Habituation: effects of regular and stochastic stimulation

M. R. DIMITRIJEVIĆ, J. FAGANEL, M. GREGORIĆ,
P. W. NATHAN[1], AND J. K. TRONTELJ

*From the Neurophysiological Institute, School of Medicine, Ljubljana, Jugoslavia,
and the National Hospital for Nervous Diseases, Queen Square, London*

SUMMARY The different effects of regular and stochastic stimulation on the flexor reflex of patients with the spinal cord totally divided and of normal subjects and on the blink reflex of normal subjects were studied.

When the cutaneous stimulus was above but less than twice threshold, with regular stimulation habituation occurred; with stochastic stimulation, habituation either did not occur or it was minimal. Stochastic stimulation was at random stimulus intervals or with random stimulus intensities.

When stimulus intensity was around threshold, habituation occurred with both kinds of stimulation, the response to stimulation soon ceasing to occur. When stimulus intensity was greater than twice threshold, habituation did not occur with both kinds of stimulation.

When regular stimulation was given after the response had ceased to occur, extinction of the response beyond zero occurred.

When a dishabituating stimulus was repeatedly applied in a regular manner, habituation to the dishabituating stimulus occurred.

With regular and stochastic stimulation given as conditioning and test series, it was seen that stochastic stimulation caused, in addition to the short-term excitatory effect, the same long-term cumulative depressing effect on excitability as did regular stimulation.

The purpose of this paper is to report the different effects obtained with regular repetitive stimulation and stochastic repetitive stimulation in man and to consider the general principles of habituation and dishabituation.

Up to the last five years, this subject came into the field of psychology rather than that of physiology. Yet one of the first physiological investigations was carried out in 1937: Pumphrey and Rawdon-Smith examined the effect of repetitive stimulation of the acoustic nerves on the response of the last abdominal ganglion of the cockroach. They observed that repetitive stimulation gave a decline in response. Examining the effects of changing the frequency and intensity of the stimulus, they found that when the response had 'disappeared almost completely', it could be brought back by an 'increase in the stimulating intensity', an 'increase in the stimulating frequency', or by the interpolation of an extra stimulus into those of the regular

series. Their work seems to have been an isolated physiological investigation for it was only within the last few years that physiologists began to be interested in habituation and dishabituation. In 1965 Buchwald, Halas, and Shramm published their investigation of repetitive evocation of flexor reflexes of the spinal cat; and in 1966 similar studies were published by Spencer, Thompson and Neilson, and Thompson and Spencer. Before this, some studies of habituation and dishabituation had been made in man: Oldfield (1937) reported observations on the auditory blink reflex; and Hagbarth and Kugelberg (1958) studied repetitive evocation of the abdominal cutaneomuscular reflex.

In this paper we are presenting some of our evidence to illustrate some of the principles of habituation and dishabituation that we have learned from studies of the flexor reflex of normal man by Faganel (1970); the flexor reflex of man with the spinal cord totally divided by Dimitrijević and Nathan (1970, 1971); and the blink reflex by Gregorić (1970). In the first

[1] External Scientific Staff, Medical Research Council, Great Britain.

paper by Dimitrijević and Nathan, the following phases of changes in the response to a regularly repeated stimulus were recognized: build-up phase, phase of fluctuation, phase of diminution, and phase of cessation of response. These terms will be used here.

METHODS

The noxious cutaneous stimulus used was an electric stimulus generated by a stimulator with built-in programme, designed by Trontelj, Trontelj, and Trontelj (1967). The stimulus consisted of trains of rectangular pulses, pulse-width 0·2–0·3 msec, frequency of 2 kHz, duration 20, 30, or 40 msec. Repetitive stimulation was either regular or random in either frequency or intensity, the randomness having a Gaussian distribution function. Electromyographic (EMG) responses were detected by surface electrodes and were amplified and displayed on a Tektronix type 565 oscilloscope with 2A61 amplifier and were recorded on tape. They were subsequently rectified and integrated by an analogue unit, designed by Trontelj and Trontelj (1968) and fed into a CAT 1000 computer. Histograms of mean EMG activity were computed. Where percentages of the amount of response are given, they are percentages of the mean of 20 responses; so that if, for instance, a response is said to have gone down to 50%, it means that the mean of the last 20 responses is 50% less than the mean of the first 20 responses.

