

DIFFERENTIAL CEREBRAL ELECTROSTIMULATION

By

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CEREBRAL electrostimulation of subconvulsive intensity causes a pronounced increase in the concentration of adrenaline-like substances in the blood (Weil-Malherbe and Bone, 1952b). This effect is presumed to be due to a central action of the current, since these investigators were unable to demonstrate any rise when both electrodes were placed on the same side of the head. The current which was used in these experiments consisted of brief rectangular impulses with a repetition rate of 100 pulses per second (Montagu, 1953). Recently, while experimenting with shorter pulses at correspondingly higher repetition rates, the author observed that the motor response diminished as the frequency was raised, the peak and average current levels remaining constant. This effect, which appeared to be due to the progressive abbreviation of the pulses to the point at which they ceased to be effective motor stimuli, suggested that these conditions might be advantageous in electrostimulation therapy, provided that the autonomic effects were not equally impaired. Firstly, however, it was necessary to determine whether the diminution in the motor effects at the higher frequencies was part of a generalized reduction in the efficiency of cerebral stimulation or whether there was a differential response. Accordingly, with the assistance of Dr. Weil-Malherbe, the blood adrenaline level has been studied in relation to the different conditions of stimulation. The results of this investigation are contained in the present report.

ELECTROTECHNIQUES

Several types of current have been used in subconvulsive stimulation therapy: faradic current (Berkwitz, 1940), alternating current (Riboli and Mancini, 1948), the Reiter current (Hirschfeld, 1950; Alexander, 1950, 1953), and Liberson's Brief Stimuli (Hirschfeld and Bell, 1951; Montagu, 1953). In general, the frequency of stimulation has been low, ranging from 28 pulses per second, the basic frequency of the Reiter current (Alexander, 1953), to 120 p.p.s. with brief rectangular impulses (Hirschfeld and Bell, 1951), although Berkwitz (1952) has recently used a faradic current at a repetition rate of about 300-400 p.p.s. In convulsive therapy, Cossa *et al.* (1948), employing "square waves" with a pulse/interval ratio of unity, used frequencies up to 600 p.p.s., while Hirschfeld and Bell (1951) have given up to 500 brief stimuli per second. The latter workers were studying the clinical effects of varying the parameters of stimulation, and it seemed to them that low frequencies of about 20 p.p.s. with a pulse duration of 1.5 milliseconds produced a greater autonomic response than shorter pulses at higher repetition rates. However, the autonomic effects have not been previously measured in relation to different conditions of cerebral stimulation.

Of the various types of electrical stimulus the rectangular form possesses certain advantages, namely:

(1) On *scientific* grounds it is accurately measurable in all dimensions: pulse duration, pulse interval, and peak current.

(2) Its adoption has been proposed on *physiological* grounds by Liberson (1945), who suggested that the pulse duration should be compatible with the chronaxie, and the interval with the refractory period, of the neurones.

APPARATUS

The current consisted of brief, unidirectional, rectangular impulses ("square waves"), which were obtained from a small high-tension battery by means of a commutator-interrupter, i.e. it was an "interrupted galvanic" current in the true sense of the term. The apparatus was similar to that which was used by Leduc (1903) at the beginning of the century.

The circuit diagram of the stimulator is shown in Fig. 1. The central

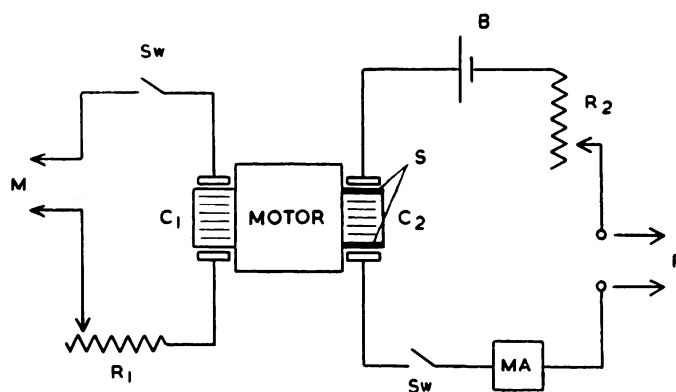


FIG. 1.—Circuit diagram of the stimulator. B—67½ volt battery. C₁ and C₂—commutators. M—mains. MA—milliammeter. P—patient. R₁ and R₂—rheostats. S—metal segments (connected together). Sw—switch.

feature is an electric motor, the armature of which carries two commutators, one at each end. One of the commutators (C₁) is connected with the armature windings and is used to drive the motor from the mains supply. A variable resistance (R₁) in this circuit enables the speed of rotation to be controlled. The other commutator (C₂) is isolated from the armature and is used to make and break a secondary circuit. It consists of two narrow metal segments, which are diametrically opposed but connected together. Two brushes, in contact with the commutator, are also diametrically opposed, so that the secondary circuit is made during a few degrees in each half-cycle of the commutator. This results in a series of brief "square waves" with a frequency equal to double the speed of the motor. The secondary circuit supplies the patient from a small 67½ volt battery and is completed, in series, by a switch, a rheostat (R₂) for controlling the current, and a milliammeter.

