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Spinal cord stimulation in multiple sclerosis: clinical results

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SUMMARY Clinical results of spinal cord stimulation by means of epidural electrodes are reported in 19 patients with multiple sclerosis. On temporary stimulation with percutaneous electrodes, significant improvement in mobility occurred in 27.7% of 18 patients and the same number showed improved sensory function. Only one of 13 patients with severe upper limb ataxia improved. The major response, both in terms of the percentage of patients responding and the extent of the responses seen was in bladder function: 75% of 16 patients with bladder symptoms improved and seven of the 11 patients with severe bladder disturbance (Kurtzke grade 3 or more) improved. Four of these seven patients had before and after cystometry and 3 showed reduced detrusor hyperreflexia. Altogether, 10 patients had a worthwhile clinical response in one or more aspects of the disease and of these, nine have so far gone on to permanent stimulation. Medium-term results (up to two years) show that, with one exception, improvement in bladder function has been maintained as long as stimulation has been continued and at least 50% of improvement in mobility has been maintained. A favourable response depends not upon the fact of stimulation but upon the type of stimulation received. This, along with other evidence, indicates that the response is not caused either by a placebo effect or by the natural fluctuation of the disease.

The use of spinal cord stimulation (SCS) in clinical practice developed from physiological advances. Melzack and Wall's (1965) theory of the gate control of pain provided a rational basis for a trial of spinal cord stimulation to alleviate intractable pain. Successful therapeutic results were first reported by Shealy *et al.* (1967). The application of this procedure to multiple sclerosis was the result of observations made by Cook and Weinstein (1973) when treating a multiple sclerosis patient for distressing and intractable backache. Spinal cord stimulation relieved the pain but, in addition, there was marked improvement in voluntary motor activity. This report passed unnoticed and ignored in this country until one of us (LSI) visited New York and observed the striking effects of SCS. Because of our interest in the effects of partial lesions on the central nervous system and the effect of repetitive stimulation (Illis, 1969, 1973), we repeated Cook's work, confirmed his results, and presented the first report of objective neurophysiological changes (Illis *et al.*, 1976). Abbate *et al.* (1977) reported clinical and urodynamic improvement in bladder dysfunction in multiple sclerosis patients, and there have been reports of improvement with SCS in other diseases, including spinal cord injury (Richardson and McLone, 1978; Campos *et al.*, 1978), cerebral palsy (Waltz and Pani, 1978), and spasmodic torticollis (Gildenberg, 1977). At a recent international workshop devoted to this topic (Sixth International Symposium on External Control of Human Extremities) six centres reported results. All demonstrated improvement in patients with SCS and all centres but one confirmed the beneficial effect of SCS.

In this paper we report our experience of 32 studies of SCS in 19 patients with multiple sclerosis over a period of two and a half years. Results obtained in patients with other neurological diseases will be reported elsewhere. Neurophysiological changes associated with SCS will be presented separately (Sedgwick *et al.*, 1980).

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Table 1 *Patients receiving stimulation and clinical response*

Patient	*Age (yr)*	*Sex*	*Duration (yr)*	*Course in last 5 yr*	*Period since last remission or improvement*	*Effect of most recent ACTH*	*Clinical state at time of stimulation*	*Response to initial stimulation*	*Permanent stimulation*	*Period of follow-up (mo)*	*Present clinical state*
1 CP	36	M	5	Relapsing	9 mo	Improved in acute relapse	Severe sensory ataxia. Absent bladder sensation and control. Touch impaired to T7 and pinprick to T10. Joint position sense impaired up to and including knees.	Legs felt lighter. Improvement of joint position sense and reduction of ataxia. Sensory level reduced to instep bilaterally. Restoration of normal bladder sensation and control.	Yes (for 18 mo)	30	Mobility worse than before stimulation. Bladder as pre-stimulation. Electrodes removed at patient's request after 18 months of permanent stimulation.
2 DS	41	M	2	Relapsing	9 mo	No change	Weakness of legs and ataxic gait. Able to walk about 300 yards. Painful spasms on right. Touch and pinprick impaired distally in legs. Joint position sense impaired in toes and vibration sense to iliac crest. Nocturia and impaired bladder sensation. Incontinent by night and and day. Intermittent claudication. Angina.	Able to walk further and more easily. Nocturnal spasms ceased. Normal sensation in feet. Normal bladder sensation and control. No further claudication. No angina. Returned to work.	Yes	30	Improvement in mobility and bladder function maintained. Some return of claudication but not of angina.
3 SE	44	F	2	Relapsing	6 mo	No change	Spastic quadriparesis. Unable to sit up without support or to take a bath on her own. Could walk with great difficulty for a few yards using a Zimmer frame. Pain in both legs and trunk. Sensory level to touch and pain at T6 on right, T7 on left. Catheterised for one year. No bladder sensation.	Twenty-four hours after start of stimulation, pain disappeared and she could use muscles innervated by C7–8 and T1 segments fully. Could sit up from supine position with arms folded across the chest. At 48 hours the sensory level decreased to T10 on right and L1 on left. At 72 hours normal bladder sensation and control. Able to walk unaided.	Yes	30	Improvement in upper limb function maintained. Most of the improvement in mobility lost. Bladder function still almost normal though occasionally has mild hesitancy, urgency and frequency.
4 NE	37	M	5	Relapsing	2½ yr	No change	Wheelchair bound because of severe weakness of the legs. Absent propricception in legs.	No response. Electrodes had to be removed because of minor infection of exit hole after only two days of stimulation. Symmetrical stimulation not achieved.	No	30	Condition unchanged from pre-stimulation.
5 EM	22	F	5	Relapsing	2 yr	No change	Severe cerebellar ataxia of both arms and legs. Able to feed herself solid food but unable to drink or pour fluids. Able to walk with help or with holding on to surrounding objects.	Minor improvement in upper limb ataxia. Able sometimes to pour water and also able to drink fluids without spillage.	No	30	Condition unchanged from pre-stimulation.