FLEXOR REFLEX OF NORMAL MAN   These experiments were performed on eight subjects, aged 20 to 28 years. Stimuli of 40 to 80 V were delivered to the skin of the medial side of the plantar surface of the foot through electrodes designed by Copland and Davies (1964). Regular stimulation usually consisted of 50 stimuli, stimulus intervals of 16·66 msec; stochastic stimulation at random frequencies was with stimulus intervals of from 333 msec to 3 sec. In the flexor reflex of the normal subjects and the patients with divided spinal cord, the response computed was that of the tibialis anterior muscle; computation was from 50 to 150 msec after the beginning of the stimulus.

FLEXOR REFLEX OF SPINAL MAN   These experiments were performed on 12 patients, aged 20 to 35 years. Stimuli of 5 to 100 V were delivered to the skin of the medial side of the plantar surface of the foot through Copland-Davies electrodes. Stimulus intervals of regular stimulation were 0·5 to 10 sec and of stochastic stimulation at random frequencies were 0·3 to 2 sec. When the stimulation rate was as fast as 5 Hz, each stimulus was on most occasions occurring at a time when the response to the previous stimulus was still continuing. When stimulus intervals were randomized, stimulus intensity was kept constant

and when stimulus intensity was randomized, stimulus intervals were kept constant. With both kinds of stimulation, the series lasted from a few seconds to several minutes. The number of stimuli in a series was between 45 and 1,040. In some experiments, habituation was carried on to beyond zero; this was shown by examination of the rate of spontaneous recovery of responsiveness.

BLINK REFLEX OF NORMAL MAN   These experiments were performed on 10 subjects aged 17 to 31 years. Stimuli of 15 to 30 V were delivered to the skin over the supraorbital foramen above the right eye through cup-shaped silver-silver chloride electrodes. The intensity of the stimulus was adjusted for each subject so that it was 50% above his threshold; this stimulus was slightly painful. Stochastic stimulation at random stimulus frequencies was with stimulus intervals of 333 msec to 3 sec; stimulus intervals of regular stimulation were 1,666 msec, this being the mean of the random stimulus intervals. The response examined was that of the ipsilateral orbicularis oculi muscle. The latency and the duration of the second component of the response were measured; the amount of the response 24 to 100 msec from the beginning of the stimulus was computed in each subject. In three subjects, there was a third component, but, as it occurred after 100 msec, no observations or computations were made on it. As the second component of the blink reflex is analogous to that of the spinal flexor reflex (Shahani and Young, 1968; Shahani, 1970) it is this component that is reported upon here.

RESULTS

Habituation is seen with rhythmical (regularly applied repetitive) stimulation; it is not seen with stochastic stimulation. This statement holds, however, only when the stimulus intensity is well above, and less than twice, threshold. These features of habituation are illustrated in Figs 1 to 3.

