Some Neurophysiological Effects of Cerebellar Stimulation in Man

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SUMMARY: *This paper presents the results of neurophysiological studies of the effects of cerebellar stimulation on H reflexes, late reflexes, blink reflexes, evoked potentials and EEG patterns in 18 human subjects (Male 13, Female 5, Age 25.8 ± 10.0, Epileptic 9, Cerebral Palsy 9).*

In addition to the effects of cerebellar stimulation on the H reflex studies on soleus we assessed V_1 and V_2, "late" responses (Upton et al., 1971), cortical somatosensory evoked potentials (SSEP) after median nerve stimulation, and visual evoked responses (VER) after flash stimulation. Experiments were extended to assess recovery curves of all the potentials and we examined the effects of changes on the rate or voltage of cerebellar stimulation.

Cerebellar stimulation was inhibitory to all the responses except the visual evoked potentials. Serial studies in five patients produced consistent results. Preoperative and postoperative results were compared in two patients with no significant difference in the results in the absence of cerebellar stimulation.

Ipsilateral cerebellar stimulation (CS) had the greatest inhibitory effects on H, V_1 and V_2 responses in the arm and leg whereas contralateral CS produced the greatest effects on cortical SSEPs. There was a greater bilateral effect on SSEPs and reflex responses after right CS than left CS and this may be the first indication of "dominance" in the cerebellar hemispheres. Cerebellar stimulation in patients on diphenylhydantoin produced minimal effects on SSEP's and this observation has led to further studies in patients taking diphenylhydantoin.

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RÉSUMÉ: *Cet article présente les résultats d'études neurophysiologiques sur les effets de la stimulation cérébelleuse sur les réflexes H, les réflexes lents, le clignotement des paupières, les potentiels évoqués et les enregistrements d'EEG chez 18 sujets (13 hommes, 5 femmes, âge 25.8 ± 10.0, 9 épileptiques et 9 cas de paralysie cérébrale).*

En plus des effets de stimulation cérébelleuse sur le réflexe H du soleus, nous avons mesuré V_1 et V_2, les réponses tardives (Upton et coll., 1971), les potentiels évoqués corticaux somatosensitifs (SSEP) après une stimulation du nerf médian, et les réponses visuelles provoquées (VER) après une stimulation lumineuse. Les expériences furent prolongées pour évaluer les courbes de récupération de tous les potentiels et nous avons examiné les effets de changements dans la vitesse et le voltage de la stimulation cérébelleuse.

La stimulation cérébelleuse était inhibitrice à toutes les réponses, excepté pour les potentiels visuels évoqués. Des études sériées chez 5 patients ont donné des résultats constants. Les résultats pré-opératoires et post-opératoires furent comparés chez 2 patients dont les différences n'étaient pas significatives durant l'absence de stimulation cérébelleuse.

La stimulation cérébelleuse ipsilatérale (CS) avait les plus grands effets inhibiteurs sur le réflexe H et les réponses V_1 et V_2 dans le bras et la jambe tandis que la stimulation cérébelleuse contralatérale produisait les plus grands effets sur les SSEP corticaux. On observe un effet bilatéral plus grand sur les SSEP et sur les réponses réflexes

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INTRODUCTION

Much of our knowledge about the effects of cerebellar stimulation on spasticity and epilepsy is based on the results of animal studies, particularly in the rat, cat and monkey. The original experiments of Lowenthal and Horsley (1897) and Sherrington (1897) demonstrated that stimulation of the paleocerebellum decreased decerebrate rigidity in the cat and Moruzzi (1950) showed that high frequency stimulation of cat cerebellar cortex decreased decerebrate rigidity. In monkeys Soriano and Fulton (1947) showed that spasticity was greater if ablation of areas four and six was associated with removal of the anterior lobe of the cerebellum.

Risien Russel (1894) showed that unilateral cerebellar ablation in dogs aggravated ipsilateral limb movements during generalized convulsions and Terzuolo (1954) found that stimulation of cerebellar cortex inhibited strychnine-induced spinal cord convulsions in the cat. Others found that such stimulation inhibited electrically induced cerebral discharges (Cooke and Snider, 1955) and hippocampal seizures (Iwata and Snider, 1959). Similar results have been obtained in the rat (Dow et al., 1962). Penicillin induced (Hutton et al., 1972) and cobalt-induced (Mutani et al., 1969) seizures in the cat can be inhibited by stimulation of cerebellar cortex. Direct stimulation of cerebellar nuclei in the cat has been shown to aggravate hippocampal cobalt epilepsy (Babb et al., 1974) so that stimulation of Purkinje cells might be expected to have the opposite effect.

Such uniformly inhibitory effects of cerebellar stimulation were consistent with the findings of Ito and

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Yoshida (1964) that discharge from the cerebellar cortex or Purkinje cells is entirely inhibitory and this was the basis for the application of prosthetically induced cerebellar stimulation in spastic and epileptic patients (Cooper, 1973; Cooper, Crighel and Amin, 1973; Cooper, Amin, Gilman and Waltz, 1973; Cooper, Amin, Riklan, Waltz and Poon, 1976; Cooper, Riklan, Amin, Waltz and Cullinan, 1976).

The present studies have confirmed that stimulation of the human cerebellar cortex produced inhibitory effects on spinal reflexes and somatosensory evoked potentials but there has been no evidence of any effect on visual evoked potentials elicited by flash stimulation.

METHODS

Subjects

Eighteen patients (13 male, 5 female, ages 14 - 59, mean 25.8± 10.0) with cerebellar stimulators were studied. Two patients were seen before and after insertion of electrodes. Two patients had had chronic cerebellar stimulation for four years, the average duration of stimulation being 60 weeks (range three days to four years). One patient was investigated on four different days and four subjects were studied twice.

Nine patients were epileptics and nine suffered from spasticity, most from birth.

Equipment

Cerebellar Stimulators

All the patients had platinum disc electrodes in four pairs in a silicone coated mesh. The electrodes lay beneath the tentorium over the anterior or posterior lobes of the cerebellar cortex. Medial and lateral anterior lobe electrodes were present in one patient but most patients had bilateral anterior electrodes. Five patients had electrodes over the anterior and posterior lobes.

Stimulation was achieved by transcutaneous inductive coupling from a twin power pack with two independent outputs.

Rates of stimulation varied from 10 Hz in spastic patients to 200 Hz in epileptic patients. One epileptic patient received 200 Hz.

Capacitance coupled stimuli were applied at voltages of 2.5 to 12 volts at the power pack but voltages at the electrodes could not be measured directly and there was evidence that voltages were higher when the stimulator was on mains voltage rather than batteries. It is possible that current measurements would vary with time; current measurements at the time of stimulation were 2.6 m.a. per electrode pair at 10 volts and 10 Hz or 1.5 m.a. at 10 volts and 200 Hz. At 10 volts current density was 0.381 ma/mm² and 0.214 ma/mm² at 10 Hz and 200 Hz respectively.

At St. Barnabas Hospital stimuli were applied by a Grass Stimulator S_4 triggered by a Devices Digitimer. Evoked potentials were recorded on a Tektronix storage oscilloscope BM64 type 3A1 2A60. Potentials were averaged on a Mnemotron CAT 400B with a preset stimulus counter 562 and the results were printed out on a Houston Instruments X-Y recorder HR-95. All the potentials were fed through an amplifier with a frequency response 3dB down at 3 kHz and 2Hz but cortical evoked potentials in spastic and athetoid patients were recorded with a frequency response 3dB down at 50 Hz in an attempt to minimize muscle artefacts.

At McMaster University Medical Centre the paired preamplifiers were the same as at St. Barnabas Hospital and a Devices Digitimer was used to trigger stimulation. Potentials were recorded on two traces of a Hewlett Packard variable persistence oscilloscope type 141B. Stimuli were applied by Devices stimulators type 3072. Potentials were averaged on a Hewlett Packard 5480 B Memory Display with a 5485A two channel input and the results were photographed on Polaroid film or printed out on a Hewlett Packard X-Y plotter type 9862A through a Hewlett Packard calculator type 9810A. With this apparatus it was possible to record the evoked potentials from both cerebral hemispheres simultaneously.

RECORDING

V_1 and V_2 "late responses

Thenar and extensor digitorum brevis (EDB) muscles were studied in all the patients and both sides were studied in ten subjects.

Surface silver strip electrodes, 0.6 cm x 6 cm were used for experiments. The skin was prepared with alcohol and the electrodes were applied with 3M tape and electrode jelly. Stimulating electrodes consisted of silver discs, one centimeter in diameter and 2.5 cm apart in a perspex holder.

For thenar recordings the electrodes were placed over the junction of the proximal third and distal two-thirds of the thenar muscles at right angles to the metacarpal bone. A reference electrode was wrapped around the distal phalanx of the little finger and a ground electrode was placed over the dorsum of the hand. The stimulating electrodes were positioned over the median nerve proximal to the palmar crease. Supramaximal stimuli were employed throughout the experiments.

For recordings from the EDB muscle the recording electrodes were situated over the end-plate zone and a reference electrode was placed well away from the muscle belly over the medial plantar aspect of the foot. A ground electrode was placed between the stimulating electrodes over the deep peroneal nerve and the recording electrode over the EDB muscle.

Supramaximal stimuli were delivered five seconds apart and ten stimuli were used for each experiment, the results being stored on the screen of a storage oscilloscope and photographed on Polaroid film. Some results were averaged (please see below).

All the patients were lying on their backs throughout the experiments.

H REFLEXES

Experiments were conducted on the soleus muscles of fourteen subjects with bilateral studies in ten. The recording electrode was a 6 cm by 0.6 cm silver strip applied longitudinally over the soleus muscle between the bifurcation of the medial and lateral gastrocnemius muscles. Reference and ground electrodes were identical silver strips over the anterior aspect of the tibia.

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The voltage of stimulation over the posterior tibial nerve was adjusted to produce a maximal amplitude of the H reflex and the amplitude of the M wave was monitored throughout the experiments.

The patients lay on their backs on a bed with a cushion behind the knee and head position was kept constant throughout the experiments. Stimuli were given irregularly at about five second intervals. Five responses were stored on the oscilloscope and photographed on polaroid film. Sixteen potentials were averaged automatically on a 62.5 millisecond sweep.

EVOKED POTENTIALS

Subdermal platinum recording electrodes were used at St. Barnabas Hospital but surface silver chloride electrodes were applied with collodion at McMaster University Medical Centre. The surface electrodes had impendances below five kilohms.

Somatosensory evoked potentials (SSEP)

Recording electrodes were applied in the C3 and C4 positions of the International 10-20 system in seventeen subjects. A reference electrode was midfrontal. A ground electrode was applied over the upper arm on the side of median nerve stimulation. The median nerve stimulation was applied for 50 μ sec to 1 msec by an isolated stimulator and the voltage was adjusted until a minimal twitch of the thumb could be observed. The median nerve was stimulated every two seconds and 64 responses were averaged.

Visual Evoked Potentials

Recording electrodes were applied in the O_1 and O_2 positions of the International 10-20 system with a reference electrode at P_z.