6	GC	48	F	20	Relapsing	3 mo	No change	Weak and grossly ataxic. Virtually wheelchair bound. Can walk with Zimmer frame for about 3–4 yards. Dysaesthesia right hand. Loss of light touch and pinprick distally in legs. Absent proprioception in toes, impaired at ankles. Mild bladder symptoms.	No change. Did not appear to switch on stimulator at all therefore no stimulation achieved.	No	30	Condition unchanged from pre-stimulation.
7	JM	50	F	8	Progressive	·5 yr	Made worse	Severe weakness of legs. Virtually wheelchair bound. Able to manage a few steps with a Zimmer frame. Some weakness of the hands. Minor, variable bladder symptoms. Hypoaesthesia of feet and left hand and impaired proprioception in toes.	Urgency less. Slight increase in power left leg and left arm. Able to stand more easily and to remain standing longer.	No	16	Continuing to have very gradual deterioration in mobility at pre-stimulation rate.
8	OB	40	F	20	Relapsing	·5 yr	Not given	Able to stand only with help. Could manage one or two steps but virtually wheelchair bound. Some weakness left arm and moderate upper limb ataxia. Moderate frequency and occasional urge incontinence.	Urgency less.	No	15	Condition unchanged from pre-stimulation.
9	SBK	46	F	9	Relapsing	·5 yr	No change	Virtually wheelchair bound. Able to transfer from chair only with great difficulty and assistance Severe frequency and urge incontinence.	Gradual improvement in bladder function over one week to normal frequency, minimal urgency and no incontinence. Slight increase in power in legs so that could rise to standing position more easily.	Yes	15	Bladder improvement maintained until one year after implantation when the electrodes had to be removed (pressure necrosis). Two weeks after electrodes removed, returned to pre-stimulation state. Electrodes to be reimplanted shortly.
10	NP	53	F	16	Progressive	·5 yr	No change	Wheelchair bound. Catheterised for some years. Upper limb ataxia. Burning and spasm in the legs.	No change.	No	15	Condition unchanged from pre-stimulation.
11	CF	57	F	9	Progressive	·5 yr	No change	Weakness and incoordination of legs so that could walk only for about 50 yards using two sticks. Tendency to fall. Able to climb the stairs only once a day. Able to stand for only short periods. Mild bladder symptoms.	Marked increase of speed, endurance (up to 400 yards) and of steadiness of walking. Using only one stick. Doing much more housework and feeling less tired. Climbing stairs many times a day. Able to stand indefinitely. Improvement in hesitancy and urgency.	Yes	14	Has maintained most of her improvement in mobility.

Table 1—*continued*

Patient	*Age (yr)*	*Sex*	*Duration (yr)*	*Course in last 5 yr*	*Period since last remission or improvement*	*Effect of most recent ACTH*	*Clinical state at time of stimulation*	*Response to initial stimulation*	*Permanent stimulation*	*Period of follow-up (mo)*	*Present clinical state*
12 MR	35	F	12	Relapsing	>5 yr	No change	Wheelchair bound. Able to stand only with support both sides. Marked upper limb ataxia. Sensory loss in all modalities to about T10. Catheterised for three months.	Slight increase in power of the legs, so that she could stand more easily. Slightly improved upper limb co-ordination: able to drink tea without spilling it. More reliable bladder sensation. Light touch and pinprick sensation restored to legs proximally.	No	12	Condition slightly worse than pre-stimulation.
13 AM	59	M	16	Progressive	>5 yr	Not given	Wheelchair bound. Able to stand only with support both sides. Severe frequency and urge incontinence. Occasionally voiding without awareness.	Progressive improvement in bladder function over several months until virtually normal. Slight improvement in leg function so that can transfer more easily.	Yes	10	Bladder function now virtually normal. No further improvement in mobility.
14 MW	40	F	6	Relapsing	1 yr	Improved in acute relapse	Severely restricted mobility due to weakness. Able to walk a few yards very slowly with a Zimmer frame. Truncal ataxia.	No definite improvement. Used the stimulator at very low levels of stimulation—well below those used by other patients.	No	7	Has continued to deteriorate at the pre-stimulation rate.
15 GM	27	M	8	Relapsing	6 mo	Made worse	Restricted mobility due to weakness. Able to walk about 100 yards slowly. Can manage stairs. Frequency and urgency. Wearing a urosheath.	No change.	No	6	Condition unchanged from pre-stimulation.
16 RT	55	F	1	Progressive	1 yr	Not given	Spastic quadriparesis. Able to walk only one or two paces with a Zimmer frame. Weakness of the hands so that unable to write. Hesitancy, frequency, urge incontinence, and frequent urinary infection.	Able to walk with elbow crutches. No urinary infection. Continent. Has normal bladder sensation and function.	Yes	15	Maintained improvement in mobility and bladder function.