Figures 1a and b show the different effects of regular stimulation and stimulation at random stimulus intervals in a patient with a total cord division; the division was at the 6th thoracic segment. In both series, stimulus intensity was 15 V. With regular stimulation 50 stimuli were given at 1 sec intervals; with stochastic stimulation 1,025 stimuli at 0·8 to 2 sec intervals were given. In Fig. 1a, it can be seen that before half of the 50 stimuli have been given, the response of the tibialis anterior muscle has reached the phase of cessation of response. Figure 1b shows the responses to the first 200 of the stochastic stimuli. After the first 14 stimuli, there is a
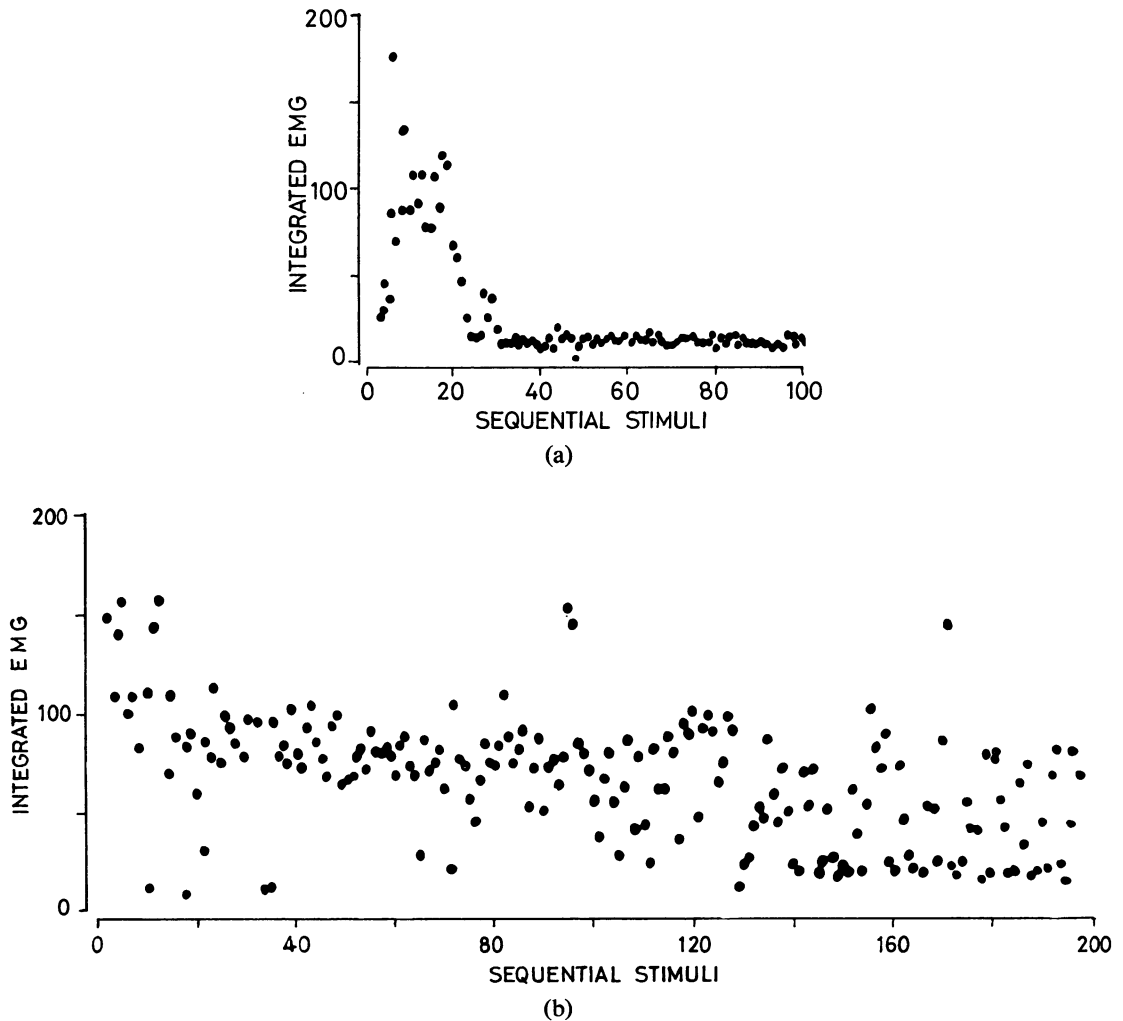
FIG. 1.   *Histogram of integrated EMG activity of tibialis anterior muscle in paraplegic patient;* (a) *regular stimulation;* (b) *stimulation at random stimulus intervals. In this and the following figures the abscissa shows sequential stimuli and the ordinate shows the amount of EMG response in arbitrary units.*

slight diminution in the response; after this, there is a minimal diminution in the later part of the curve.

Figures 2a and b show the different effects of regular stimulation and stimulation at random stimulus intensities, in the same patient. Both show the phase of build-up of the response. After the build-up phase, Fig. 2a shows the phases of diminution and then fluctuation of response; Fig. 2b shows none of the phases of habituation. In both series, stimulus interval was 1 sec; with regular stimulation, stimulus intensity was 22 V; with stochastic stimulation,

the mean stimulus intensity was 22 V, with a range of ± 50%.

The same difference between regular and stochastic stimulation occurs in intact man. This is illustrated for a normal subject in Figs 3a and b, with stimulation at random stimulus intervals. Stimulus intensity was 50 V, which was 25% above threshold.