A system of this type enjoys some advantages, and a few disadvantages, when compared with the more complex electronic circuits:

A. Advantages

(1) *Simplicity.* The apparatus is cheap, robust, and compact. The last of these points is illustrated photographically in Fig. 2.

(2) *Safety.* This derives from the mutual isolation of the primary and secondary circuits, the mains serving no other function than that of driving the motor.

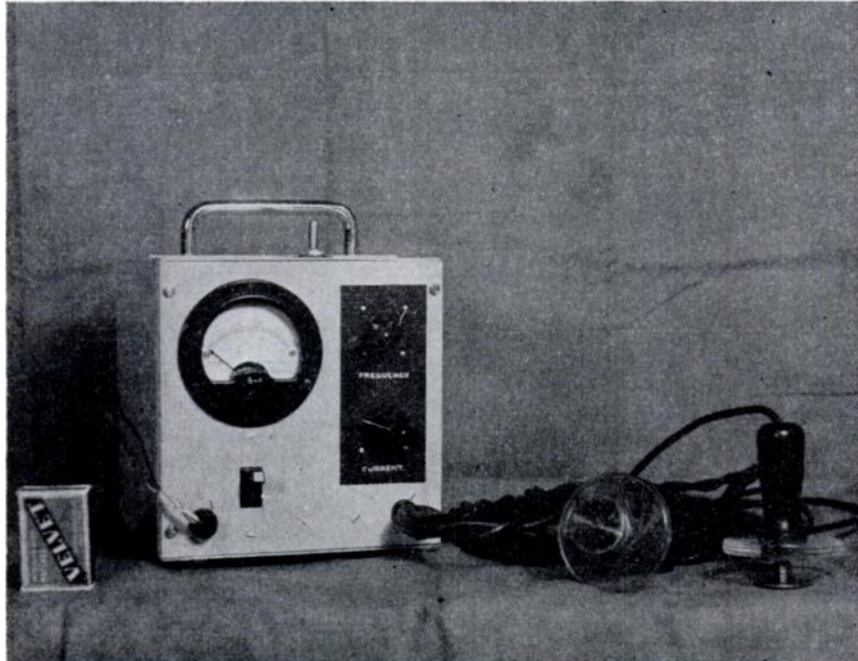


FIG. 2.—Photograph of the stimulator and electrodes. The size is shown by comparison with a match-box.

(3) *Variable frequency* may be easily obtained, within moderate limits, by a simple control of the speed of the motor.

(4) *Constant quantity output* which is independent of frequency. The relative values of pulse duration and pulse interval are determined by the design of the commutator and the position of the brushes. Leduc (1903) used an adjustable brush whereby the pulse duration could be varied at the expense of the interval, but in the present instance the ratio was fixed. The absolute values, on the other hand, depend upon the speed of the motor. However, since any alteration in the speed of rotation is accompanied by an inversely proportional change in both pulse and interval (see Fig. 3), the average output remains constant, for any given peak current, at all frequencies. This condition was required for the present investigation.

B. Disadvantages

The disadvantages of a commutator-interrupter relate, principally, to the accuracy and constancy of the electrical characteristics.

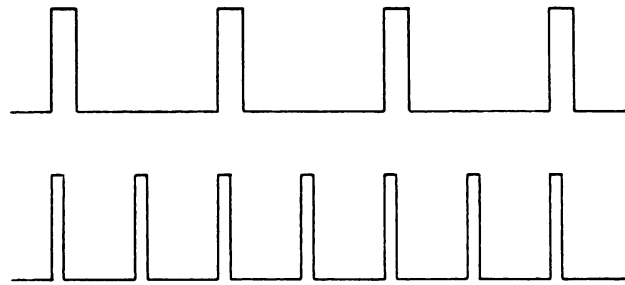


FIG. 3.—Diagram of the wave-form (not to scale), showing the effect of doubling the frequency.