17	HS	59	F	30	Progressive	>5 yr	Made worse	Restricted mobility due to weakness, spasticity and severe painful flexor spasms. Manages a few yards with a Zimmer frame. Moderate frequency and urgency, urge incontinence and nocturia.	Increased power left leg. This was not reflected in improved gait because patient developed right femoral nerve palsy due to a retroperitoneal haemorrhage on anti-coagulants for DVT. Spasms completely controlled. Great reduction of urgency and no urge incontinence or nocturia.	Yes	3	Bladder improvement maintained. Increasingly able to take advantage of improvement of left leg as femoral nerve palsy recovers. Spasms still controlled.
18	JL	34	F	10	Relapsing	18 mo	Minor improvement in walking	Mild paraparesis. Able to walk several hundred yards at moderate speed with support on one side. Impaired proprioception and light touch in feet. Catheterised for four years for frequency and urge incontinence. No bladder sensation for three years.	Bladder sensation restored in two days. After four days, able to spigot off catheter for greater than two hours without leakage. Catheter removed. Still having some frequency and occasionally slight leakage by day but dry most nights. Able to treat previously intractable urinary tract infection. Able to feel her feet on the ground when walking for the first time in years.	Yes	1	Occasional incontinence and still has some frequency and urgency.
19	SBT	45	F	15	Relapsing	2½ yr	Improved vision	Restricted mobility due to leg weakness. Can manage 10–20 yards with Zimmer frame. Pain and numbness in legs but minimal objective sensory loss. Severe frequency and urge incontinence. Occasional hesitancy.	Increased endurance (up to 90 yards). Great reduction in urgency and dry all the time. No nocturia. Still has frequency. Cystometry improvement.	Yes	1	Improvement in bladder function and in endurance maintained.

Patients and methods

All patients gave informed consent to the procedure after its nature and possible hazards had been explained and discussed with them and their relatives. Clinical data are summarised in Table 1. All patients but one fulfilled the criteria of Schumacher *et al.* (1965), and in addition 17 patients had abnormal visual evoked potentials and 10 had abnormal brainstem evoked potentials. One patient (RT) did not fulfil all the criteria of Schumacher *et al.* She had a progressive spastic quadriparesis with bladder involvement, normal myelogram and CSF, abnormal cervical evoked potentials but normal visual evoked potentials. The most probable clinical diagnosis is multiple sclerosis. All patients had been observed for at least one year before stimulation, and had been clinically stable or steadily deteriorating for at least six months at the time of treatment, with the exception of one patient (GC, table 1).

Patients with fluctuating symptoms, doubtful diagnosis, intercurrent infection, or who were unable to understand the experimental procedure were excluded. Otherwise no attempt was made to select patients. This was a deliberate policy as we could not predict which patients would respond. We included patients with both long and short durations of illness, with a significant degree of disability, and with a variety of manifestations of multiple sclerosis. Seven patients were virtually confined to a wheelchair.

For practical and ethical reasons it has not been possible to have a parallel group of matched control subjects, still less to have "blind" patients or assessing physicians. The patients, however, served as their own controls, all but one were known to us for at least one year before stimulation, and seven had been followed personally since the onset of their multiple sclerosis (two to five years). Many patients have had at least two periods of SCS separated by three to nine months, and their clinical states before and after stimulation were compared on each occasion. In addition, clinical observations were correlated with measurement of objective physiological parameters.

METHODS OF ASSESSMENT

All patients were graded according to the Kurtzke disability scale (Kurtzke, 1961, table 2). Repeated clinical and neurophysiological (Sedgwick *et al.*, 1979) assessment as an inpatient was carried out for at least one week before stimulation. Urodynamic studies were performed before and during stimulation in nine patients. Residual urine was measured, cystometry was performed with rectal subtraction (infusing at 50 ml per minute), and a record was obtained of the urethral pressure profile in accordance with the method of Brown and Wickham (1969). The apparatus used was a Devices recorder with an Elcomatic transducer EM750.

Cerebrospinal fluid analysis was made before and towards the end of stimulation using standard laboratory tests in six patients.

Full blood count, sedimentation rate, blood urea and electrolytes, microscopy and culture of urine, radiographs of chest and spine were carried out routinely. Two patients with severe urinary problems had intravenous pyelography, micturating cystogram, and cystoscopy (Mr J Jenkins) performed to assess any possible structural disturbance. Intake and output charts were kept on three patients before stimulation and these patients were kept to the same fluid input during stimulation.

Table 2 *Functional groups according to the Kurtzke disability scale*

Pyramidal functions
0 Normal
1 Abnormal signs without disability
2 Minimal disability
3 Mild or moderate paraparesis or hemiparesis; severe monoparesis
4 Marked paraparesis or hemiparesis; moderate quadiparesis; or monoplegia
5 Paraplegia, hemiplegia, or marked quadriparesis
6 Quadriplegia
V Unknown

Sensory functions
0 Normal
1 Vibration or figure-writing decrease only
2 Mild decrease in touch or pain; moderate decrease in position, vibration or discrimination
3 Marked hyposensitivity (not complete)
4 Analgesia or anaesthesia to groin; hemianaesthesia or hemianalgesia
5 Analgesia and anaesthesia to neck
V Unknown

Cerebellar functions
0 Normal
1 Abnormal signs without disability
2 Mild ataxia
3 Moderate truncal or limb ataxia
4 Severe ataxia all limbs
5 Unable to perform co-ordinated movements due to ataxia
V Unknown
X is used after 0–3 when weakness of grade 3 or more interferes with testing.