In Fig. 3a the diminishing response to regular stimulation can be seen. In Fig. 3b it can be seen that even after 100 stimuli there is no appreciable diminution in the amount of response, except for that to the first six stimuli. It will also be seen
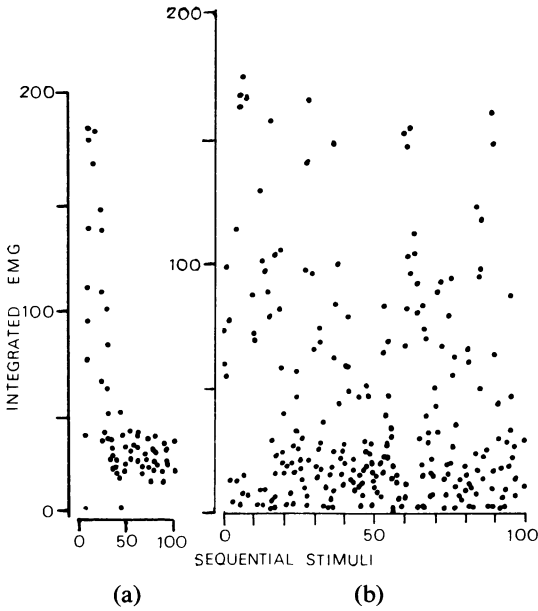
FIG. 2. *Histogram of integrated EMG activity of tibialis anterior muscle in paraplegic patient;* (a) *regular stimulation;* (b) *stimulation with random stimulus intensities.*

in Fig. 3b that there was no build-up phase. The build-up phase was often absent in normal subjects. Also in the patients with cord transections, with stochastic stimulation the build-up phase was often replaced by an immediate large response, which was followed by a large variation in the amount of response.

In six normal subjects, regular stimulation with stimuli 25% to 50% above threshold caused more than 80% decrement in the response after 50 stimuli; in one subject the decrement was 55% and in another it was 21%; in four, the response ceased before the whole series of 50 stimuli had been given. Stimulation at random stimulus intervals in all six subjects caused a minimal diminution in the response. There was a slight diminution in the amount of the response after the maximal response to the second, third, or fourth stimuli. Then there was a fluctuation in the response to the next 100 stimuli. After this, there was a slight trend for the response to diminish; this was present in all subjects but in no single subject was a diminution in the amount of response statistically significant.

In two normal subjects, stimulation at random stimulus intervals caused a very slight increase in the response. In these subjects, the dishabituating effect of stochastic stimulation overcame the habituating effect.

For all the normal subjects put together, the amount of the response of the tibialis anterior muscle was calculated on an arbitrary scale. With 50 stimuli given regularly, the amount of response diminished from $521 \pm 11 \cdot 7$ to $65 \cdot 2 \pm 23 \cdot 6$; with 100 stimuli given at random stimulus intervals, it diminished from $455 \cdot 8 \pm 11 \cdot 05$ to $430 \cdot 8 \pm 15 \cdot 5$ (arbitrary units).

When the stimulus intensity was at or just above threshold, with both regular and stochastic stimulation, the phase of cessation of
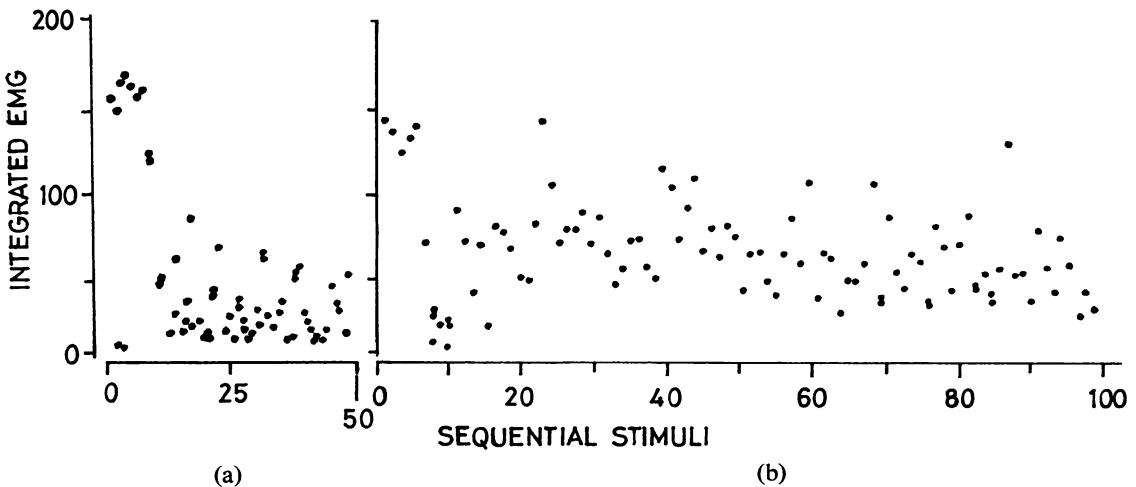