Flash stimuli with an energy of about 0.29 Joules per flash were delivered by a Grass research photic stimulator (Setting 2) placed twelve

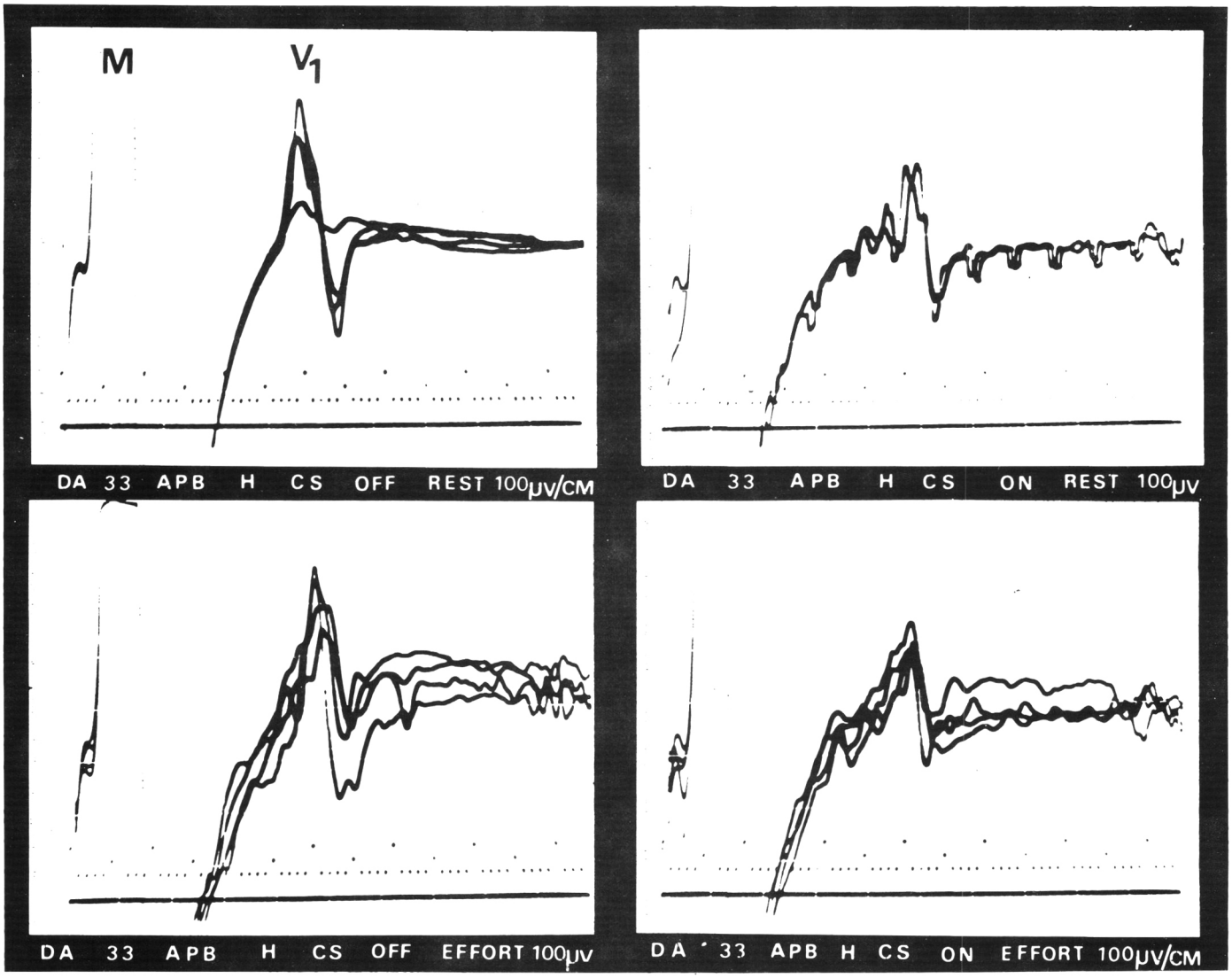

Figure 1 — D.A. 33. M. Cerebral Palsy. Bilateral Anterior cerebellar stimulators at 200 Hz and 10 volts.

V_1 and V_2 responses were recorded at rest (top pictures) and during effort (lower pictures) in the right thenar muscles after supramaximal stimulation of the right median nerve. Each picture shows superimposed oscilloscope tracings at an amplification of 100 μv/cm. It can be seen that the late reflex responses are of smaller amplitude in the right sided pictures when the right cerebellar stimulator was on at 200 Hz and 10 volts. Such results are more formally presented in Figs. 2, 3, 4.

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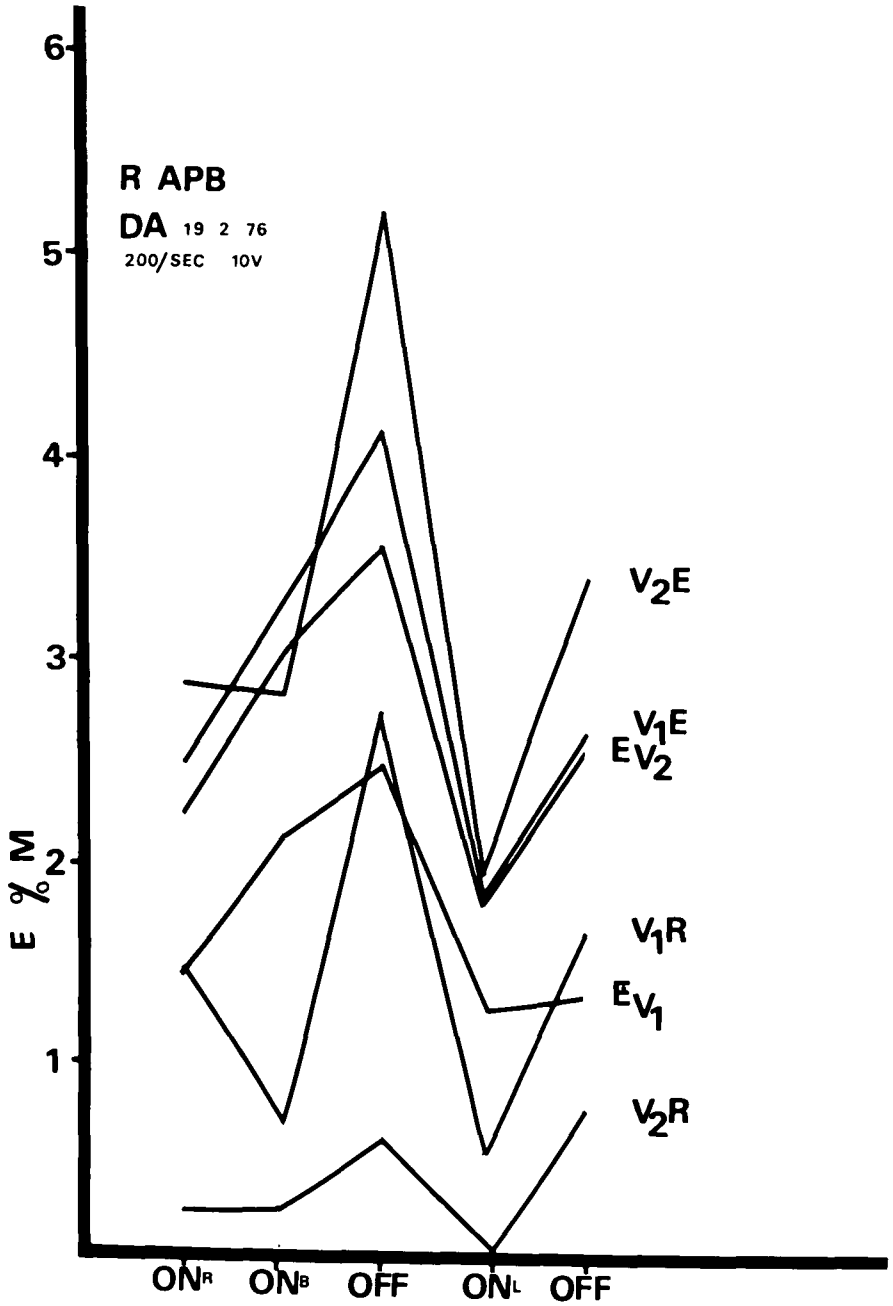

inches from the glabella. The patient was stimulated with a background of normal room lighting and with the light dimmed.

Stimuli were given at two second intervals and 64 potentials were averaged. In spastic patients a 300 Hz filter was found to allow too much muscle artefact and the preamplifiers were set to be 3dB down at 50 Hz.

RESULTS

Late Reflex Responses

Cerebellar stimulation in eighteen patients produced remarkably consistent results with a decrease in amplitude of the ipsilateral H reflex or V_1 response in seventeen patients at rest and during effort (Figs. 1, 2, 3, 4). There was a minimal effect on the contralateral H reflex or V_1 response in 12 patients. In one patient we did not detect any effect on the late reflex responses even when we adjusted the voltage and rate of stimulation. Recovery of the amplitude of the H reflex or V_1 response took eight to 30 minutes after one minute of stimulation (Fig. 5, 6, 7). After the initial studies of late reflexes at rest and during effort we concentrated on the responses at rest as this reduced the problems of collisions between orthodromically and antidromically elicited nerve action potentials and the variations in the amount of volitional activity were minimized (Upton et al., 1971); unfortunately we could not avoid some occasional involuntary movements and variations in background muscle activity in the

Figure 2 — D.A. age 33. M. Cerebral Palsy. Anterior cerebellar stimulation at 200 Hz and 10 volts.

The arithmetic average of ten consecutive V_1 and V_2 responses in thenar muscles after supramaximal medium nerve stimulation have been assessed at rest (R) and during effort (E). Median nerve stimuli were applied at intervals of five seconds and the experiments were five minutes apart. Cerebellar stimulation was continued for one minute on the right (On.R), left (On.L.) and bilaterally (On.B).

EV_1 and EV_2 represent the extra fraction of motoneurones taking part in the V_1 and V_2 responses during effort. All the results are expressed as a percentage of the maximal motor response (M).

It can be seen that there is a decrease in the amplitude of V_1 and V_2 waves when cerebellar stimulation is ON Right (On.R) and Left (On.L). Anterior cerebellar stimulation is almost as effective as bilateral stimulation in producing a reduction in the amplitude of late reflexes at rest and during effort.

These early experiments indicated prolonged effects (at least five minutes) of one minute of cerebellar stimulation so that assessment of recovery curves became necessary.

In this patient it was possible to record a V_2 response at rest and this is never seen in normal subjects but it is commonly seen in spastics and in patients suffering from cerebral palsy.

The similarity of the results at rest and during effort and the uncertainty of the amount of voluntary effort in such patients caused us to confine further studies to the assessment of V_1 and V_2 responses at rest.

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spastic and athetoid patients. We found that the V_1 and V_2 responses in the legs were often of small amplitude and the H reflexes in the soleus muscle provided a more easily measurable response (Fig. 8). In the hands, the V_1 and V_2 waves were always elicited in thenar muscles. (Fig. 5, 6, 7)

In one epileptic patient (B.D.) we found that reducing the stimulation voltage from 10 volts to 4.5 volts produced an increased inhibition of V_1 and V_2 responses.

In another patient with cerebral palsy (C.H.) it was necessary to increase stimulator voltage from 8 volts to 10 volts before inhibition of the V_1 could be detected even though some effect on the V_2 response was detectable at the lower voltage (Fig. 7). Hence these simple neurophysiological tests may provide a method of assessing thresholds for stimulating voltages but serial clinical and neurophysiological assessments will be necessary before it is possible to predict the clinical correlates of such reflex studies.