Bowel and bladder functions
0 Normal
1 Mild hesitancy, urgency or retention
2 Moderate hesitancy, urgency, retention or rare urinary incontinence
3 Frequent incontinence
4 In need of almost constant catheterisation but with intact bladder sensation; severe bowel retention and/or incontinence
5 Lack of sensation and control of bowel and bladder function
V Unknown

METHOD OF STIMULATION

The procedure was carried out with normal sterile techniques. With the patient prone, on an X-ray table, 1.5% xylocaine was injected subcutaneously in the lower thoracic area to produce local anaesthesia. Under fluoroscopic control an epidural needle (we have used various sizes) was introduced in the interspinous space to reach the epidural space in the midline. The stylet of the needle was removed, and it was ascertained that there was no leakage of CSF. An electrode was passed through the needle pointing rostrally and advanced under fluoroscopic control to mid or high thoracic levels and positioned in the midline in the epidural space. The needle was removed and a second electrode was introduced in the same way, so that the two were positioned in the midline about one to three vertebral bodies apart. In some patients a third (recording) electrode was placed in position. The electrodes were fixed to the skin with either sutures or Steri-strips and anteroposterior and lateral radiographs were obtained to document their position. The electrodes were then connected to a receiver, usually with the positive electrode rostral. The loop antenna from the stimulator was placed over the receiver and a sterile dressing was applied to secure the electrodes and the receiver.

Patients were told that they may or may not feel a sensation of stimulation. Some were told they may feel nothing at all but others realised from talking to previous patients that the stimulator sensation aimed for was a symmetrical tingling into both legs. The reason for choosing this as optimum stimulation was based on our initial experience (Illis *et al.*, 1976). Because of the difficulty in placing electrodes and because of frequent electrode slippage, optimum stimulation was not always achieved even after several attempts.

Stimulation was carried out at 33 Hz with 200 μs width electric pulses at a voltage adjusted by the patient to give a pleasant warm tingling sensation. The current requirements of 11 patients were measured accurately. Patients were stimulated until 10 days of satisfactory stimulation had been given (this usually took two to three weeks), and the electrodes were then removed. Patients were seen at least monthly for follow-up. Those who had a satisfactory response were offered permanent stimulation, and were readmitted three to six months after initial stimulation for a repeat of percutaneous stimulation. If a consistent response was obtained, the electrodes were implanted subcutaneously and connected to a subcutaneous receiver. Our three most recent patients have had a permanent implant immediately after a successful trial of percutaneous stimulation without the three to six month gap. In our first three patients permanent electrodes were implanted via laminectomy and stitched to the dura mater to prevent movement but we have subsequently dispensed with this and have not observed an increased tendency to slipping. The receiver was usually placed in the right anterior axillary line.

Initially we used Davis and Geck platinum tipped electrodes but these have now been withdrawn and we now use Avery or Medtronic electrodes and other equipment (Avery Co, Farmingdale, USA: Medtronic, Shirley Lodge, Slough SL3 8QY).

Results

TYPE OF STIMULATION

Three patients had surface stimulation for three days with cutaneous electrodes in the mid dorsal areas and two patients had electrodes inserted and connected but with no batteries in the apparatus for two days. There was no change in these patients. Nine patients had stimulation sensation in the chest, shoulder, or into one leg only. There was no clinical change in these patients with the exception of one who had increased spasms (reversible). Sixteen patients had symmetrical sensation into both legs, and 11 showed clinical response (table 3). Some of the patients who had

Table 3 *Clinical response with different types of stimulation on initial stimulation indicating that response is related to the type not the fact of stimulation*

Patient	*Number of Kurtzke grades of improvement (most responsive function)*	
	Symmetrical stimulation into legs	*Other types of stimulation (chest/shoulder/one leg)*
1 CP	5	–
2 DS	3	–
3 SE	5	–
4 NE	–	0
5 EM	1	–
6 GC	–	0
7 JM	0	Increased spasms (reversible)
8 OB*	0	0
9 SBK*	2	–
10 NP*	–	0
11 CF	1	–
12 MR*	1	0
13 AM*	2	0
14 MW*	0	–
15 GM*	0	0
16 RT	3	–
17 HS*	1	0
18 JL	3	–
19 SBT	0	0
Improvement	11	0
No change	5	9
Worse	0	1

*Patient aware of projected stimulation.
–Stimulation not obtained.

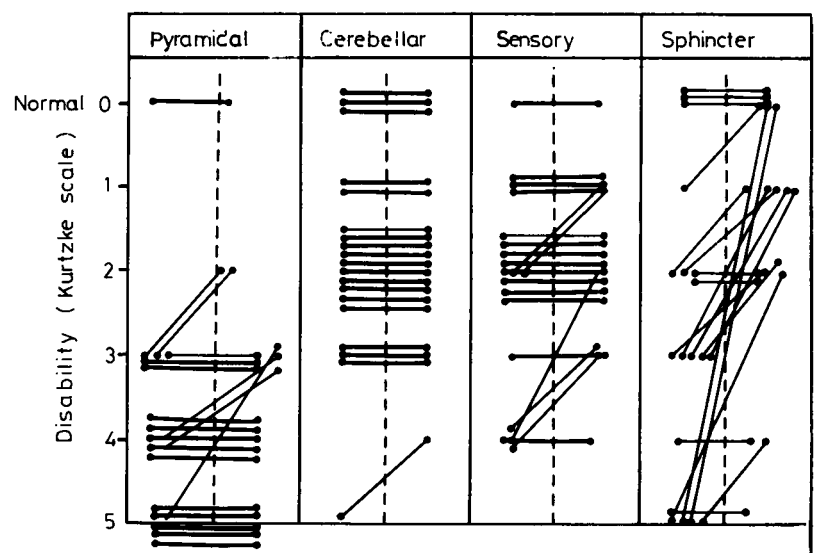
shown no clinical response with unilateral stimulation responded to symmetrical stimulation. There was no difference in response between patients who were aware of the projected sensation and those who were not.

One patient (CP) had a good response to stimulation and went onto permanent implant. After three months of continuous improvement he deteriorated to his pre-stimulation state clinically and physiologically, and the stimulator sensation became localised to a unilateral distribution on the chest wall. Radiography indicated that one electrode had slipped 5 mm from the midline. When this was replaced he again showed clinical and physiological improvement.