FIG. 3. *Histogram of integrated EMG activity of tibialis anterior muscle in a normal subject;* (a) *regular stimulation;* (b) *stimulation at random stimulus intervals.*

response arrived after only a few stimuli. When the stimulus intensity was 100% or more above threshold, there was also no difference in the response to both kinds of stimulation: with regular and stochastic stimulation habituation in a series of stimulations was not seen. The lack of habituation with regular stimulation at an intensity of stimulation 100% above threshold is shown in Fig. 4 in a normal subject. The response to 65 stimuli at 95 V is shown.
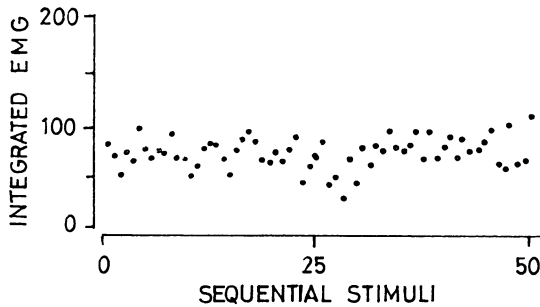

FIG. 4. *Histogram of integrated EMG activity of tibialis anterior muscle in a normal subject; regular stimulation.*

On many occasions in the patients with total cord division, regular stimulation was continued for minutes after the cessation of response. It was found that the time for spontaneous recovery took longer than it did when no more stimuli were given after the first occurrence of an absent response. It was also seen that when a dishabituating stimulus was regularly given in conjunction with the habituating stimulus, it had less exciting effect and a less lasting effect than when it was given alone, without the habituating stimulus. Both these facts show that the regularly applied stimulus continued to exert a depressing effect even when the response to it cannot be seen. There is extinction beyond zero. These two facts show also that it is the stimulus and not the response that results in habituation.

The features of habituation and dishabituation are not exclusively spinal. Similar effects of the two kinds of stimulation occur in the blink reflex. With this higher level reflex, stochastic stimulation at random stimulus intervals showed some habituation but it was slight. Habituation with regular and very slight habituation with stimulation at random stimulus intervals in the

blink reflex of a normal subject is illustrated in Figs 5a and b.

In Fig. 5a the response can be seen to diminish to almost nil after 120 stimuli had been given regularly. In Fig. 5b, the response was slowly and slightly diminishing throughout the series of 125 stimuli given at random stimulus intervals.

In the series of the blink reflexes, some habituation was seen in seven of the 10 subjects with stimulation at random stimulus intervals. It was much less and it required a far greater number of stimuli than with regular stimulation.

In all experiments with the flexor and with the blink reflexes, it was found that the greater the
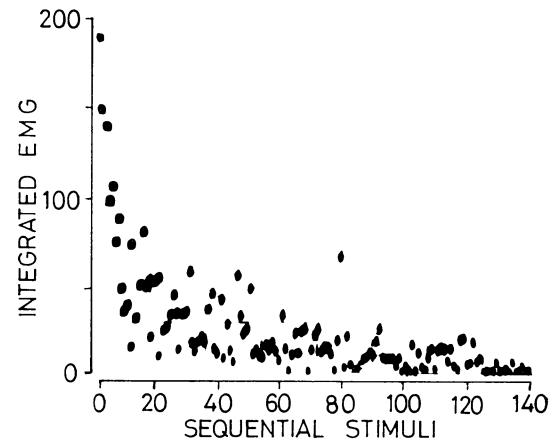
(a)
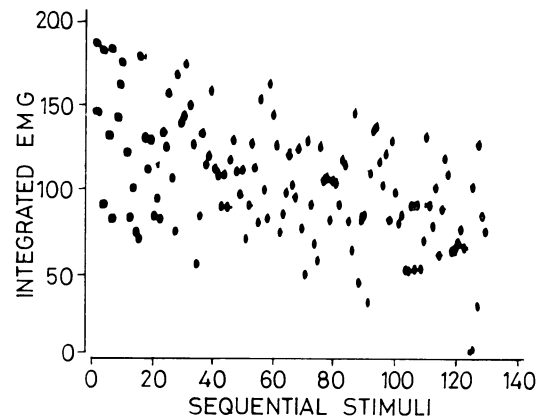
(b)

FIG. 5. *Histogram of integrated EMG activity of orbicularis oculi muscle in a normal subject;* (a) *regular stimulation;* (b) *stimulation at random stimulus intervals.*

variance of frequency or intensity of stimulation, the more habituation was suppressed.

