with similar characteristics to the antagonist contractions recorded in the same subjects during the muscle stimulation over TS (see Fig. 5). Such reflexes are larger in SCI than in the able-bodied population and typically habitu-ate quickly (Shahani and Young, 1971). The extra contrac-tions seen in this study may be due to a wind-up phenomenon occurring during the long stimulation trains and appear distinct from the flexion reflex contractions. Contractions due to plateau activation in animal studies tend to increase with repeated stimulations due to the wind-up described above (Bennett *et al.*, 1998b; Herrero *et al.*, 2000). Thus one interpretation of the data is that the extra contractions include a component due to plateau-like behaviour and that the flexion reflexes are a different phenomenon. However, flexion reflexes in humans recently have been linked with plateau phenomena (Hornby *et al.*, 2003).

This study has shown formally that surface stimulation over lower limb muscles following spinal cord injury can produce unexpected force increments that vary in size but that can be dissociated from obvious hyper-reflexia. Persistent motoneuron firing after stimulation occurred in most (12 out of 14) patients, and this has been observed with similar inputs in able-bodied subjects (Collins *et al.*, 2001, 2002; Nozaki *et al.*, 2003) and after voluntary contractions in thenar muscles of patients with cervical lesions of the spinal cord (Zijdewind and Thomas, 2003). The probable mechanism of action is afferent feedback, coupled with feedback circuits within the spinal cord, leading to a large synaptic input into neurons driving them into a plateau state that in turn gives rise to motoneuronal firing. The mechanism is likely to be contained within the spinal cord, as demonstrated by the appearance of the phenomenon in patients with clinically complete spinal cord lesions.

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