CLINICAL RESPONSE ON INITIAL STIMULATION

We have studied 19 patients receiving temporary stimulation with percutaneous electrodes. The aim was to give 10 days continuous symmetrical stimulation but because of technical difficulties, in particular electrode slippage, this was not always achieved. Table 1 gives the response to initial (temporary) stimulation. Electrodes were placed between C6 and C7, and T9 and T10 vertebral levels, and there was no relationship between electrode position and clinical response within these limits. Levels of the spinal cord outside this region were not stimulated systematically. Figure 1 indicates the changes seen on initial stimulation in terms of Kurtzke grading. As can be seen from table 1 and fig 1, the major benefit is in bladder function, both in terms of the number of patients and the degree of improvement. Out of 18 patients with mobility problems, significant improvement occurred in five (27.7%). Thirteen patients had definite upper limb ataxia (Kurtzke grade 2 or more), and only one of these had improvement in this disability. Of 18 patients with sensory impairment, five (27.7%) showed improvement. Bladder symptoms were present in 16 patients and 12 (75%) showed improvement. Improvements sufficient to produce a change in life style, including reduced dependency on others, were seen even in patients confined or virtually confined to a wheelchair—for example, SBK and AM—and in patients who had been permanently catheterised and with no bladder sensation—for example SE and JL.

Further details of response of bladder dysfunction are given in Table 4. Of 11 patients with severe bladder disturbance (Kurtzke grade 3 or more) nine improved by at least one Kurtzke grade and six by two or more grades. A seventh patient who improved initially by only one grade sub-



	Pyramidal	Cerebellar	Sensory	Sphincter
Improved	5 (27·7%)	1	5 (27·7%)	12 (75%)
Not improved	13	15	13	4
Worse	0	0	0	0
Symptom not present	1	3	1	3
Total	19	19	19	19

Fig 1 *Response to initial stimulation.*

Table 4 *Response of bladder dysfunction to spinal cord stimulation*

Patient	*Duration of bladder symptoms*	*Nature of bladder symptoms*	*Cystometry*	*Response to stimulation*
1 CP	15 mo	Absent bladder sensation. Expressing bladder two hourly day and night in an attempt to prevent incontinence.	Detrusor arreflexia	Normal bladder sensation and control restored. Improvement maintained for nine months and then deteriorated to pre-stimulation state.
2 DS	9 mo	Impaired bladder sensation. Urgency. Voiding hourly in attempt to prevent incontinence but often incontinent.	—	Normal bladder sensation and control. No frequency or urgency. Improvement maintained up to present, ie 24 months from permanent stimulation.
3 SE	1 yr	Catheterised one year for retention of urine. Attempts to remove catheter unsuccessful. Absent bladder sensation.	—	Normal bladder sensation and control. Catheter removed. Recently (24 months after permanent stimulation) has developed mild frequency and urgency and occasional incontinence.
6 GC	5 yr	Mild urgency and frequency with very occasional incontinence at time of stimulation.	—	No change. (Symmetrical stimulation never achieved—see Table 3).
7 JM	Uncertain	Mild, rather variable urgency and frequency without incontinence.	Detrusor hyperreflexia	Urgency less obvious. No cystometric change.
8 OB	8 mo	Moderate urgency with rare urge incontinence.	—	Urgency less obvious.
9 SBK	3 yr	Severe urgency and frequency and frequent urge incontinence. Spending night and day on a small bed pan.	Detrusor hyperreflexia	Normal frequency and urgency. No longer incontinent. (See text) Dispensed with bed pan. Cystometric improvement.
10 NP	9 yr	Absent bladder sensation. Catheterised for two years. Unsuccessful bladder neck resection.	—	No change. (Symmetrical stimulation never achieved.)
11 CF	Uncertain	Mild symptoms: urgency, frequency, hesitancy.	Normal	Slight improvement in hesitancy and urgency.
12 MR	4 yr	Impaired bladder sensation for one year. Catheterised three months for urge incontinence.	Detrusor hyperreflexia	Restored bladder sensation. Severe urgency and frequency, catheter could not be removed.
13 AM	4 yr	Severe frequency, urgency. Frequent urge incontinence. Living with urine bottle to hand. Occasionally unaware of voiding.	Detrusor hyperreflexia	Progressive improvement over several months until now (six months after starting permanent stimulation) bladder function normal. Cystometric improvement.
15 GM	5 yr	Urgency and frequency of variable severity. Wearing urosheath.	Detrusor hyperreflexia	No change.
16 RT	1 yr	Frequency, urgency, urge incontinence, hesitancy. Frequent urinary infection.	—	Normal bladder sensation and control. No urinary infection.
17 HS	5 yr	Moderate frequency and urgency. Occasional urge incontinence. Nocturia × 2–3.	Normal	Urgency greatly reduced. No urge incontinence. No nocturia.
18 JL	5 yr	Catheterised for four years for frequency and urge incontinence. No bladder sensation for three years.	Detrusor hyperreflexia	Normal bladder sensation. Catheter removed.
19 SBT	10 yr	Severe frequency and urge incontinence. Wet nearly all the time. Occasional hesitancy. Severe nocturia.	Detrusor hyperreflexia	Urgency reduced and dry all the time. No nocturia but still has frequency by day. Cystometric improvement.

sequently showed further improvement. Of the nine patients who had before and after urodynamic studies, seven had detrusor hyperreflexia and two had normal findings. Of the seven patients with detrusor hyperreflexia, four showed clinical improvement and in three this was very striking. These showed a cystometric improvement with decreased tendency to premature contractions and consequently increased bladder capacity (fig 2). Before stimulation this patient (AM) had a first