Although stochastic stimulation stopped habituation, it was found that it caused the same long-term effects as regularly repeated stimulation. This was so for the flexor reflex of the patients and of the normal subjects and for the blink reflex of normal subjects. This aspect of the subject was not shown in our previous papers. To make manifest this cumulative effect of both kinds of repetitive stimulation, repeated stimuli were given in series, separated by rest periods. First, a conditioning series of regular stimuli was followed after a rest period of 15 minutes by a test of series or regular stimuli; then after a rest period of 30 minutes a conditioning series of stochastic stimuli was given, again followed after a 15 minutes' rest period by a test series of regular stimuli. A typical series is shown in

Figs 6a and b. In this example, the reflex examined was the flexion reflex of a normal subject. Stimulus intensity was 50 V; stimulus intervals were 0·5 sec for regular stimulation, 333 msec to 3 sec for stochastic stimulation. After 48 stimuli had been given regularly, the response fell to 25% of the original amount. After the rest period of 15 minutes, 48 further stimuli were given regularly. The amounts of the first responses of this test series were less than those of the conditioning series. After the 48 test stimuli had been given, the response fell to 8% of the original amount at the start of the test series. There was then a rest period of 30 minutes, during which the subject walked around. The stimulus was then given 100 times at random stimulus intervals. The response fell to 71% of the amount at the beginning of this series. After the rest period of 15 minutes, 48 stimuli were given regularly. The response fell to 18% of the response at the beginning of this series. Thus the series of stochastically given stimuli has had a similar long-term effect as the series of regularly given stimuli.

The experiments done with conditioning and test series of stimuli have shown that the long-term effect of stochastic stimulation is similar to that of regular stimulation: the excitability of the response is reduced. It is apparent that each non-periodic stimulus evokes a large response, regardless of the diminishing responses of the periodic stimuli; but the total input of repeated stimuli still causes a long-term depression in the reactivity of the spinal cord.
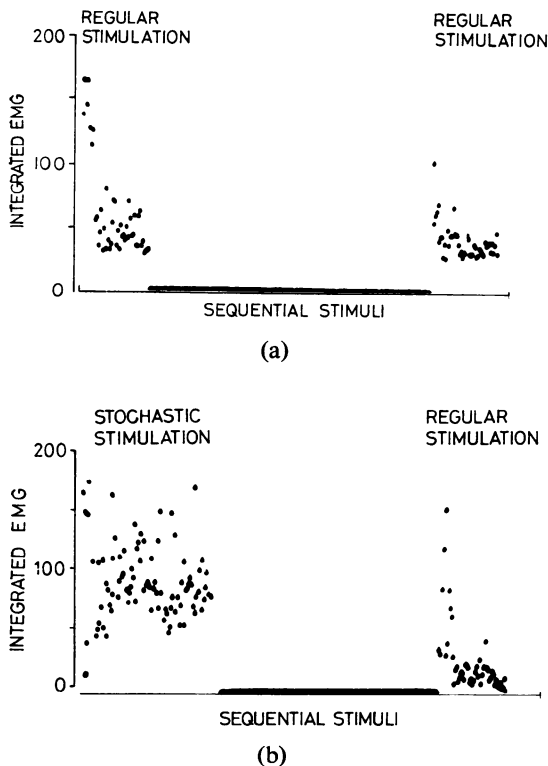

FIG. 6. *Histogram of integrated EMG activity of tibialis anterior muscle in a normal subject. Stimulation given in conditioning and test series.* (a) *regular followed by regular stimulation;* (b) *stimulation at random stimulus intervals followed by regular stimulation.*

DISCUSSION

Everything written in this discussion applies only if the stimulus intensity is above but less than twice threshold and the stimulus intervals short enough to cause habituation. It applies only to the situation that we have studied—the rapidly repeated application of stimuli. In this situation, and particularly in the patients with spinal cord divided, there may still be continuing motoneurone activity due to the previous stimulus when the next stimulus is given; and this means that each stimulus may be given in different circumstances from previous stimuli. It is clear that various repetition rates entail varying amounts of continuing activity. We are not concerned here with the changes in excitability between two stimuli, which are often examined by one conditioning and one test stimulus. The

effect of adding the same or other kinds of stimuli in other places of the ipsi- or contralateral limb was the subject of the paper by Dimitrijević and Nathan (1971), and so no evidence about this form of dishabituation will be given here.