Blink Responses

In one patient (D.A.) the blink responses were recorded by surface electrodes above and below the orbit after flash stimulation. An average of 32 responses before and after bilateral cerebellar stimulation showed a 30% reduction in amplitude of the blink responses even though there was no measurable change in the visual evoked potentials. It is clear that further studies are required but these preliminary

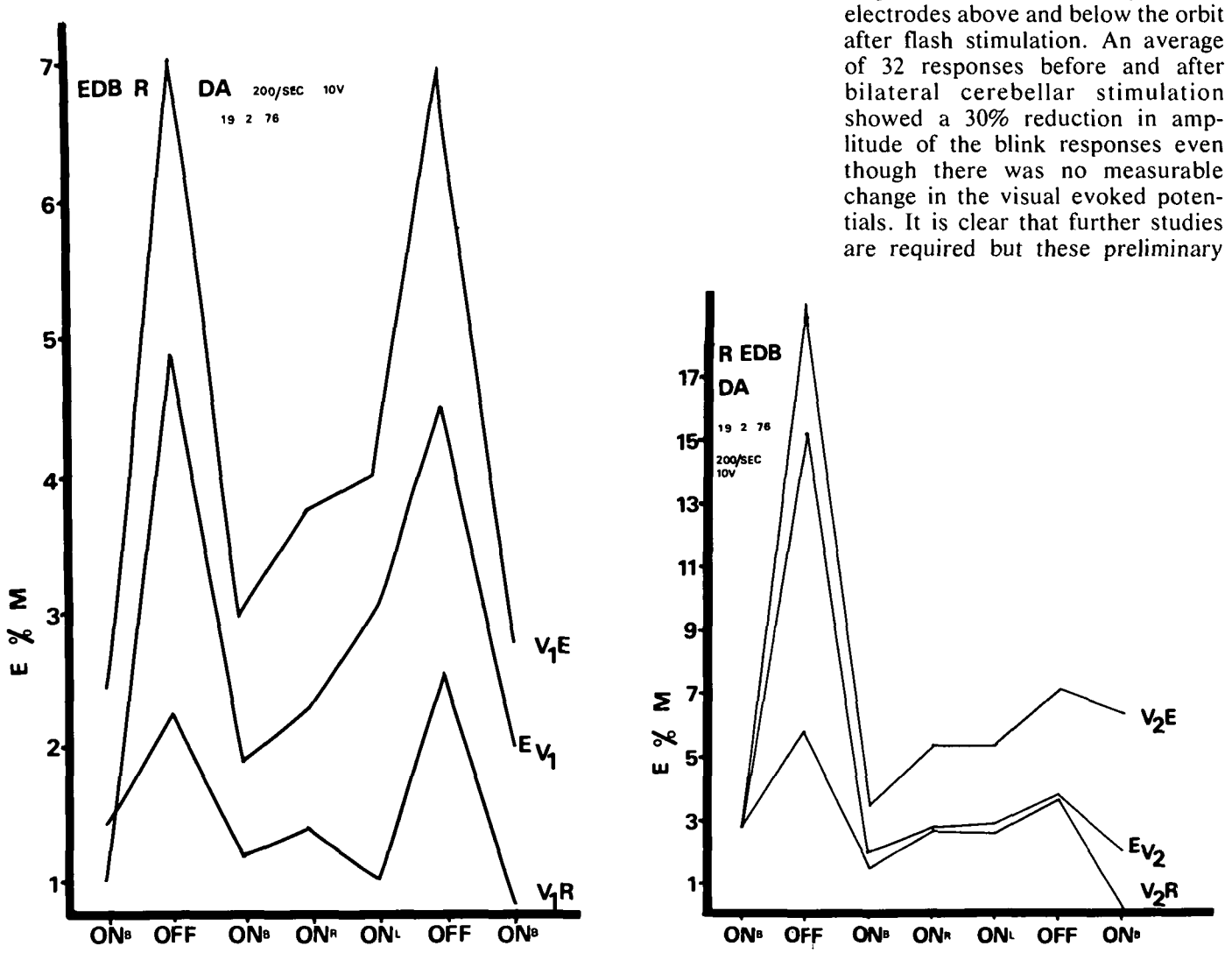

Figure 3 — D.A. M. Age 33. Cerebral palsy. Anterior cerebellar stimulation at 200 Hz and 10 volts.

The changes in the V_1 and V_2 responses in the extensor digitorum brevis muscle before, (EDB) during and after cerebellar stimulation are remarkably similar to those in the thenar muscles of the same subject.

Each point on the graphs represents an arithmetic average of ten potentials obtained in EDB after supramaximal stimulation of the deep peroneal nerve. Surface electrodes were used in all the experiments. The V_1 and V_2 responses at rest (V_1R, V_2R) can be compared with the V_1 and V_2 responses during effort (V_1E, V_2). EV_1 and EV_2 represent the extra fraction of motoneurones taking part in the responses during effort and all results are expressed as a percentage of the maximal motor response (M). Stimuli to the deep peroneal nerve were applied every five seconds and experiments were performed five minutes apart.

It can be seen that there is reduced motoneuron excitability during cerebellar stimulation on the right (On.R), left (On.L) or bilaterally (On.B) with an increase in motoneuron excitability when the stimulators were OFF.

Such similar findings in thenar and EDB muscles in the same patient were seen in most patients (please see Figs. 4, 5, 6, 7, 8).

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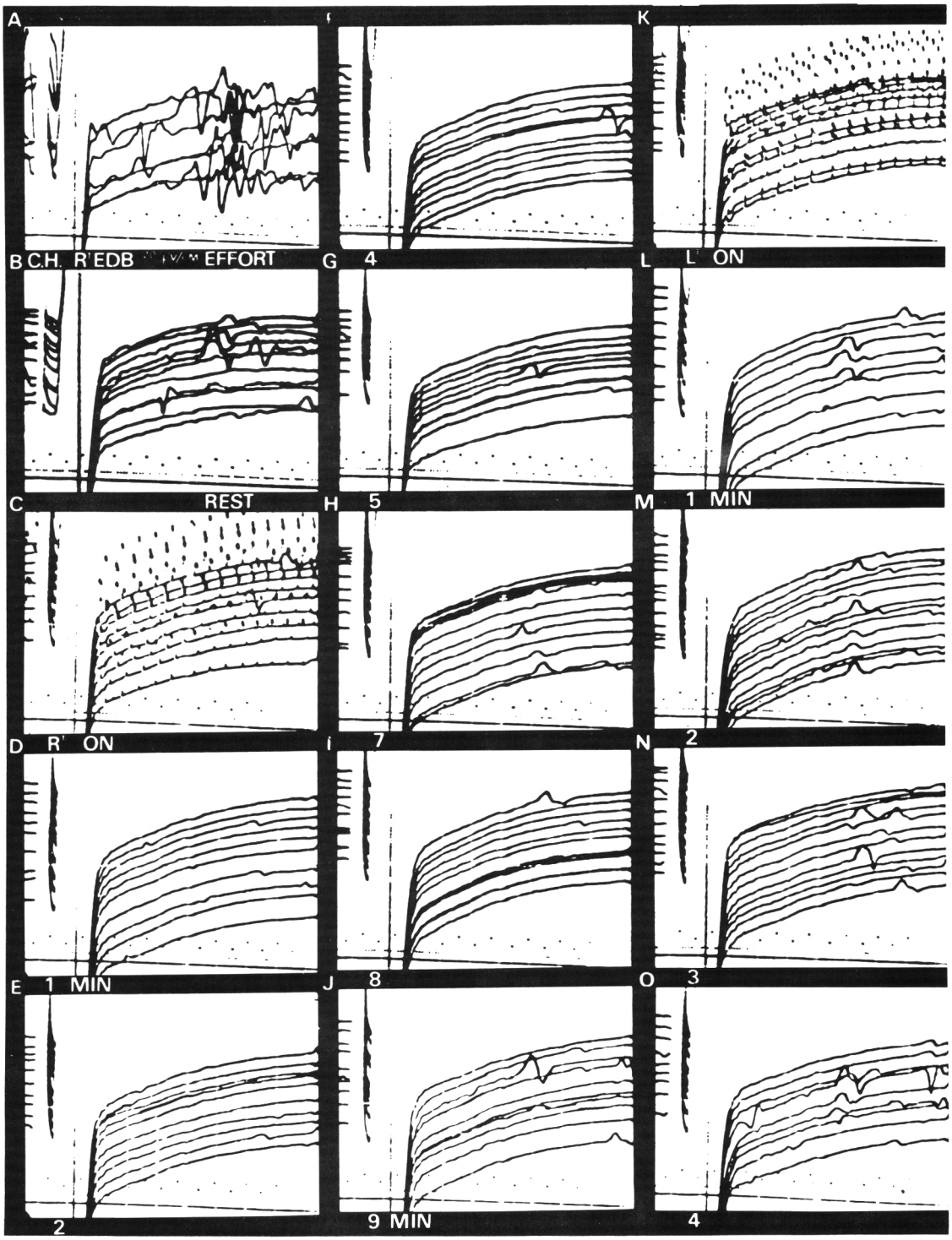

Figure 4 — C.H. M. Age 18. Cerebral palsy. Bilateral anterior cerebellar stimulation at 200 Hz and 10 volts.

The M, V_1 and V_2 responses can be seen in these recordings from the right extensor digitorum brevis muscle after supramaximal stimulation of the deep peroneal nerve at the ankle. The responses during effort (A) and rest (B) are seen at a gain of 200μ V/cm.

Right (ipsilateral) cerebellar stimulation for one minute (C) was associated with a marked reduction in the amplitude of the V_1 and rather dispersed V_2 responses. Recovery was incomplete 9 minutes (J) after cerebellar stimulation. Left (contralateral) cerebellar stimulation (K) had less effect on the V_1 and V_2 responses (LMNO).

These results are similar to those obtained in the right thenar muscles of the same subject (Fig. 5, 6, 7).

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TABLE I

NAME	Age	Sex	CP	E	Stimulation Duration	V_1 Anterior I	C	B	V_1 Posterior I	C	B	V_2 Anterior I	C	B	H Anterior I	C	B	SSEP Anterior I	C	B	SSEP Posterior I	C	B	VEP ICB	Rate Hz	Ep.Dis. in EEG A	P	B	Times Seen	Stimulator Ant.	Post.
DA	33	M	✓		12/12	↓	↓	↓				↓	↓	↓	↓	↓	↓	↓	↓	↓				000	200				4	B	
DW	35	M	✓		1/52	↓	↓	↓				↓	↓	↓	↓	↓	↓	↓	↓	↓					200				2	B	
CB	14	F	✓		2/52	↓	↓	↓				↓	↓	↓	↓	↓	↓	↓	↓	↓					200				1	B	
KR	28	M	✓		1/52	↓	↓	↓				↓	↓	↓	↓	↓	↓	↓	↓	↓					200				2†	B	
CH	18	M	✓		1/52	↓	↓	↓				↓	↓	↓	↓	↓	↓	↓	↓	↓					200				2†	B	
JR	26	M	✓		1/52	o	o	o				o	o	o	o	o	o								200				1	B	
VC	21	F	✓		2/52	↓	↓	↓				↓	↓	↓	↓	↓	↓	↓	↓						200				1	B	
BM	29	M	✓		42/12	↓	↓		↓	↓		↓	↓		↓	↓		↓	↓		↓	↓			200				1	L	L
RM	16	M	✓		42/12	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓		200				1	LA	B
WA	24	M		✓	48/12	↓	↓					↓	↓		↓	↓		↓	↓						10				1	R	
BD*	26	M		✓	24/12	↓	↓	↓				↓	↓	↓				o*	o*	o*					200	↓	↓	↓	1	B+R	L
CW	17	F		✓:	7/12	↓	↓	↓				↓	↓	↓	↓	↓	↓	↓	↓	↓					10				1	B	
MB	59	F		✓	42/12	↓	↓		↓	↓		↓	↓		↓	↓		↓	↓						10	↓	↓		1	RA	R
SJ	22	M		✓	3 days	↓	↓	↓				↓	↓	↓	↓	↓		↓	↓	↓					10				1	B	
BB	26	M		✓	44/12	↓	↓		↓	↓		↓	↓		↓	↓		↓	↓		↓	↓			10				2	B	L
SD*	21	M		✓	1/52	↓	↓	↓				↓	↓	↓				M*	M*	M*					10				1	B	
RH	27	M		✓	2/52	↓	↓	↓				↓	↓	↓	↓	↓	↓	↓	↓	↓					10				1	B	L
CW*	22	F		✓	7/52	↓	↓	↓				↓	↓	↓	↓	↓	↓	o*	o*	o*					10				1	B	
$\bar{x}$	25.8 ± 10				60/52																										

* on diphenyl-hydantoin

The effects of cerebellar stimulation on the neurophysiological results of eighteen patients are summarised. The effects of cerebellar stimulation on the V_1, V_2, H reflex (H), somatosensory evoked responses (SSEP) and visual evoked potentials (VEP) are seen in vertical columns. The patients have been grouped under the diagnosis of cerebral palsy (CP) or epilepsy (E).