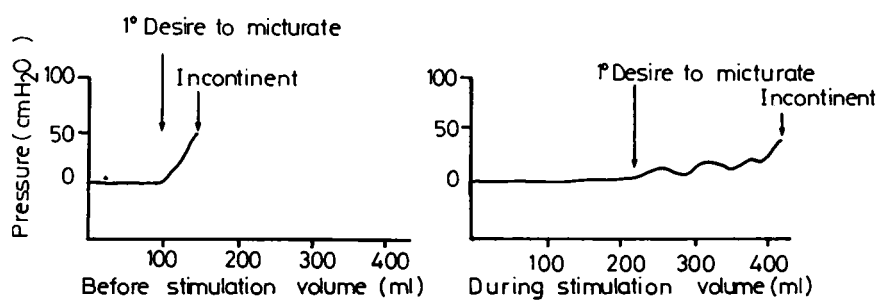


Fig 2 *Detrusor or hyperreflexia: improvement of cystometrogram during stimulation.*

sensation of the desire to void, associated with a sharp rise in bladder pressure and rapidly followed by voiding, after about 120 ml had been instilled. During stimulation, the desire to void was not felt until over 200 ml had been instilled. The contractions which then followed were of low amplitude, and voiding could be voluntarily controlled until over 400 ml had been instilled. No changes were noted in the urethral pressure profile. As shown in fig 3, the response of bladder symptoms to SCS seems to correlate to some extent with their duration. In the case of the 11 patients with severe symptoms, there seems to be less chance of a good response with symptoms greater than five years duration. The severity of bladder symptoms does not appear to be a bar to improvement.

Overall, 10 of 19 patients (52.6%) showed a worthwhile clinical response in terms of alteration of life and of dependency on others. All 10 were included among the 16 patients who received symmetrical stimulation; so of the patients receiving symmetrical stimulation 62.5% had a worthwhile clinical response. Anything less than this was considered insufficient to justify offering permanent stimulation through implanted electrodes. Figure 4 shows the Kurtzke grade for bladder, motor, and sensory function of the nine patients who at the time of writing have gone on to receive permanent stimulation through implanted electrodes. Note the stability during the preceding nine months.

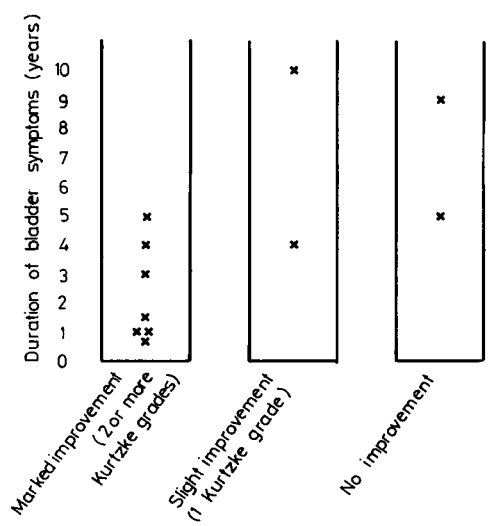


Fig 3 *Influence of duration of bladder symptoms on response to SCS in 11 patients with severe symptoms (Kurtzke grade 3 or worse).*

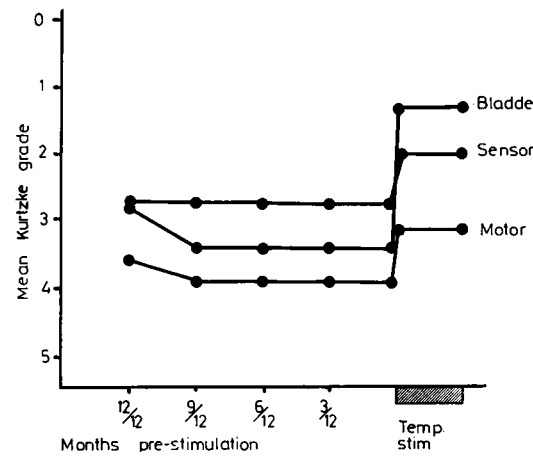


Fig 4 *Response to initial stimulation in nine patients going on to permanent stimulation.*

CURRENT REQUIREMENTS

In 15 patients the current required to produce a stimulator sensation was determined. Of the 13 patients receiving bilateral symmetrical tingling sensation the current requirement was 8.98±3.7 mA (range 5.2–17 mA), while six, in which other sensations were perceived, chose a current of 15.5±11.0 mA (range 8–36 mA). Four patients appear in both groups as they had "bad" and "good" sensations at different times. The difference between the groups was not statistically significant as judged by the Wilcoxon rank sum test.

RESPONSE TO PERMANENT STIMULATION

After initial stimulation the electrodes were withdrawn. Those patients who had a good response to initial stimulation were offered permanent stimulation. Because of the problems of electrode slippage, the first three patients had permanent stimulation carried out by suturing the electrodes to the dura mater without actually puncturing the latter. There were no problems or morbidity associated with this but the procedure included laminectomy and we now, therefore, carry out the implantation with the electrodes free in the epidural space. All implant operations were carried out by Mr John Garfield.