(1) *Wave-form.* This is liable to distortion by the occurrence of sparking at the brushes, a condition which is manifested, oscillographically, in spiked or fuzzy contours. A single impulse from the present apparatus is illustrated in Fig. 4, which demonstrates its freedom from this effect.

(2) *Pulse duration.* The present system produces two pulses during each revolution of the motor. Alternate pulses will therefore differ in duration if the

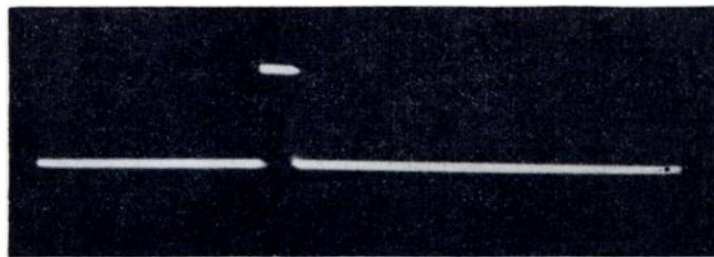


FIG. 4.—Oscillographic trace of a single pulse.

brushes or the segments are not both in exact diametrical opposition. This is illustrated in Fig. 5, which shows two consecutive pulses superimposed, as indicated by the double trailing edge. The difference in duration between the two pulses amounts to 10 per cent. of the mean duration.

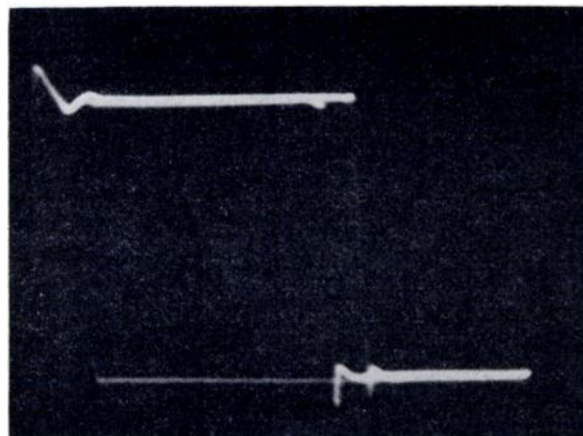


FIG. 5.—Triggered and expanded trace showing the alternate pulses superimposed, as indicated by the two trailing edges. The spot, at the left end of the base line, has been blanked out.

(3) *Frequency*. This is determined by the speed of the motor, which in turn varies with the input voltage and with sundry frictional losses. These factors introduce a liability to shift of frequency over a certain range, but this occurs proportionately at all levels.

By oscillographic methods the pulse/interval ratio of the present system was found to be almost exactly 1 : 24, while the maximum frequency, at mains voltage, was 500 pulses per second. Under these conditions the durations of pulse and interval at various available frequencies are, by calculation, as follows:

Frequency p.p.s.	Pulse Duration μ sec.	Pulse Interval msec.
100	400	9.6
200	200	4.8
300	133	3.2
400	100	2.4
500	80	1.9

The ratio of peak current, determined on the oscillograph, to average output, as recorded by the milliammeter, was, however, only 20 : 1, compared with the cycle/pulse ratio of 25 : 1. This discrepancy was the result of a combination of slight errors from several sources, e.g. wave-form, meter, etc. Accordingly, with a peak current of 100 mA. the average output was 5 mA. This remained absolutely constant over the entire range of frequencies. Owing to this small consumption one miniature 67½ volt battery survived continuous use for six months, during which time it delivered approximately 400 treatments each of five minutes' duration. The circuit shown in Fig. 1 has an approximately constant voltage characteristic, so that good electrode contacts are necessary; otherwise an adequate current cannot flow. Nevertheless, in the following experiments the current, not the voltage, was recorded, and the tendency to variation was found to be negligible once the required level had been attained.

METHODS

The subjects of this investigation were 15 males suffering from anxiety states who had been admitted to Roffey Park Rehabilitation Centre. All were receiving treatment by subconvulsive electrostimulation. The electrodes were circular, 3 cm. in diameter, and were applied bitemporally about one inch above the attachments of the pinnae. After preliminary anaesthesia with thiopentone, and application of the electrodes, the current was switched on and was raised rapidly to 4 mA. (80 mA. peaks). This was usually the highest intensity which could be maintained without causing undue respiratory embarrassment at the lower frequencies. On one exceptional occasion it became apparent immediately that this current would not be endured, and the level was reduced to 3½ mA. (70 mA. peaks). On all other occasions the initial apnoea was transient and the higher intensity was maintained for the duration of the experiment.