An inhibitory effect (↓) and little or no effect (o) has been recorded. A blank space indicates that the investigation was not performed.

Ipsilateral (I), contralateral (C) and bilateral (B) cerebellar stimulation are recorded for anterior or posterior cerebellar electrodes.

Most of the CP patients were studied at stimulation rates of 200 Hz whereas all but one of the epileptic patients received cerebellar stimulation at 10 Hz. Some of these patients were studied at different rates of stimulation (not recorded in the table). Since the voltage of stimulation was varied and the voltage at the electrodes could not be determined precisely, this information is not given in the table.

The effect of cerebellar stimulation on paroxysmal discharges in the EEG is noted under stimulation of the anterior (A), posterior (P) or bilateral (B) cerebellar electrodes.

In some patients on diphenylhydantoin (*) there was a small (M) or minimal (O) effect of cerebellar stimulation on the somatosensory evoked responses (SSEP's).

Two patients were seen before and after implantation of their cerebellar stimulators (2).

Electrode placements are recorded in the last column. Bilateral (B), right (R) and left (L) electrodes are noted under the headings of anterior (Ant.) and posterior (Post.) electrodes.

findings are consistent with the results of the other reflex experiments.

Visual Evoked Potentials

We were unable to detect any change of flash evoked cortical responses in one spastic patient on three separate occasions (Fig. 9). He was being stimulated at 10 volts at 200 Hz and we employed right, left and bilateral stimulation for periods of one to four minutes. Since this patient showed a marked reduction in the amplitudes of blink responses, late reflexes, spontaneous muscle activity and somatosensory evoked cortical responses (Fig. 1, 2, 3, 10) there is strong evidence that his stimulator was working well. It is clear that further studies and the use of pattern evoked responses will be

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necessary to assess the significance of these initial results.

Somatosensory Evoked Potentials

We found that the greatest inhibition of somatosensory evoked potentials after median nerve stimulation occurs contralaterally but bilateral effects were always detectable in fifteen patients. In one patient (D.A.) we recorded the evoked potentials simultaneously over both hemispheres on three different days (Fig. 10, 11) whereas we recorded unilaterally in the other patients.

In three epileptic patients we saw minimal effects of cerebellar stimulation on somatosensory evoked potentials whereas we saw marked reduction of 30 to 80% in the voltage of SSEPs in all the other fourteen spastic and epileptic patients. The three patients with minimal changes in their SSEPs were on diphenylhydantoin (DPH) at the time of the studies and it is possible that it may modify the effects of cerebellar stimulation.

The main effects of cerebellar stimulation on SSEPs were seen at latencies of 30 to 130 msec. Decreased amplitudes of the evoked potentials were seen for up to 30 minutes after one minute of cerebellar stimulation (Fig. 11).

Repeated cerebellar stimulation in three patients for one minute on and one minute off produced progressive decreases in the amplitudes of the evoked responses. Anterior cerebellar stimulation produced greater depression of evoked potentials than posterior stimulation. Right cerebellar stimulation had greater contralateral and ipsilateral effects than left cerebellar stimulation in eight patients.

Depression of the amplitude of SSEPs was seen at the same voltages of stimulation that produced depression of late reflexes.

In five spastic patients and one epileptic patient we were unable to see any difference in the effects of high (200 Hz) or low (10 Hz) rates of stimulation.

EEG

Our early studies of evoked potentials and spinal reflexes in epileptic patients did not include continuous monitoring of the electroencephalograph but we found that subclinical paroxysmal activity of a spike and wave configuration modified the evoked potentials and reduced the amplitudes of late reflex responses in two patients. Previous experiments (Fernandez-Guardiola et al., 1973) have shown a depression of monosynaptic reflex responses at the end of a seizure with some facilitation about 20 milliseconds after a clonic wave and inhibition during the tonic phase of electrocortical discharges. Since subclinical paroxysmal activity may modify evoked responses it is important to include monitoring of the EEG in studies on epileptic patients.

In two epileptic patients we observed a decrease in the number and duration of paroxysmal spike and wave discharges during cerebellar stimulation with a return of such discharges within 15 to 20 seconds after one minute of stimulation. Prolonged periods of alternating stimulation of right and left anterior electrodes for one minute at a time at 10 Hz and left anterior and posterior electrodes at 200 Hz, was associated with a decrease in the number of paroxysmal discharges in comparison with equivalent epochs (e.g. 30 minutes) without stimulation. There was a "rebound" effect when the number and duration of discharges increased about 15 seconds after cessation of stimulation.

DISCUSSION

We have seen uniformly inhibitory effects of cerebellar stimulation on late reflexes and somatosensory evoked potentials in man but our studies have been limited to abnormal patients since stimulators are not implanted in normal controls. The similar findings in epileptic and spastic patients and the results of animal studies would indicate that our results may have some application to other groups of patients and some general principles appear to be involved.

Late reflex responses (V_1 V_2, and H)

Upton et al., (1971) demonstrated that supramaximal stimulation of mixed peripheral nerves produced two later reflex responses; the first response, the V_1 wave, appeared at a latency of 24 to 32 msec in the hand and was shown to consist of an F wave and an H reflex; the second response, the V_2 wave, appeared at latencies of 48 to 60 msec in the hand and its origin was difficult to define. Both the V_1 and V_2 responses were potentiated by effort and this potentiation was impaired by subclinical lesions of upper motoneuron pathways (Sica et al., 1971). Subsequently, it was shown that these late reflex responses were particularly large in weight lifters (Milner-Brown et al., 1975) and in elite sprinters, the largest responses being recorded in the eventual winner of the 100 meter dash at the 1976 Olympics (Upton and Radford 1976). Another indication that these late reflex responses were related to movement was that the amplitude of the responses correlated with the maximal speed of alternated movement in the 20 second tapping test (Radford and Upton 1976) and the V_2 response was particularly large in untreated Parkinsonian patients. Another indication was that the V_2 response was always absent at rest in normal controls but often could be recorded in the resting muscles of spastic patients (Fig. 4, 5). More recently the V_1 and V_2 (M_1, M_2) responses have been seen after sudden limb displacements (Marsden et al., 1973) and these authors thought that the V_2 response represented a long loop reflex involving cerebral cortex, a view supported by the work of Lee and Tatton (1975). However, the V_2 response could be mediated by cerebellum or brain stem with the cerebral cortex modifying the excitability of the pathways and it is of interest that direct stimulation of the motor cortex failed to potentiate or elicit a V_2 response (Milner-Brown et al., 1975). Most of these studies have not taken account of the effects of cutaneous stimulation (Caccia et al., 1973), which may modify the late reflex responses. It may well be that such discussions of the relative importance of various C.N.S. structures is of little value since all the

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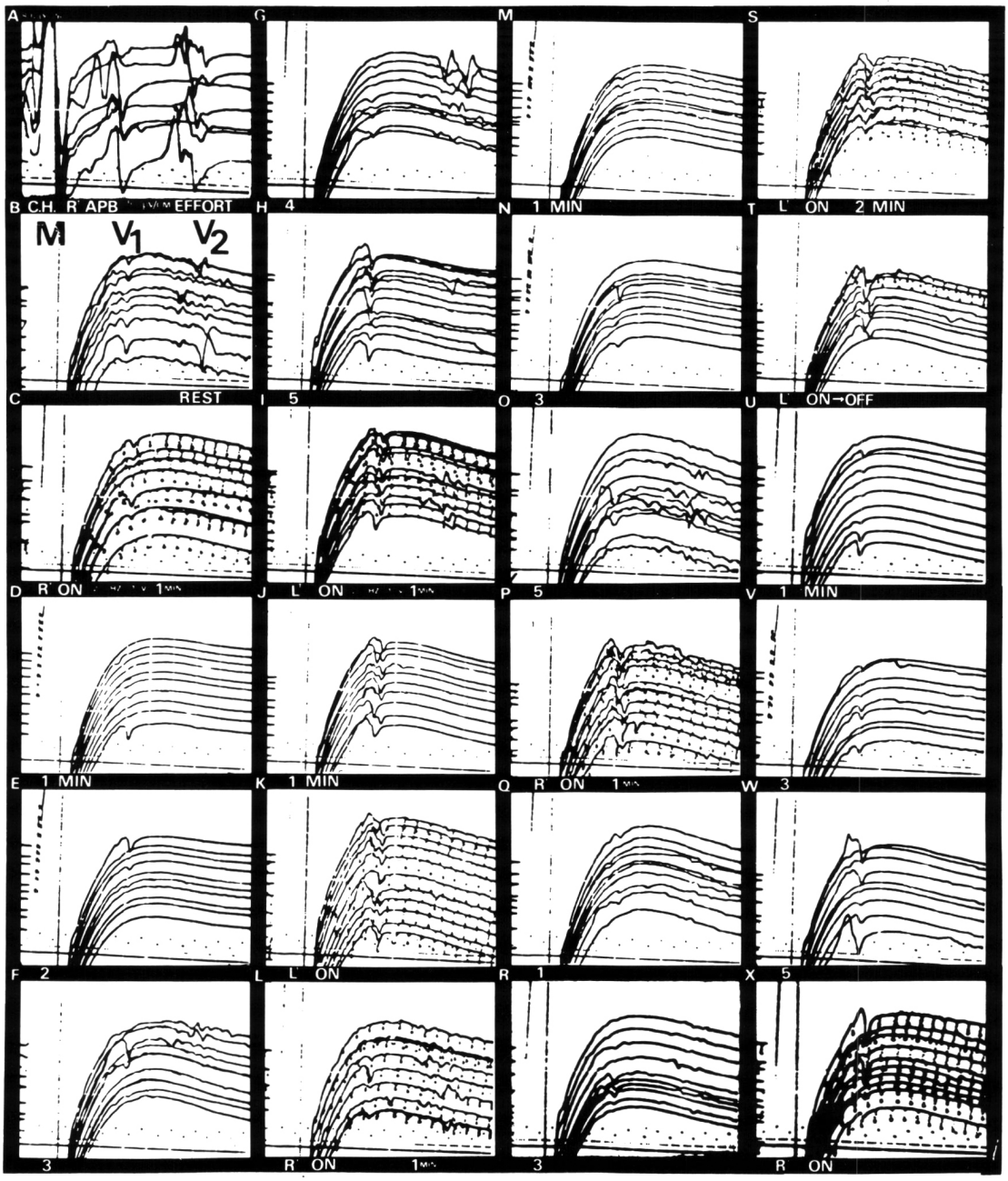

Figure 5 — C.H. M. Age 18. Cerebral palsy. The cerebellar stimulators were over both anterior cerebellar lobes. Stimuli were applied at 10 volts at 200 Hz.