The response to initial stimulation is a good indication of the response with permanent stimulation (usually carried out three to six months later). Figure 5 shows the changes in mean Kurtzke grades of patients who had permanent stimulation, compared with the mean Kurtzke grade six months before stimulation. It indicates (a) the pre-stimulation period of stability; (b) the

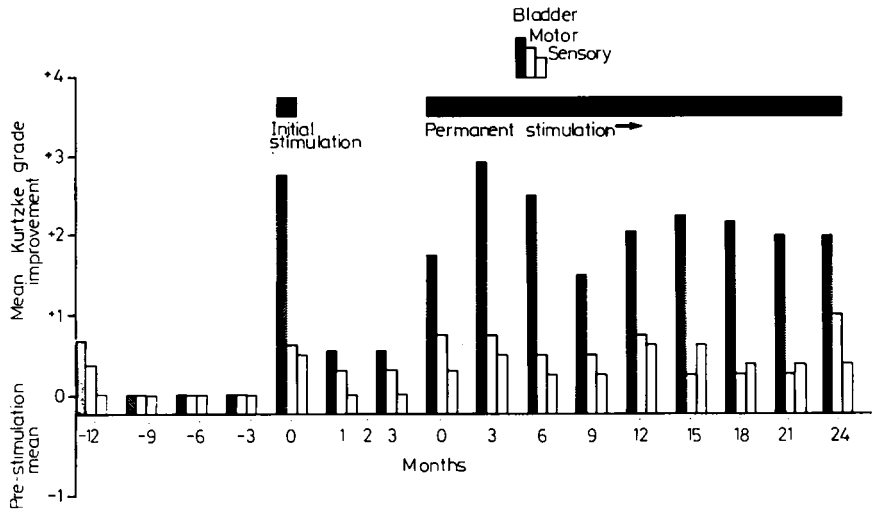


Fig 5 *Change in mean Kurtzke grade of patients with permanent stimulation compared with pre-stimulation mean.*

response to initial stimulation; (c) the return towards pre-stimulation levels after cessation of temporary stimulation; (d) the consistent response to a second period of stimulation; and (e) the long-term (up to 24 months) effect with permanent stimulation.

Of the patients with permanent implants, with one exception, improvement in bladder function has been maintained for as long as stimulation has continued, and improvement in mobility has either been maintained or decreased to about 50% of initial improvement. The one exception is a patient who had a dramatic improvement with spinal cord stimulation but after several months deteriorated to the pre-stimulated state clinically and physiologically at the same time as the stimulator sensation changed. Radiology showed that one electrode had moved 5 mm from the midline. When this was replaced, stimulator sensation and clinical and physiological changes reverted to the improved state, and this was maintained for a further two months. He subsequently deteriorated progressively and is now more or less in the pre-stimulation state except that mobility is worse. We think that the present deterioration is the result of an exacerbation of multiple sclerosis.

TIME RELATIONSHIP OF SCS TO CLINICAL RESPONSE

Figure 6 indicates the time relationships of SCS for initial and permanent stimulation in terms of response (first response and peak) and decay to pre-stimulation level. There appears to be no relationship between the timing of initial and peak response, or between initial response and decay time. The onset of the response to SCS occurs from between six hours and three days though the peak response may not be reached until eight weeks after the start of SCS. The decay to pre-stimulation level after stopping SCS begins from one day to eight weeks, and patients reach their pre-stimulation level from one day to six months. In one patient bladder symptoms never returned to the pre-stimulation level.

CSF STUDIES

Cerebrospinal fluid was obtained from six patients before and about 10 days after the onset of initial stimulation. One patient showed an increase in lymphocytes from 0 to 12/mm^3 but no other patient showed a cellular reaction. In no case was there a significant alteration of total protein or percentage of IgG.

Discussion

From the work described here and from the work of others listed in the introduction and summarised in the recent international workshop on external control of human extremities, there is no doubt that spinal cord stimulation, as first described by Cook, produces worthwhile improvement in patients with chronic multiple sclerosis. The improvement surpasses that produced by any other current method, but long-term effects are still being studied.

It is also clear that bladder dysfunction is the

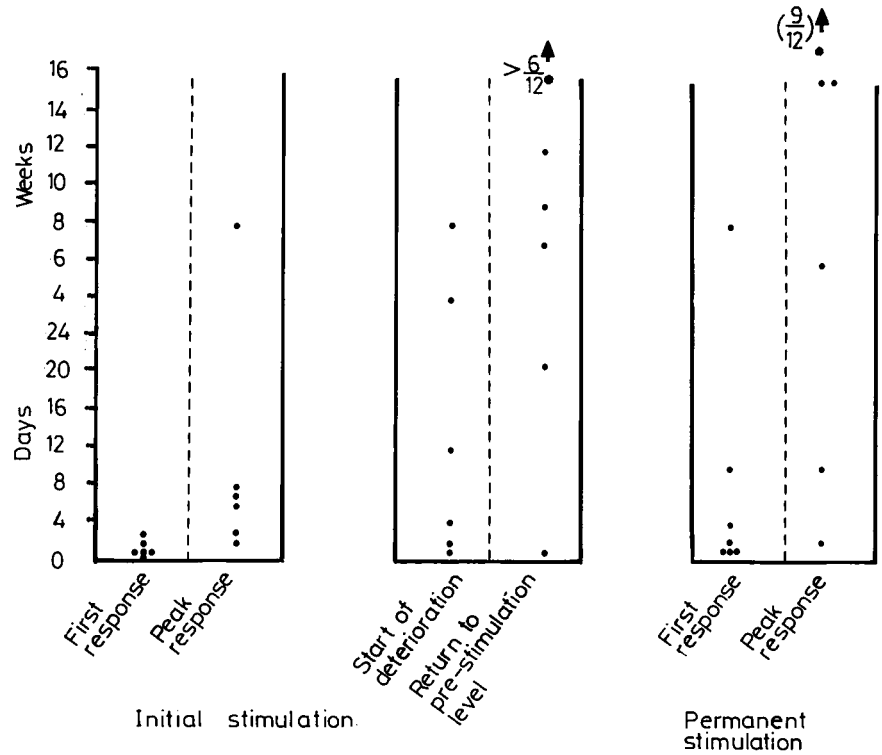


Fig 6 *Time relations of response to spinal cord stimulation (from start or end of symmetrical stimulation).*