Samples of blood were collected by withdrawing 15 ml. into 5 ml. of a special fluoride-thiosulphate solution (Weil-Malherbe and Bone, 1952a). An initial specimen was obtained immediately before the injection of thiopentone, and a second one was taken about a minute after the injection. A number of specimens were then collected at intervals during stimulation at various frequencies, the intensity remaining unaltered throughout. In every instance at least 1½ minutes was allowed to elapse after a change of frequency before the withdrawal of the next sample was begun. A final specimen was taken one to

two minutes after the current was switched off. The blood samples were centrifuged, and the plasma adrenaline and noradrenaline concentrations were estimated at Runwell Hospital by the method of Weil-Malherbe and Bone (1952a, 1953).

MOTOR EFFECTS

Initial trials with the present apparatus began with frequencies of 100–200 p.p.s. (pulse durations of 400–200 μ sec. respectively) and with peak currents of 60–80 mA. These conditions are similar to those which had been used previously, viz. 100 p.p.s. with a pulse duration of 300 μ sec. (Montagu, 1953), and similar motor effects were obtained. These included spasm of the facial muscles, tonic contractions of the arms and, to a lesser extent, of the legs, respiratory embarrassment above a certain intensity of current, and pronounced stimulation of respiration below that level. The frequency was then steadily raised to 500 p.p.s. at the same peak current, the pulse duration diminishing correspondingly to 80 μ sec. This resulted in progressive relaxation; the arms fell to the patient's side, and the respirations lost their forced character and assumed a normal rhythm. During this process the muscles of the shoulder girdle were the first to lose their tonus, followed in sequence by those of the upper arm, forearm, and hand. Although some change was seen throughout the entire range of frequencies, the most noticeable alteration occurred in the vicinity of 300 p.p.s. At 400 p.p.s. the patient already appeared relaxed. When the frequency was reduced, the effects were reversed. At the lower end of the scale, down to 100 p.p.s. and below, the tonus became more intense and more generalized, the facial contortion steadily increased, and the respirations assumed the alarming character of shallow, jerky grunts. This cycle of events could be produced and reversed as often as the frequency was raised and lowered.

SENSORY EFFECTS

Cerebral stimulation at low frequencies is known to be antagonistic to barbiturate narcosis (Hirschfeld, 1950; Robie, 1950). It reduces, to about one half, the normal duration of anaesthesia following intravenous induction. The patient, however, usually relapses into stupor when the current is discontinued. Within five minutes of receiving 0.5 gm. of thiopentone intravenously most patients, under continuous stimulation at 200 p.p.s. or below, make a purposive response by raising their hands to the electrodes. Continued stimulation may be experienced as a most unpleasant vibration within the head. If, however, the frequency is raised to 500 p.p.s. as soon as a response is elicited, the hands return to the side, and the patient accepts the current at the same intensity for a period which may be as long as the initial interval. A reduction of frequency during this time again brings the hands up to the electrodes, when an increase will once more abolish the response. When, on the other hand, stimulation is maintained at 500 p.p.s., the patient may ultimately obey a simple request or even reply to a question before making any defensive movements, and if, at this point, the current is discontinued, he frequently denies any painful experience. Others describe a sensation of vibration which they do not, in general, regard as unpleasant. Although, however, the higher frequencies appear to cause less intense sensory stimulation than the lower ones, it has not been found practicable to dispense with the preliminary anaesthesia.

AUTONOMIC EFFECTS

The blood adrenaline and noradrenaline concentrations were estimated as indices of sympathetic activity. It was found, however, that in the present series of experiments the noradrenaline level showed only slight and inconsistent variations as a result of the stimulation. This observation has been subsequently explained by Weil-Malherbe (1954), who has demonstrated that pentothal anaesthesia prevents the increase in noradrenaline which normally occurs after E.C.T. Accordingly, only the adrenaline results will be considered.