Each picture, A to X, shows the results of ten sequential oscilloscope tracings (above to below) from right thenar muscles after the application of supramaximal stimuli to the median nerve at the wrist. There is a five millisecond delay before the stimulus and each tracing represents 90 milliseconds at a gain of 200 microvolts per centimeter (μ V/cm). All the results were obtained at rest except for the first seven results (A) obtained during voluntary contraction of the thenar (APB) muscles at a gain of 500 μV/cm.

Note the M, V_1 and V_2 responses during effort (A) and rest (B). The V_2 response is never present in normal patients at rest but is frequently present in spastic patients. The right (ipsilateral) cerebellar stimulator was switched on for one minute (C) and there was a marked decrease in the amplitudes of the V_1 and V_2 responses (E,F). There was good recovery five minutes after cessation of stimulation (H).

Left (contralateral) cerebellar stimulation (I) decreased the amplitude of the V_2 responses with little effect on the V_1 response (J). Further left sided stimulation (K) had little effect on the V_1 response but right sided stimulation (L) produced a marked reduction in the V_1 response (M). There was some recovery of the V_1 and V_2 responses by five minutes (O) with a further reduction in the responses (Q) after another minute of right cerebellar stimulation.

After recovery of the V_1 and V_2 responses (not shown) a period of two minutes of left cerebellar stimulation (S,T) produced some decrease in the amplitude of the V_1 response with recovery over five minutes (W).

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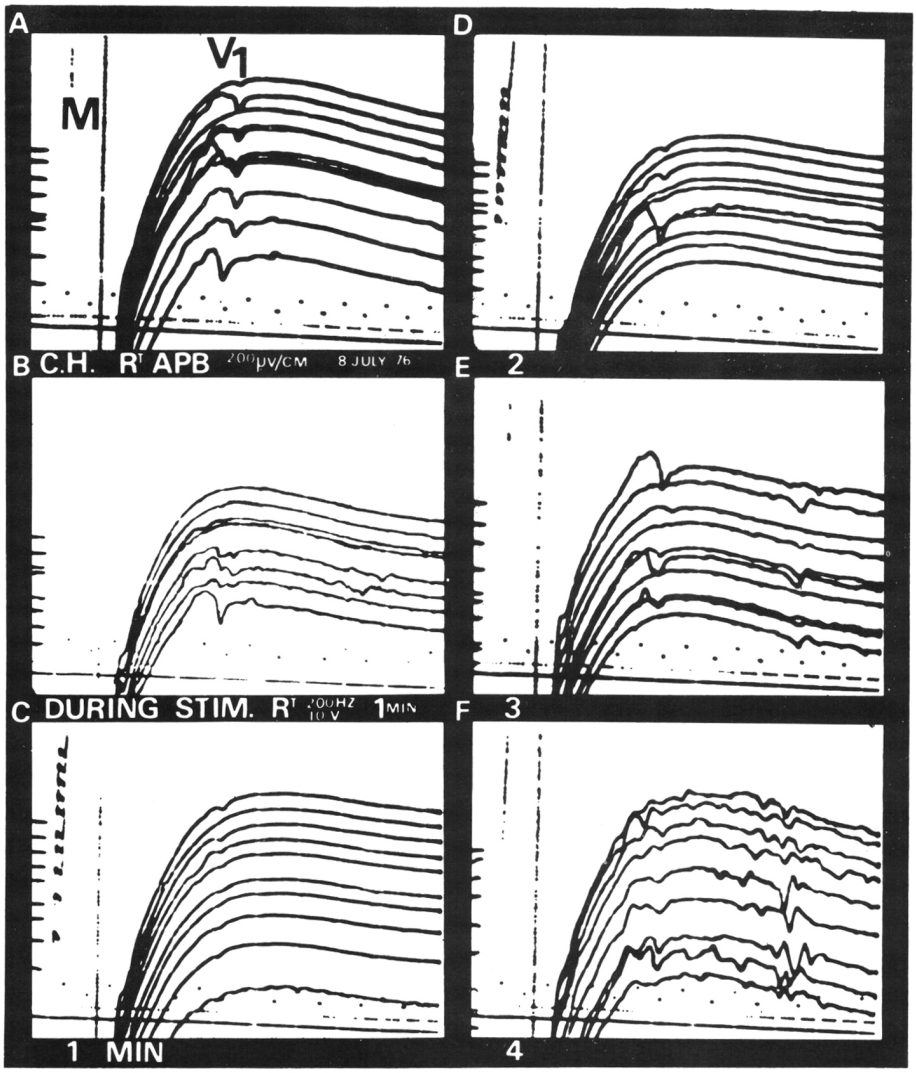

Figure 6 — C.H. M. Age 18. Cerebral palsy. Bilateral anterior cerebellar stimulators at 200 Hz and 10 volts.

The M, V_1 and V_2 responses were recorded from the right thenar muscles after supramaximal stimulation of the right median nerve. Sequential tracings were stored on the storage oscilloscope from the bottom tracings upwards. The gain was 200 μV/cm and median nerve stimuli were applied every five seconds.

The V_1 responses at rest (A) gradually disappeared during one minute of right (ipsilateral) cerebellar stimulation (B) and recovered over four minutes. The V_1 responses can be seen clearly in the first tracing, the lowest one, in picture B but the responses have virtually disappeared by the fifth stimulus. No response can be seen in the eighth tracing at the top of picture B.

structures are interconnected and probably act as a whole.

Our results indicate a predominantly ipsilateral effect of cerebellar stimulation on V_1 responses but bilateral effects were more marked on the V_2 responses at rest and during effort. Since the V_1 response consists of an F wave (antidromic motor response) and an H reflex (Upton et al., 1971) and since the H reflex component is altered by effort and upper motoneuron lesions, it would seem likely that cerebellar depression of the V_1 response during effort is due to inhibition of the reflex component, probably as a result of a change in descending facilitatory pathways. However, the V_1 response at rest may be eliminated by cerebellar stimulation and the elimination of the F wave as well as the H reflex would indicate a direct change in motorneuron excitability as measured by the effects of an antidromic stimulus in the motor axon. Such reductions in the amplitudes of the V_1 response in thenar and extensor digitorum brevis muscles (Fig. 1, 2, 3, 4, 5, 6, 7) are also seen in the amplitudes of H reflexes on soleus muscles after submaximal stimulation of the posterior tibial nerve (Fig. 8) and may well be synaptically mediated.

The amplitude of the V_2 response is reduced bilaterally after cerebellar stimulation. Ipsilateral cerebellar stimulation produced greatest effects but contralateral effects were often seen in the absence of any change in the V_1 response. Such changes in the V_2 response after cerebellar stimulation contrast with the negative results of stimulation of the motor cortex (Milner-Brown et al., 1975). We found that there was depression in the amplitudes of somatosensory evoked potentials, H, V_1, and V_2 responses at the same voltage of cerebellar stimulation so that it is possible that depression of cortical mechanisms might be responsible for the changes in the V_2 waves but basal ganglia, brain stem, cerebellum and spinal cord are likely to be involved as well. Cerebellar stimulation might alter V_1 and V_2 responses by modification of the inhibition produced by excitation of cutaneous afferents (Caccia et al., 1973) and a diffuse inhibition of interneurons in the spinal cord may be responsible for some of the suppressive effects of cerebellar stimulation on spinal cord seizures (Terzuolo, 1954). It is clear that further studies are required to examine these interesting possibilities. The clinical relevance of these studies is indicated by the clinical improvement in spasticity and involuntary movements during cerebellar stimulation (Fig. 12) and this correlates with the changes in reflexes and evoked potentials in the same subjects (Fig. 1, 2, 3, 10, 11).

Evoked Potentials

Although photic, auditory and somatosensory evoked potentials can be recorded from the cerebellum (Snider and Stowell, 1944) and cerebellar stimulation can produce

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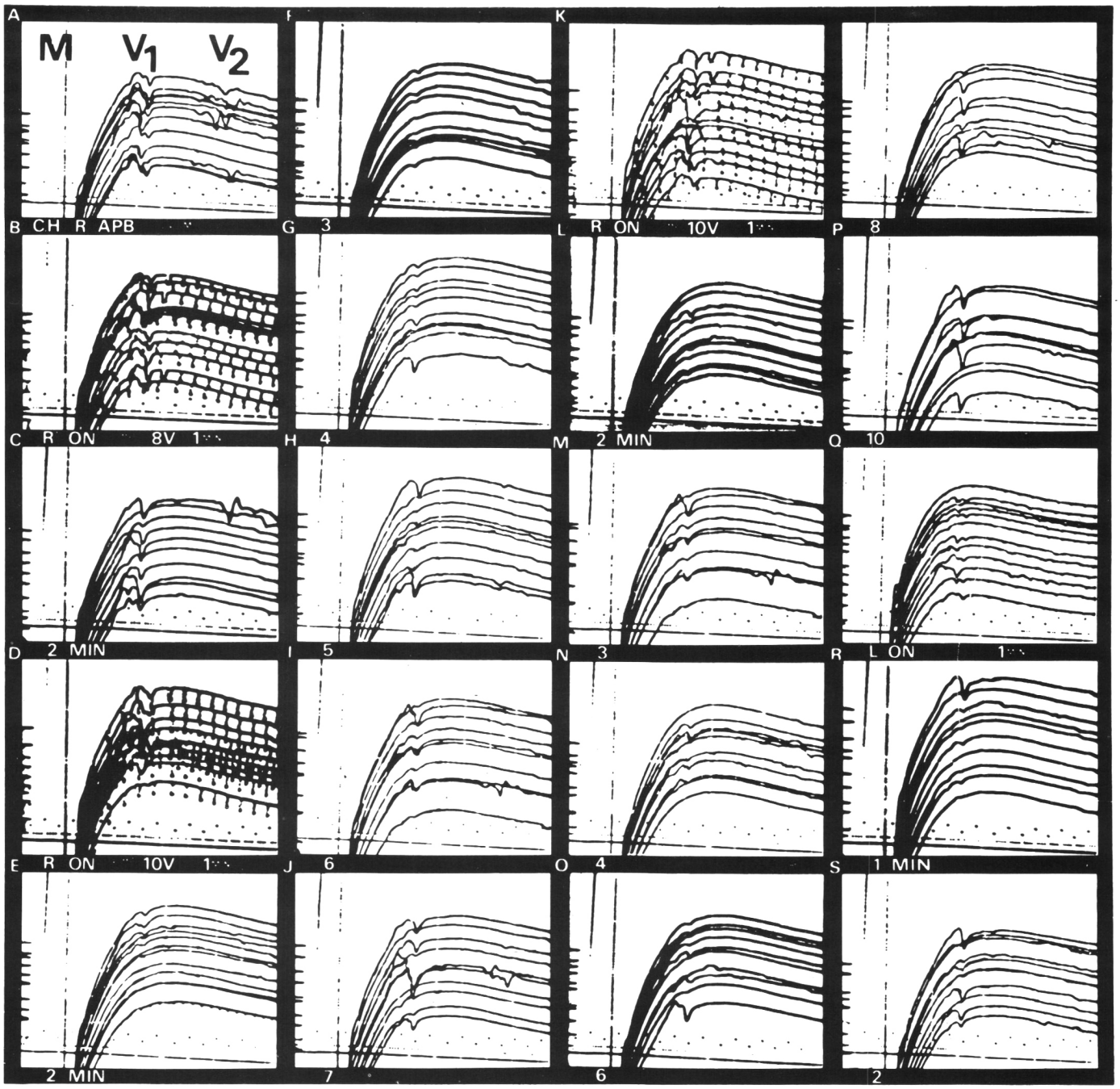

Figure 7 — C. H. M. Age 18. Cerebral Palsy. Bilateral anterior stimulators 8 to 10 volts and 200 Hz. The right median nerve was supramaximally stimulated and the recordings are from right thenar muscles.