manifestation of multiple sclerosis which responds best to spinal cord stimulation. This is especially relevant because, as Miller *et al.* (1965) have pointed out, bladder disturbance is the most important single factor which determines a patient's admission to hospital. Our urodynamic studies are incomplete but in all patients with severe symptoms who had a significant clinical improvement and who had before and after urodynamic studies there was a cystometric improvement. In five patients, with moderate or mild symptoms and mild symptomatic improvement, there was no urodynamic improvement. Two of these patients had normal cystometry before and after stimulation. The improvements seen in these five cases may have been due to better co-ordination between detrusor contraction and sphincter relaxation. With the urodynamic methods we have available we would not be able to demonstrate changes in this. The discrepancy between symptomatic and cystometric improvement was also found by Abbate and others (1977) with spinal cord stimulation in multiple sclerosis and has been noted in other conditions, as, for instance, in the treatment of bladder symptoms caused by lumbar spondylosis by lumbar laminectomy (Sharr *et al.*, 1976).

It has been suggested that these results could be the result of a placebo response and that to demonstrate otherwise would require a double-blind trial. A double-blind trial was not practical as the patients always knew when they were being stimulated, and there are ethical objections to inserting and leaving electrodes in patients without stimulating them. It is unlikely that patients would give their informed consent to such a procedure. Even without a double-blind trial, however, there is evidence which discounts a placebo effect.

There is no doubt from the results presented that neurological improvement occurs in association with SCS. Improvement did not *precede* SCS as might be expected if hospitalisation and motivation were the causes of the improvement. The patients had been neurologically stable for at least nine months before SCS so any spontaneous improvement would be unlikely to coincide with SCS in one patient, let alone in 10 out of 19 patients. It is even less likely that a further epsiode of

improvement would coincide with the second period of stimulation unless the improvements and the stimulation were causally related.

A number of features emerge from the present study, all of which discount the possibility that the response is due to placebo effect. In this series 75% of patients showed an improvement in bladder function and this is considerably more than any reported placebo effect, as well as being greater than any reported improvement with other therapy.

The two patients who were "stimulated" without batteries and the three who had surface stimulation did not improve even though they received the same treatment in other respects. When SCS was begun they all responded. Moreover, our results show that it was not the mere fact of stimulation which produced improvement but a definite type of stimulation namely that which produces bilateral sensation into the legs (table 3). Some patients had inappropriate radicular sensation and did not improve but when their electrodes were adjusted to produce bilateral tingling in the legs, improvement began. One patient who responded well and had a permanent implant began to deteriorate after four months when his stimulation sensation altered. Radiology showed that one electrode had moved 5 mm from the midline. After this electrode was replaced he improved again.

There are also neurophysiological changes associated with SCS which cannot be attributed to a placebo effect (Sedgwick *et al.*, 1978, 1979). The neurophysiological responses with the possible exception of the contingent negative variation are not under voluntary control, and it is difficult to see how they could be placebo mediated. The contingent negative variation is a cortical evoked response which *can* be altered by the patient's motivation. Contingent negative variation responses in our patients were not altered by SCS (Sedgwick *et al.*, 1979).

All these observations make it impossible to explain the patients' improvement on the basis of a placebo effect. If, however, it was shown that physiotherapy or "motivation" or any other type of therapy could produce comparable and consistent results with related neurophysiological changes then we would have to reconsider this conclusion.

The safety of methods used for SCS has been discussed fully (Jobling *et al.*, 1978). The average power dissipation between electrodes is less than 5 mW which is too low to cause hazard. Interference effects and stimulator malfunction are not a problem since SCS is not, unlike cardiac pacing, a life support system. Electrochemical reactions at the stimulating electrodes are a potential cause of danger through release of noxious substances, local pH change, and corrosion of electrodes with resultant increase in current density. We have found no evidence for this and have not observed corrosion of electrodes removed from patients. Nevertheless, there is a need for ceaseless vigilance, particularly when experimenting with unusual parameters of stimulation.

Apart from minor skin changes at the site of entry through the skin, we have encountered no problems of infection. One of our patients, implanted elsewhere, had a minor infection, and to be on the safe side we removed the apparatus and replaced it some months later. Another patient (SBK) had erosion of one electrode lead through the skin because implantation had been too superficial and this needed replacement. We have had no other complications directly caused by SCS.

There are now enough clinical and physiological data to make it clear that we are dealing with a real phenomenon. The mechanism of action, however, remains unexplained. Spinal cord stimulation may act on different aspects of central nervous system function—by altering the molecular environment and changing conduction properties; by modifying functional and anatomical reorganisation consequent upon a lesion of the CNS; by altering the central excitatory state and neurotransmitter release and altering afferent inflow. These factors act upon a nervous system which has already reacted to a partial lesion or several partial lesions. The end result of spinal cord stimulation may be to raise the level of activity so that remaining inhibitory mechanisms can operate.

The use of SCS in chronic neurological disease always involves more than a single simple procedure and in our view it should be confined, at present, to centres where comprehensive evaluation can be carried out, where there are the combined resources of a neurologist, neurophysiologist, and engineer, and where long-term, indeed permanent, follow-up is intended. There are still many unsolved problems such as electrode slippage, the mechanism of action, and the long-term effects. Unless systematic studies are continued in centres which have the necessary facilities these problems will remain.

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