In the work reported here the stimulus was always electric; this was painful in normal subjects. The same phenomena have been observed in the flexor reflex with natural stimuli such as pinching and pricking the skin, dragging a heavy point along the sole, and spraying the skin with ethyl chloride. This is a cutaneo-muscular reflex. Shahani (1968, 1969) and Shahani and Young (1968) have shown that in the blink reflex both components are due to purely cutaneous stimuli; and so this reflex is also a cutaneomuscular reflex. In the case of the flexion reflex the entire pathway is spinal and so the phenomena we are observing can occur within the isolated human spinal cord. The changes in this reflex observed and reported in this and the two previous papers on the spinal reflex are examples of how the spinal cord organizes its behaviour towards repeated identical stimuli.

Cutaneous stimuli are adapted to when they occur in a regular rhythm; adaptation is minimal when they occur stochastically. It is rhythmical stimulation that demonstrates the existence of habituation, for habituation is not seen with stochastic stimulation. We expect that the same will be found for other examples of repetitive stimulation. The reflexes we have examined are polysynaptic cutaneomuscular reflexes. Whether the same phenomena occur with other kinds of reflexes and with monosynaptic reflexes remains to be found out.

It was stated by Dimitrijević and Nathan (1971) that stimuli of an intensity less than that of the regularly applied stimuli do not cause dishabituation. Further work by one of us (Trontelj, 1971) has now shown that this is not so. Although a single slight stimulus interpolated in a series of regular stimuli does not cause an increased response, other ways of examining the effects of stimuli of slighter intensity than those of the regularly applied series have shown that these stimuli do have a dishabituating effect.

Yet stochastic stimulation has slightly different effects in accordance with whether it is the stimulus intervals or the stimulus intensities that are made random; this was shown by Dimitrijević, Gyergyek, and Trontelj (1970). With the usual range of stimulus intensities used, some stimuli will be too weak to cause dishabituation, for they will be at or below threshold. When stimulus intervals are made random, every stimulus causes dishabituation.

One asks here about the size of the cutaneous field of the habituated response. This is really two questions: there is the size of field with regard to getting a restored response on applying an extra stimulus; and there is the size of field that has been affected in any way by the total input of regular repeated stimulation. With regard to the size of field habituated so that an extra stimulus does not evoke a larger response, it was found that this field is very small; it extends less than 2 cm from the point of the repeated stimulus. With regard to the size of field that has been affected in any way at all by repetitive stimulation, no systematic observations were made. Observations, however, made throughout the course of many experiments show that this field must be very large. It includes the whole of the ipsilateral lower limb if stimulation has continued at a rate of one a second or faster for 15 minutes or more. If stimulation has been continued during a session of three to four hours, stimulation series being separated by rest periods of 15 minutes or more, then the field takes in the whole body below the lesion dividing the spinal cord; this is probably the same phenomenon previously called 'tiring' by Dimitrijević and Nathan (1970).

The general principles of habituation and dishabituation with regular and stochastic stimulation are seen in their most stereotyped form in the spinal segments below a cord transection. They are less obvious in the intact nervous system. In normal subjects, they are more obvious in the flexor reflex than in the blink reflex. It is the second component of these two reflexes that is most varied by conscious factors in normal subjects. In the blink reflex of normal subjects, the build-up phase was minimal or was not seen. This would seem to be related to the psychological set of the subject, to what he was expecting from the stimulus. In this reflex in normal subjects there were large individual differences in the course of habituation and in a single individual done on more than one occasion. It seems that the essential features of these phenomena are seen in spinal man and that they are modified by the higher levels of the brain.

The different sensations experienced with regular and with stochastic stimulation by all

subjects should be noted. Stochastic stimulation is much more unpleasant than regular stimulation. In the experiments on normal subjects an intensity of stimulation was first found that was bearable when stimulation was regular. When this stimulus was given stochastically, it was almost unbearable. One or two of our subjects were convinced that the stimuli had been made of greater intensity when they were given stochastically. Not only does the stimulus feel more painful, it is also psychologically more upsetting: one feels apprehensive and unpleasantly alert throughout a series of stochastic stimuli.