At rest (A) the M, V_1 and V_2 responses are seen in the 90 millisecond trace. Right (ipsilateral) cerebellar stimulation (B) at 8 volts for one minute produced little change in the V_1 or V_2 responses (C). Right cerebellar stimulation at ten volts for one minute (D) produced a marked reduction in the V_1 and V_2 responses (E) with some recovery over seven minutes (J). Further right cerebellar stimulation (K) produced a further decrease in the amplitudes of the V_1 responses with good recovery at ten minutes after stimulation (P). Left (contralateral) cerebellar stimulation (Q) was associated with some reduction in the amplitude of the V_1 responses (R).

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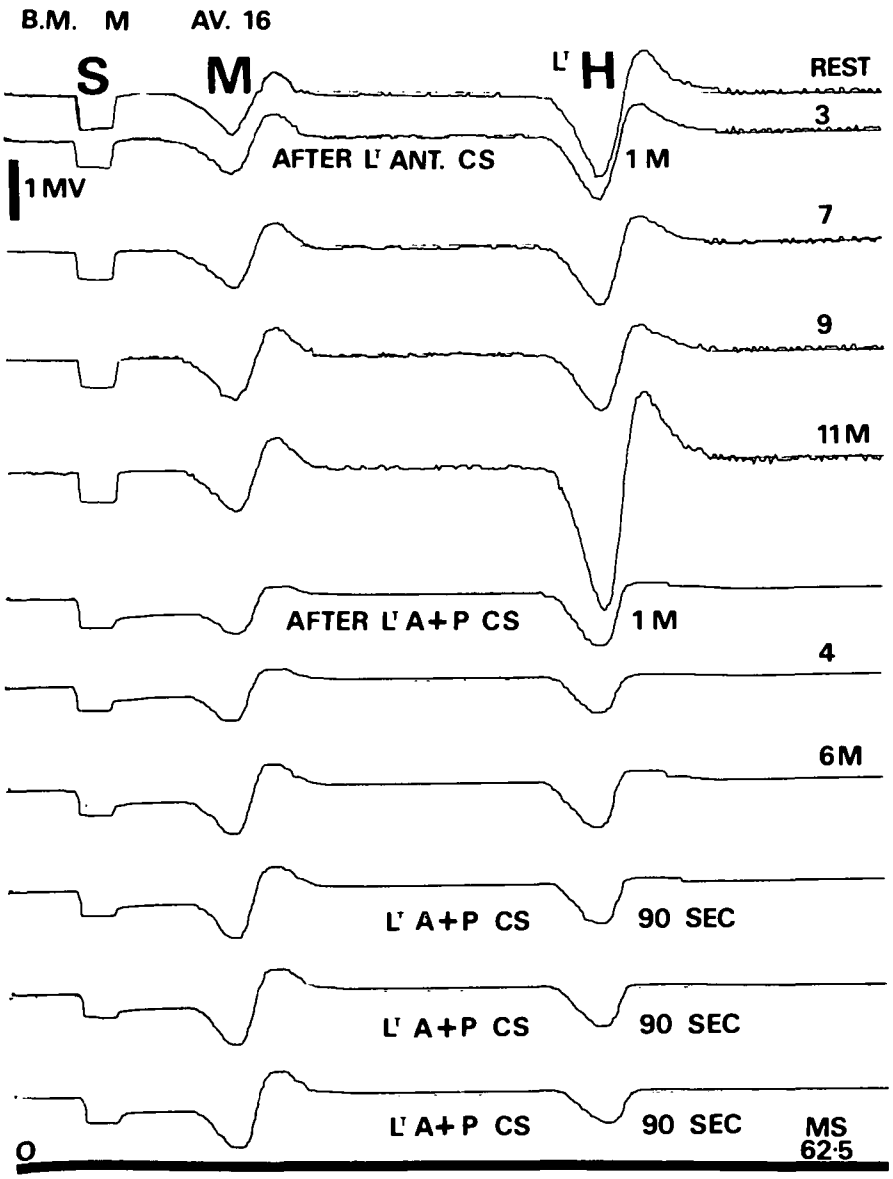

Figure 8 — B.M. M. 29. Pontine lesion. Spastic. Left anterior and posterior cerebellar stimulation at 10 volts and 200 Hz. Maximal H reflex responses were obtained in the left soleus muscle at rest. The stimulus artefact(s), motor response (M) and H reflex (H) are shown in each 62.5 msec tracing which represents the average of sixteen potentials.

The top tracing was obtained at rest before any cerebellar stimulation. The next tracings were seen at 3, 7, 9, and 11 minutes after left anterior cerebellar stimulation for one minute at 200 Hz and 10 volts. Note the depression of voltage H reflex response without any significant change in the amplitudes of the M wave and then the "rebound" in amplitude of the H response seen at 11 minutes (11 M) after stimulation. Combined anterior and posterior cerebellar stimulation was associated with greater depression in the amplitude of the H response than was seen with anterior stimulation alone and there is some recovery at six months (6 M). Further anterior and posterior stimulation was associated with some further depression in the amplitude of the H response.

These results should be compared with those in figures 1, 2, 3, 4, 5, 6, 7.

evoked potentials in sensory cortex (Henneman et al., 1950) there have been no systematic studies of the effects of cerebellar stimulation on the somatosensory evoked potentials in man. Our studies have shown inhibitory effects of cerebellar stimulation on somatosensory evoked potentials, the main effects being seen at latencies of 30 to 130 milliseconds after median nerve stimulation (Larson et al., 1976).

Interpretation of the different shapes of cortical evoked potentials obtained in this study is complicated by a number of factors. For example, it is well known that there are gross anatomical differences between the two cerebral hemispheres in man (Rubens et al., 1976) so that symmetrically placed electrodes may not be over homologous areas of cortex. There are inevitable errors in the measurement and placement of electrodes on different occasions. The patients in this study suffered from epilepsy or cerebral palsy with uncertain physiological or anatomical abnormalities of their brains. Medications such as anticonvulsants modify evoked potentials and may produce anatomical as well as physiological changes in the nervous system. These difficulties are largely avoided if amplitudes and shapes of evoked potentials at the same latencies are serially compared in the same patient during each experiment. One further problem was that movement and irregular muscular contractions could not be eliminated in the spastic and athetoid patients and we found it necessary to adjust the preamplifier to reduce the amplitude of potentials by 3dB at 50 Hz.

Boone et al., (1973) thought that cerebellar inhibition of evoked potentials acted through the fastigial pathways since they found predominantly ipsilateral effects on cerebral evoked potentials in the cat whereas in man we have observed predominantly contralateral effects which may involve the dentate or interpositus nuclei. There were some ipsilateral effects of cerebellar stimulation in 10 patients but these were always less than the contralateral effects. Since the cerebellum is

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topographically organized one might expect medial cerebellar stimulation to involve fastigio-bulbar pathways whereas more lateral stimulation would be expected to affect the dentate nucleus (Janssen and Brodal, 1954).

Visual Evoked Potentials

We were unable to demonstrate any effects of cerebellar stimulation on the visual evoked potentials after flash stimulation but stimulation of cerebellar cortex has been shown to inhibit cerebral photic evoked responses in rats (Dow et al., 1962) and cats (Boone et al., 1973) Boone et al (1973) showed that lower voltages of stimulation (e.g. 2.0 volts) produced ipsilateral inhibition with partial contralateral inhibition of flash evoked cortical responses, whereas complete bilateral inhibition occurred at four volts. Stimulation of the dentate produced similar results and greatest inhibition was seen at high (e.g. 300 Hz) stimulation rates. There were no facial or lingual movements during these experiments and this was taken to indicate that brainstem structures were not being stimulated by spread of non-specific electrical current. The same authors thought that inhibition took place at the thalamic level and they reported inhibition of photic evoked responses in the lateral geniculate body.

Although further studies are required, the difference between our results in man and the results of Boone et al (1973) in cats may be attributable to species differences.

EEG Changes

In two patients we observed a reduction in the number of spike and wave discharges in the EEG during cerebellar stimulation; anterior, posterior and bilateral stimulation was associated with a reduction in the number of paroxysmal discharges but bilateral stimulation was most effective. Clinical experience has indicated that many patients may terminate or prevent their seizures by the use of the "jam" button when bilateral stimulation occurs. In view of the improvement in some seizure patients during and after feedback of focal epileptic discharges by auditory or peripheral nerve stimulation (Upton and Longmire 1975), we believe it will be possible to combine feedback techniques with cerebellar stimulation by triggering the stimulator from large and discreet focal discharges in the EEG. Such techniques might allow the duration of cerebellar stimulation to be minimised and the delay in producing inhibitory effects would be shortened after cerebellar rather than peripheral nerve stimulation. Stimulation on demand would reduce the possibility of cerebellar