In the first three cases the effects of "high" and of "low" frequencies were measured in separate experiments. In the morning the patient was treated by stimulation at 200 p.p.s., and blood samples were taken before and after the induction of anaesthesia, 3 minutes after the onset of stimulation, and a minute after switching off. In the afternoon of the same day the procedure was repeated with stimulation at 500 p.p.s. but under otherwise identical conditions of anaesthesia, timing, and intensity. The results of these experiments are presented in Fig. 6. This shows that on each occasion the stimulation caused an

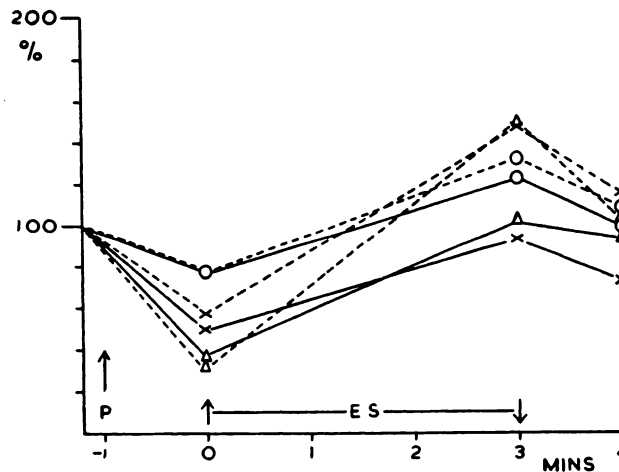


FIG. 6.—The effects of stimulation at 200 p.p.s. (solid lines) and at 500 p.p.s. (broken lines) on the blood adrenaline in 3 patients. Adrenaline concentrations are expressed as percentages of the initial levels. P denotes injection of pentothal.

increase in circulating adrenaline, which was more pronounced in response to the higher frequency in all three cases. The brisk initial fall in adrenaline following pentothal has been previously reported by Weil-Malherbe and Bone (1952a) and was a constant feature of the present experiments.

This method of comparing the effects of different electrical conditions appeared to be unnecessarily laborious; it seemed preferable to study them consecutively in one experiment. Three cases were therefore stimulated at 200 p.p.s. for 3 minutes and then at 500 p.p.s. for a further 3 minutes, blood samples being taken at the end of each period. The results are presented in Fig. 7, which shows, in each case, an increase in blood adrenaline in response to the lower frequency, followed by an additional, and almost equal, increase after the rise in frequency. These results, however, do not take into account the effect of the waning anaesthesia, nor the fact that a minimal period must elapse before the

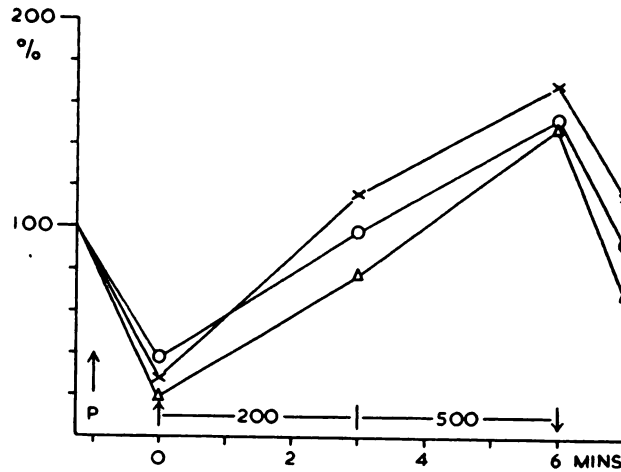


FIG. 7.—The effect of consecutive stimulation at 200 p.p.s. and at 500 p.p.s. on the blood adrenaline in 3 patients. Adrenaline concentrations are expressed as percentages of the initial levels. P denotes injection of pentothal.

adrenaline concentration reaches its new level. Both of these factors could contribute to a continued increase in adrenaline during the second part of the stimulation. To test the influence of these factors a third group of three subjects was investigated in the same manner as the second group, but the frequencies were applied in the reverse order. The results of these experiments are shown in Fig. 8. Here again it can be seen that the higher frequency produced

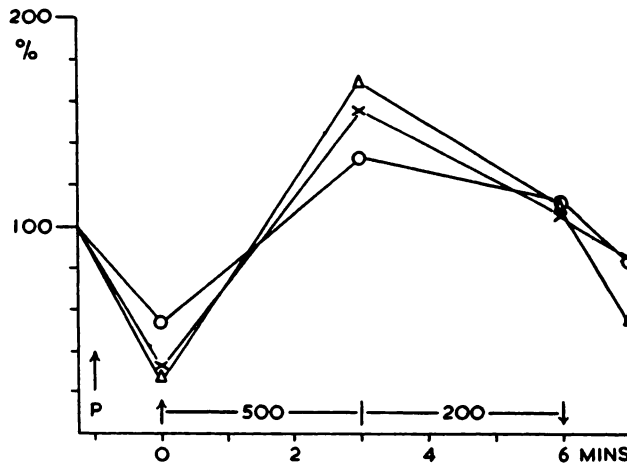


FIG. 8.—The effect of consecutive stimulation at 500 p.p.s. and at 200 p.p.s. on the blood adrenaline in 3 patients. Adrenaline concentrations are expressed as percentages of the initial levels. P denotes injection of pentothal.

the greater response, as evidenced by a fall in the blood adrenaline during the second half of each experiment.