The course of habituation is not linear. In the reflexes studied the build-up phase usually occurs as an increasing response to only the first two or three stimuli. The phases of diminution and fluctuation usually merge into each other; they continue for a long time before the phase of cessation of response occurs. On some occasions the course of habituation followed an exponential curve.

The existence of habituation within the spinal cord shows that this part of the nervous system (apart from higher levels also) is possessed of an accurate timing mechanism. Once the period of rhythmical stimuli has been appreciated, changes from that period of a second or so are reacted to; the reaction is to decrease the response progressively. Seen from the point of view of information, the information content of a repeated identical stimulus tends towards nil. If the stimulus is displaced or if its intensity or rate is increased or decreased, the central nervous system reacts to this information, for it reacts to what is new.

Stochastic stimulation causes both dishabituation and habituation. Every single adequate random stimulus causes an increased response and thus apparently dishabituates some of the effects of habituation. But the total input of adequate stochastic stimuli has a similar habituating effect to that of the total input of regular stimuli; this was illustrated in Fig. 6. The cumulative effect of repetitive stimulation finally overrides the dishabituating effect of each stimulus. When repetitive stimuli are given in repeated series, a long-term effect is disclosed by the fact that habituation occurs more quickly in each series. This occurs both with regular and stochastic stimulation.

If the stimulus intensity is very high, the depressing effect of regular stimulation is overcome by the excitatory effect. But the cumulative depressing habituating effect is occurring latently, as is shown by the effect of the total input. If the stimulus intensity is very low, the excitatory effect of stochastic stimulation is overcome by the depressing effect of habituation; and so habituation is seen equally with stochastic and regular stimulation.

All those who have examined examples of habituation and dishabituation have noted that the excitatory effect of the dishabituating stimulus is transient: the response continues to diminish in spite of repetitive application of the dishabituating stimulus. Many examples of this were given in the previous paper by Dimitrijević and Nathan (1971). When a dishabituating stimulus is regularly repeated, there is in effect habituation to the dishabituating stimulus. This is not therefore a special feature of dishabituation, as has often been said; it is an example of habituation, being the same phenomenon as habituation to the habituating stimulus. It is immaterial that the new stimulus was first given as a single stimulus if it continues to be given in a regular manner. The only effective repeated dishabituating stimulus is stochastic stimulation: because it is unexpected in period, intensity, and place.

Dimitrijević and Nathan (1970) gave reasons for concluding that the diminishing response is not due to depletion of transmitter substance throughout the reflex pathway. Briefly, these were that the first muscle to respond is also the last muscle to respond before the cessation of response, and that the more intense the stimulus, the less habituation occurs. To these reasons we now add that the facts of stochastic stimulation also show that the depletion of transmitter is an unlikely hypothesis. For, to get a full response, all that is needed is to omit one stimulus; the next stimulus then comes after an interval of twice the usual period. Or a full response can be obtained to a stimulus interval less than the periodic one. It would seem most unlikely that if transmitter substance is being depleted anywhere on the pathway, it could be fully restored in these circumstances.

At present we cannot suggest a known mechanism to account for habituation. For inhibition, either pre-synaptic or post-synaptic, has far too short a duration to account for habituation occurring at these relatively slow rates of stimulation. It is possible that with repeated stimulation there is a progressive withdrawal of tonic facilitation that is needed to get

a response of motoneurones. This facilitation might be anywhere on the interneuronal pathway and/or at the motoneurones. In the intact nervous system, the facilitation could be in any neural pathways and not restricted to those of the spinal cord. The evidence from our work leads us to propose that, apart from in the build-up phase, each stimulus causes both an excitatory and a depressing effect.

Habituation has often been considered as a mechanism whereby the animal neglects a habitual response so that it is free to receive and attend to new events. But in life stochastic stimulation is far more common than regular rhythmical stimulation. Regular stimulation is the special case. It is a laboratory manoeuvre that serves to demonstrate the existence of habituation which otherwise might not have been seen.

We propose that the term habituation should be confined to changes in the response that are not lasting or permanent. Thorpe (1950), discussing habituation in the behaviour of animals, typifies it as learning not to respond to stimuli that tend to be without significance. He is right to use the word 'learning' here; for the changes he is describing are permanent or almost permanent. As permanent changes are rightly called learning, there is no point in using the word 'habituation' as well. This leaves the word 'habituation' to categorize the diminishing response, examples of which have been given above. These changes do not persist.

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