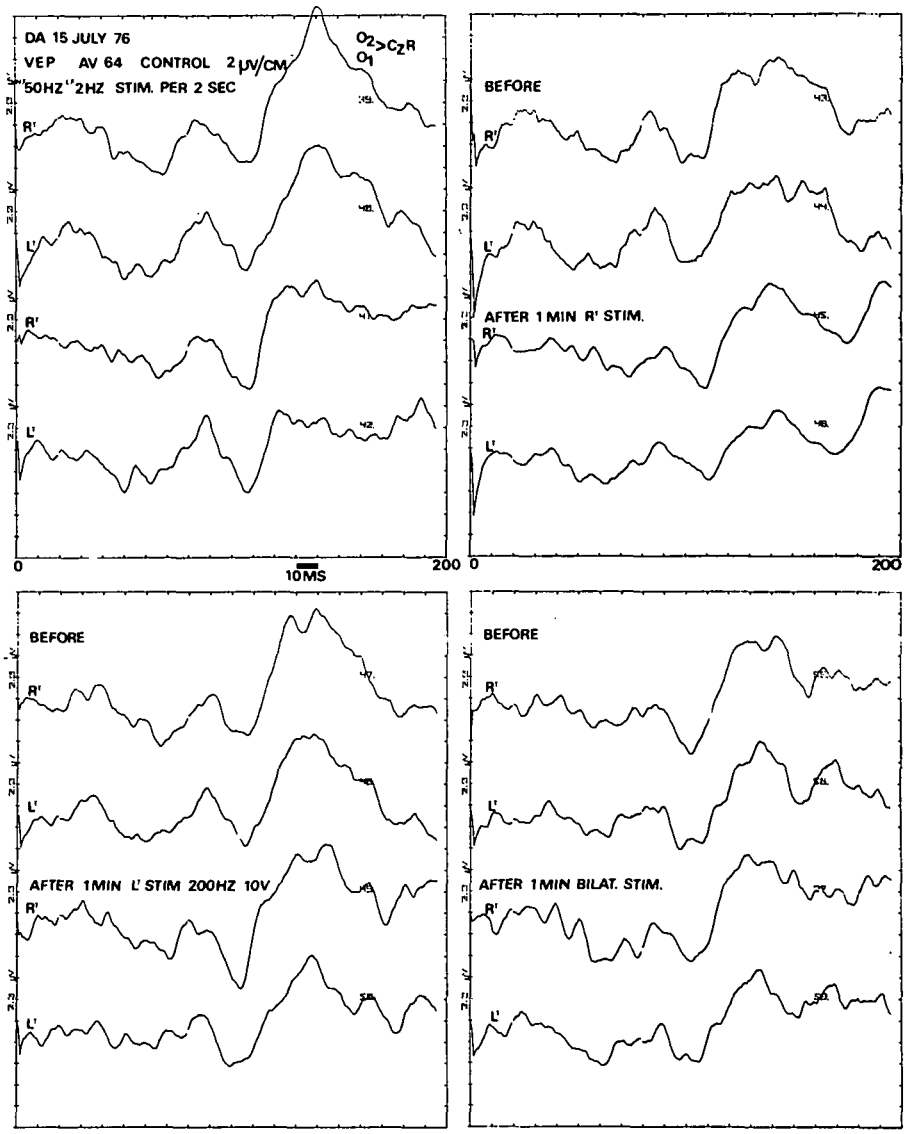

Figure 9 — D.A. M. age 33. Cerebral palsy. Anterior cerebellar stimulation at 200 Hz and 10 volts.

Bilateral visual evoked potentials (VEPs) were obtained after flash stimulation every two seconds. Surface silver chloride electrodes were applied with collodion in the O_1 and O_2 positions of the International 10-20 system with a reference electrode at Pz. Right and left VEPs were recorded simulfaneously and each VEP represents an average of 64 stimulations. As in all spastic patients a 50 Hz H. F. filter was used so that potentials were 3dB down at 50 Hz.

The upper left picture represents four potentials at rest. All the other pictures represent VEPs immediately before and after one minute of either right (RT), left (LT) or bilateral (BILAT) stimulation.

There was no evidence of any change in VEPs after cerebellar stimulation during repeated experiments on three different occasions.

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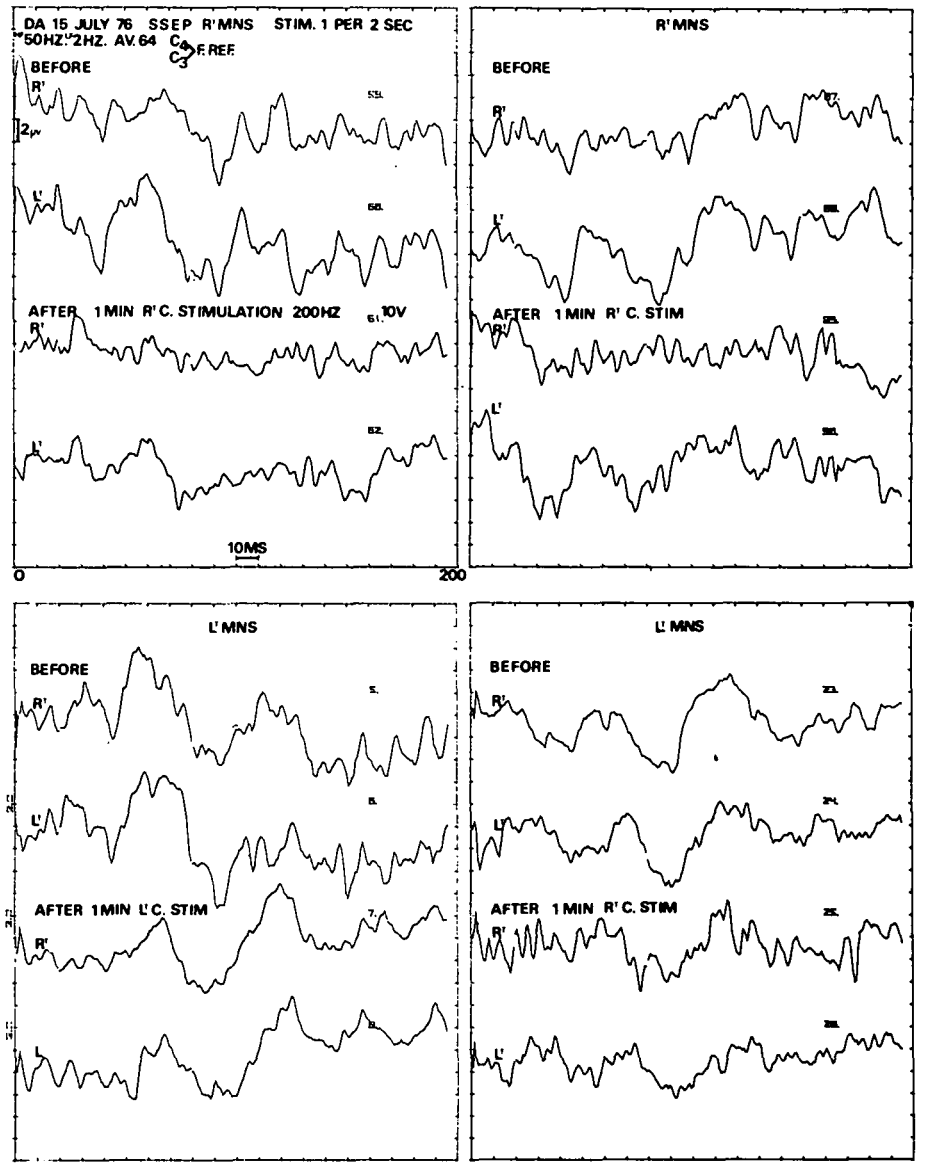

Figure 10 — D.A. M. Age 33. Anterior cerebellar stimulation at 200 Hz and 10 volts.

Bilateral somatosensory evoked potentials (SSEPs) were obtained from surface silver chloride electrodes applied with collodion in the C3 and C4 positions of the International 10-20 system with a reference electrode in the midfrontal region. Electrode impedances were below 5 Kilohms. Fifty microsecond median nerve stimuli were applied every two seconds and the voltage was adjusted to produce a minimal twitch of the thumb. Involuntary movement and muscular contraction in patients with cerebral palsy necessitated the limitation of the preamplifiers by 50 Hz filters (Potentials 3dB down at 50 Hz). SSEPs were obtained simultaneously from both hemispheres and each SSEP is an average of 64 potentials.

There is a reduction in the amplitude of right (RT) and left (LT) SSEPs after right (RT) and left (LT) anterior cerebellar stimulation. There was a consistently greater effect of right in comparison with left cerebellar stimulation. Right cerebellar stimulation had a greater effect on left (contralateral) SSEPs.

damage and the bursts of stimuli might be adjusted to avoid "rebound" effects after cessation of stimulation.

Rate of Cerebellar Stimulation

As yet we have been unable to demonstrate any difference in the effects of high rather than low rates of cerebellar stimulation. We are aware of the animal work demonstrating that high frequency stimulation decreases muscular rigidity but low frequency stimulation of the cerebellum produces total inhibition of Purkinje cell activity (Anderson et al., 1964). However, Cooke and Snider (1955) found that high and low rates of cerebellar stimulation were equally effective in reducing seizure discharges after stimulation of the cerebral cortex. Not only may the chronicity of the lesion (Steriade 1960) and the use of anaesthetic agents complicate the interpretation of animal studies (Dauth et al., 1973) but there may well be species differences in the effects of cerebellar stimulation. For example, fast rates of cerebellar stimulation may be effective in reducing cobalt induced seizure discharges in the rat (Dow et al., 1962), but not in the cat (Reimer et al., 1967). In primates (Macaca mulatta) there has been some evidence that low rates of stimulation may be ineffective in controlling seizure discharges from alumina-cream foci but high rates of stimulation (100 Hz) precipitated seizures in two monkeys (Hablitz et al., 1975). However, there has been some preliminary clinical data and results in macaca mulatta suggesting that low frequency stimulation may be more effective than rapid stimulation in inhibiting seizures (Cooper and Snider 1973) and the same authors reported occasional precipitation of seizures by high rates of stimulation. It will require further neurophysiological studies, particularly quantification of paroxysmal discharges in the EEG, before the different effects of high and low rates of stimulation can be established in man.

Effects of Diphenylhydantoin (DPH) Therapy

There appear to be a number of

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possible explanations for the minimal effects of cerebellar stimulation on the amplitudes of somatosensory evoked potentials in patients taking diphenylhydantoin. It is well known that toxic doses of diphenylhydantoin may produce cerebellar deficiency or cerebellar degeneration (Utterback et al., 1958; Kokenge et al., 1965; del Carro and Snider, 1972) and therefore cerebellar stimulation might act on reduced numbers of sick Purkinje cells in patients on this drug. Rajjoub et al., (1976) found that reduced numbers of Purkinje cells in epileptic patients were associated with improvement in seizure control during cerebellar stimulation and they speculated that Purkinje cell discharges might be reduced during cerebellar stimulation. On the other hand, removal or cooling of the cerebellar cortex has been associated with augmentation of seizure activity (Terzuolo, 1954; Dow et al., 1962). It is clear that there must be some doubt about the proportions of different types of neurons that are excited by stimulation of the cerebellar cortex. In addition to Purkinje cells, other neural elements such as climbing fibers, mossy fibers, granule cells and basket cells may be activated in the region of the stimulating electrodes. The current view is that efferent cerebellar outflow is entirely mediated by Purkinje cells (Eccles et al., 1967).

Julien and Halpern (1972) demonstrated a threefold to fourfold increase (25 Hz to 120 Hz) in firing rates of Purkinje cells in patients on 10 mg/kg doses of DPH and it is possible that cerebellar stimulation may not cause any further increase in Purkinje cell activity; another possibility is that a chronic rise in Purkinje cell activity may cause habituation which would reduce the effect of any further increases in firing rates of Purkinje cells.

Of interest is the fact that intravenous sodium pentobarbital (30 mg/kg) has been shown to completely prevent cerebellar inhibition of photic evoked responses in the visual cortex and lateral geniculate body of the cat (Boone et al., 1973).