The effects observed in the above nine cases are presented collectively in

Fig. 9.* In every instance stimulation at 500 p.p.s. caused a greater liberation of adrenaline than a repetition rate of 200 p.p.s., the peak and average currents remaining constant. To obtain further information concerning the nature of the adrenaline-frequency relationship six more experiments were performed with the inclusion of the intermediate steps of 300 and 400 p.p.s. In three cases all

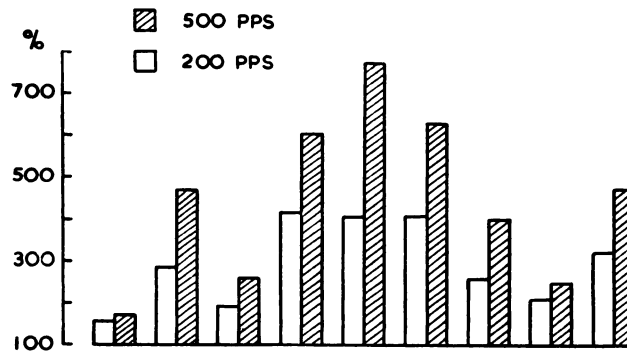


FIG. 9.—Block diagram comparing the effects of stimulation at 200 p.p.s. and at 500 p.p.s. on the blood adrenaline in 9 patients. The scale represents adrenaline concentration expressed as a percentage of the basal level after induction of anaesthesia.

four frequencies were used consecutively in different orders, blood samples being taken 1½–2 minutes after each change of frequency. In a fourth case the three higher frequencies were applied in descending order before the patient started to “object” to the current, and in the last two cases the two highest frequencies alone were used in reverse orders. The results of these experiments are demonstrated in Fig. 10.* This shows that, with one exception, each

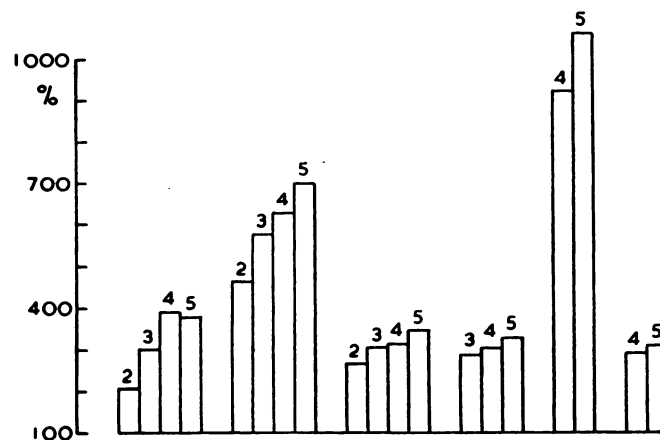


FIG. 10.—Block diagram comparing the effects of stimulation at various frequencies on the blood adrenaline in 6 patients. The figure above each column denotes the frequency in p.p.s. divided by 100. The scale represents adrenaline concentration expressed as a percentage of the basal level after induction of anaesthesia.

* In Figs. 9 and 10 the response to stimulation appears to vary greatly from case to case. This impression is deceptive. The adrenaline levels are expressed as percentages of the basal levels after induction of anaesthesia, so that the diagrams also reflect variations in response to the anaesthetic. In fact, the base lines ranged from 0.20 to 1.58 μg . adrenaline per litre, which largely accounts for the great differences in percentage increase.

successive rise in frequency caused an additional increase in circulating adrenaline and, conversely, that each reduction in frequency resulted in a fall. In the exceptional case (shown on the left in Fig. 10) there was a slight decrease in adrenaline when the frequency was raised from 400 p.p.s. to 500 p.p.s. The nature of the relationship between frequency and blood adrenaline is particularly well illustrated in one experiment of this series, which is reproduced graphically in Fig. 11.