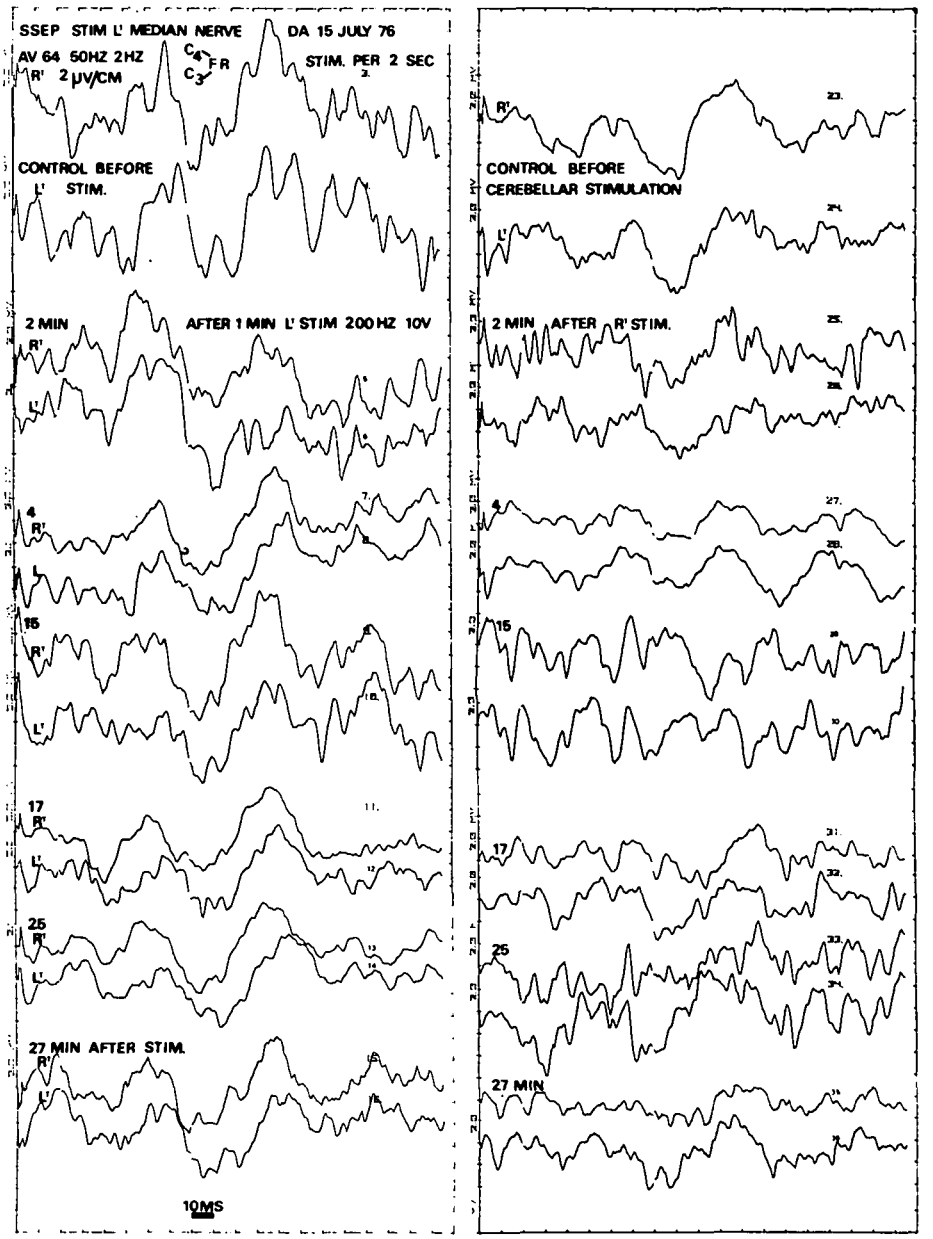

Figure 11 — D.A. M. Age 33. Cerebral palsy. Bilateral anterior cerebellar stimulation at 200 Hz and 10 volts.

Serial somatosensory evoked potentials (SSEPs) from both hemispheres are seen after left (left side of picture) and right (right side of picture) anterior cerebellar stimulation. The left median nerve was stimulated every two seconds and each tracing represents an average of 64 potentials.

It can be seen that there is greater inhibition of SSEPs after right in comparison with left cerebellar stimulation. Spasticity, involuntary movements and muscular contraction produces some artefact but the amplitude of the evoked potentials remains depressed after 27 minutes (bottom tracings), the depression being less marked after left cerebellar stimulation. Such prolonged effects of one minute of cerebellar stimulation are also seen in H, V_1 and V_2 responses.

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Diphenylhydantoin may reduce post tetanic potentiation (Raines and Standaert, 1967; Esplin, 1957) and is known to inhibit the spread of action potentials (Gangloff and Monnier 1957). There might be a reduction in the effects of repetitive electrical stimulation of the cerebellar cortex in patients on DPH therapy particularly as the drug is selectively concentrated in the cerebellum (Kokenje et al., 1965).

Damaging Effects of Cerebellar Stimulation

There have been suggestions that prolonged cerebellar stimulation may damage cerebellar neurons and it is clear that charge density may be related to the breakdown of the blood brain barrier (BBB). Pudenz et al., (1975) found that they could stimulate cat cortex in a biphasic, bipolar mode for 36 hours continuously without causing any impairment of the blood brain barrier if the stimulus charge per phase was 0.3 microcoulombs (μc) or less. Charges of 0.45 μc per phase caused some dysfunction in the BBB in some experiments and such pulses may not produce any sensorimotor response when applied to the surface of the human brain.

Mortimer et al., (1970) observed no change in the BBB with an average power density per electrode of 0.05 W/in^2 for capacitatively coupled or bidirectional pulses. Rowland et al., (1960) saw no evidence of brain damage when bidirectional pulses with cumulative charges up to 20μc per pulse were applied in trains but Dobelle et al., (1973) found minimal histological changes when 50 Hz biphasic potentials of 5 mA and 0.5 msec duration were applied to cat cerebral cortex for periods up to 110 hours.

The resistance of the electrodes may change with time but we have evidence of neurophysiological effects at four volts and 200 Hz and 10 volts at 10 Hz in two patients who had received chronic cerebellar stimulation for four and a half years.

In their criticism of the current methods of cerebellar stimulation, Gilman et al (1975) based their conclusions on the results in a single 3.2 Kg monkey in which human electrodes were continually stimulated for seven hours per day, five hours per week for three months. Some of the damage might have been attributable to the prolonged period of stimulation but the posterior fossa of the monkey is very small and the large human electrodes may have produced direct pressure effects (Larson et al., 1976). Human studies have failed to show significant damage after prolonged periods of cerebellar stimulation (Cooper et al., 1976 and Larson et al, 1976) Our neurophysiological studies failed to show any difference in the effects of cerebellar stimulation in patients beginning cerebellar stimulation and in patients who had received such stimulation for three to four years at the same voltage setting on their stimulators (Larson et al, 1976).

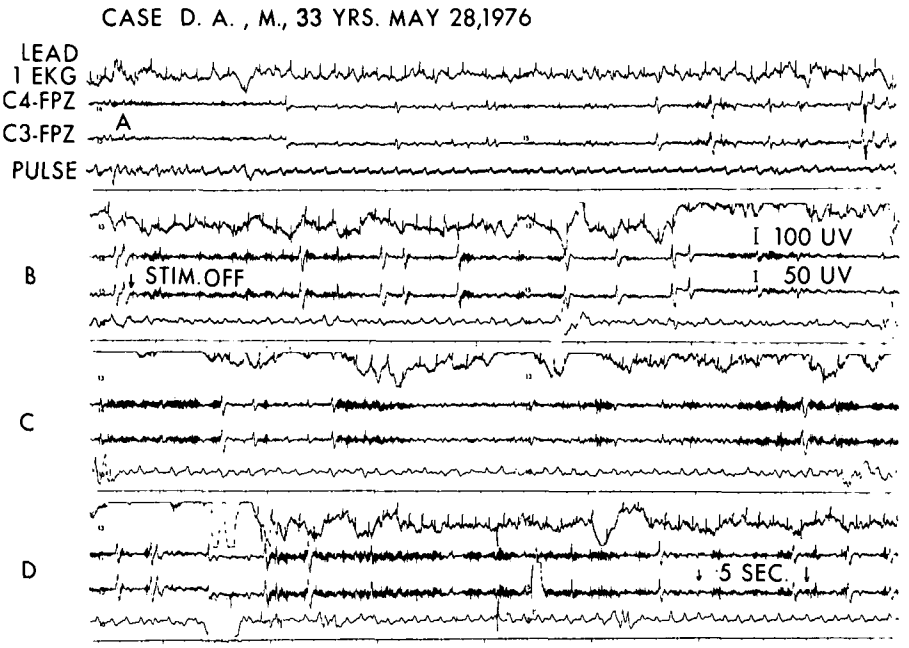

Figure 12 — D.A. Male. Age 33. Cerebral palsy. The cerebellar stimulator was at 10 volts and 200 Hz with stimulation alternating from right and left anterior cerebellar cortex every minute.

EKG, 2 E.E.G. and pulse electrodes show the changes in muscle tone and involuntary movements during and after cerebellar stimulation. Each horizontal line of four traces represents 38 seconds and it can be seen that there is a gradual increase in muscular activity and movement in the 100 seconds after the cerebellar stimulator was switched off. Clinically, it was apparent that muscle tone and involuntary movements increased after the stimulator was switched off and decreased when stimulation was restarted. These results correlate with the inhibition of H reflexes and late reflexes (V_1 and V_2).

Further evidence that current stimulation parameters are physiologically correct at the stimulating electrodes is provided by the finding that little neurophysiological effect on late reflexes or evoked potentials could be seen at 8 volts (10 Hz) in one patient whereas there was a marked change in the potentials at 10 volts. However, it is clear that thresholds need to be established for each patient since we found that 2.5 volts produced inhibition of H reflexes as well as V_1 and V_2 waves in one patient and four volts rather than 10 volts was more effective in another. Application of the neurophysiological techniques described in this paper provide one way in which such thresholds might be established for each patient, a process we might call "biocalibration".

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SUMMARY

(Continued from page 237)

Recovery of amplitude of the reflex and cortical responses took eight to 30 minutes after one minute of cerebellar stimulation. Serial CS of one minute on and one minute off produced increasing inhibition of SSEP's and reflexes for up to five stimulations. Recovery after cessation of cerebellar stimultion was associated with rebound excitation in six patients, the rebound being noted in the amplitude of H reflexes and SSEP's as well as in the frequency of paroxysmal spike and wave discharges in the EEG.

The correlation of the results of such quantitative neurophysiological tests with clinical improvement may allow prediction of clinical results after cerebellar stimulation. These techniques have already been used to measure the threshold of stimulation and may allow optimal stimulation characteristics to be assessed. The prolonged neurophysiological effects of stimulation may allow the use of maximum effective intervals between optimal epochs of stimulation so that any cerebellar damage can be minimized.

RÉSUMÉ

(Continued from page 237)

après une CS droite qu'après une CS gauche et ceci pourrait être une première indication de "dominance" dans les hémisphères cérébelleux. La stimulation cérébelleuse chez les patients traités au Dilantin produisait des effets minimes sur les SSEP et cette observation nous incite à poursuivre nos études chez ces patients.

La récupération de l'amplitude des réponses réflexes et corticales prenait de 8 à 30 minutes après une minute de stimulation cérébelleuse. Une série de CS d'une minute suivie d'un repos d'une minute produisait une inhibition accrue des SSEP et des réflexes jusqu'à 5 stimulations. La récupération après l'arrêt de la stimulation cérébelleuse fut associée à un rebond d'excitation chez 6 patients, ce rebond étant noté dans l'amplitude des réflexes H et des SSEP tout comme dans la fréquence de décharges paroxystiques pointes-ondes dans l'EEG.

La corrélation des résultats de tels tests neurophysiologiques avec l'amélioration clinique pourrait permettre de prédire les résultats cliniques après stimulation cérébelleuse. Ces techniques ont déjà été utilisées pour mesurer le seuil de stimulation et peuvent permettre d'évaluer les caractéristiques de la stimulation optimale. Les effets neurophysiologiques prolongés de la stimulation peuvent permettre l'utilisation d'intervalles efficaces maximaux entre les périodes de stimulation optimale, afin que les dommages cérébelleux soient minimisés.

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