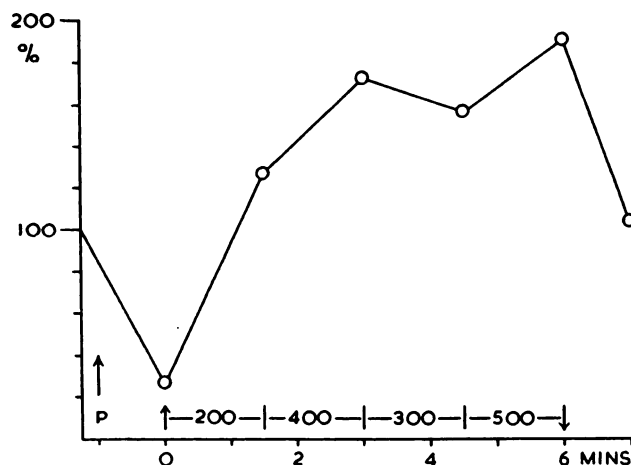


FIG. 11.—The effect of consecutive stimulation at four different frequencies (expressed in p.p.s.) on the blood adrenaline. Adrenaline concentrations are expressed as percentages of the initial level. P denotes injection of pentothal.

DISCUSSION

The results have shown that the sensory and motor effects diminished, while the sympathetic response increased, when the frequency of stimulation was raised from 200 to 500 p.p.s. at the expense of the pulse duration (peak and average currents constant). This observation conflicts with the impression of Hirschfeld and Bell (1951) that the autonomic nervous system responds better to lower frequencies with longer pulses.

There are two possible explanations for the present findings, namely:

(1) That the different frequency responses are due to intrinsic differences in the sensory, motor, and sympathetic systems.

(2) That at higher frequencies there is less spread of the current with its consequent localization to the inter-electrode line. Since the electrode placement has been chosen so that the inter-electrode line passes through the diencephalon (Hirschfeld, 1950), any restriction of the path of the current would intensify diencephalic stimulation and would reduce the effects on remoter structures.

The second of these postulated mechanisms can easily be put to the test by moving the electrodes to some indifferent area. If the assumption is correct and the current becomes more localized at the higher frequencies, there will be less stimulation of the diencephalon under these conditions, so that the blood adrenaline-frequency relationship will be the converse of that which has been

previously found. This test has, in fact, been done. Two subjects were re-investigated during consecutive stimulation at 200 and at 500 p.p.s. but with the electrodes placed high up on the frontal regions. The results are presented in Fig. 12, which shows that the adrenaline responses, although less pronounced,

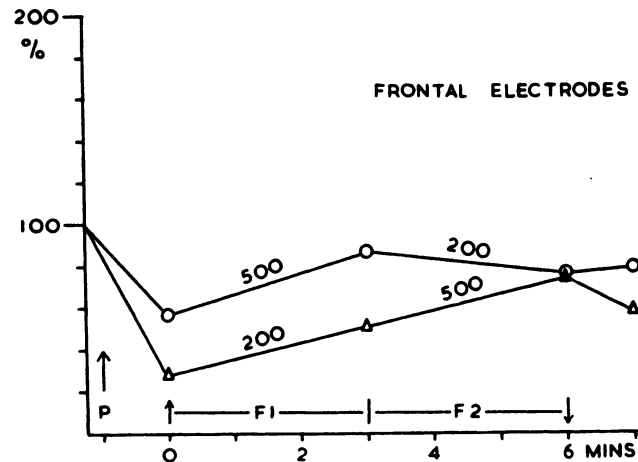


FIG. 12.—The effect of consecutive stimulation at different frequencies through high frontal electrodes on the blood adrenaline in 2 patients. The figures above the curves denote the frequencies F_1 and F_2 in p.p.s. P denotes injection of pentothal.

are qualitatively similar to those which were obtained with the normal electrode placement. There is, therefore, no evidence of any change in the distribution of the current under the different conditions of stimulation.

The explanation for the differential response to the higher frequencies is most likely to be found in the relative chronaxies and refractory periods of the different types of neurone, but little supporting evidence can be adduced from the present results. Although, for the sake of convenience, the electrical conditions have been expressed throughout in terms of the frequency, this term, in fact, has little meaning when applied to other than sinusoidal currents. It is merely an expression of the combined pulse duration and interval, which are the determining factors. As Liberson (1945) has emphasized, the pulse duration should be compatible with the chronaxie, and the interval with the refractory period, of the neurones. In the present experiments the pulse duration diminished from 400 μ sec. to 80 μ sec. as the frequency rose from 100 to 500 p.p.s. During this process the most noticeable change in the motor response occurred in the vicinity of 300 p.p.s., at which point the pulse duration was about 130 μ sec. It is interesting to note that this figure is of the same order as the chronaxie of the motor nerves (Best and Taylor, 1950), although the significance of the agreement is doubtful since the intensity of stimulation relative to the rheobase is unknown. The issue is further complicated by the effects of summation and facilitation. Of greater significance is the fact that the proximal muscles of the arms were the first, the distal muscles the last, to lose their tonus as the pulse duration diminished. This effect is in conformity with the observations of Wyss and Obrador (1937), who found that the chronaxie of the motor cortex for distal movements was less than that for proximal movements. The available evidence is therefore compatible with the suggested explanation of the results, but more definite conclusions cannot be drawn from the present

data. However, on the assumption that the explanation is correct, the differential response to the briefer pulses indicates that the sympathetic centres have a chronaxie that is considerably shorter than those of the sensory and motor structures.

The increasing sympathetic response at higher frequencies of stimulation showed no signs of reaching a peak in the present experiments, except in one case. An attempt was made to boost the speed of the motor by raising the input voltage, and in this way the output frequency was increased to nearly 1,000 p.p.s. However, it was considered that the motor was unlikely to stand up to such high speeds for long, and so the attempt to extend the frequency range was abandoned. This was not the only limitation of the present apparatus. As mentioned earlier, it was not anyway subject to great constancy in respect of the frequency. Furthermore, the pulse/interval ratio was invariable, so that the results obtained are applicable to only one particular set of conditions. In consequence, although the present experiments have demonstrated a differential response, it has not been possible to measure the full extent of this phenomenon nor to determine the optimal conditions for sympathetic stimulation. A more versatile apparatus is required for these studies.

SUMMARY

The motor, sensory, and sympathetic effects of sub-convulsive electrotherapy have been studied in relation to different frequencies of stimulation. The blood adrenaline and nor-adrenaline concentrations were used as indices of sympathetic activity. Electrostimulation was performed under pentothal anaesthesia.

The current consisted of brief, unidirectional, rectangular impulses, which were produced by means of a commutator-interrupter. The pulse/interval ratio was constant, so that any change in frequency was accompanied by an inversely proportional change in both pulse duration and interval. Hence, at any given peak current the average output remained the same at all frequencies. The frequency was continuously variable from 100 to 500 pulses per second, corresponding to a pulse duration of 400 to 80 microseconds respectively. The electrodes were applied bitemporally just above each ear.

The results were as follows:

- (1) The motor, sensory, and respiratory effects of the current diminished progressively as the frequency was raised.
- (2) The output of adrenaline increased progressively as the frequency was raised.
- (3) The circulating noradrenaline showed only slight and inconsistent variations. It is believed that the pentothal prevented the changes which otherwise would probably have occurred.

It was considered that these effects might be caused by an increased localization of the current at the higher frequencies. However, this possibility was eliminated by moving the electrodes to an indifferent area away from the diencephalon, when the adrenaline-frequency response was found to remain qualitatively unchanged. It was concluded that the effects were probably due to differences in chronaxie and refractory period in the different types of neurone.

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REFERENCES

- ALEXANDER, L., *Amer. J. Psychiat.*, 1950, **107**, 241.
Idem, *Treatment of Mental Disorder*, 1953. Philadelphia and London: Saunders.
 BERKWITZ, N. J., *Arch. Neurol. Psychiat.*, Chicago, 1940, **44**, 760.
Idem, *Dis. nerv. Syst.*, 1952, **13**, 323.
 BEST, C. H., and TAYLOR, N. M., *The Physiological Basis of Medical Practice*, 1950, p. 905.
 5th ed. London: Baillière, Tindall & Cox.

- COSSA, P., MARTIN, P., and LOMBARD, A., *Ann. méd.-psychol.*, 1948, **106**, i, 612.
HIRSCHFELD, G. R., *Psychiat. Quart. Suppl.*, 1950, **24**, 297.
Idem and BELL, J., *Dis. nerv. Syst.*, 1951, **12**, 264.
LEDUC, S., *Arch. Élect. méd.*, 1903, **11**, 521.
LIBERSON, W. T., *Yale J. Biol. Med.*, 1945, **17**, 571.
MONTAGU, J. D., *J. Ment. Sci.*, 1953, **99**, 112.
RIBOLI, B., and MANCINI, E., *Note Psichiat.*, Pesaro, 1948, **74**, 175.
ROBIE, T. R., *J. med. Soc. N. J.*, 1950, **47**, 370.
WEIL-MALHERBE, H., 1954. Unpublished data.
Idem and BONE, A. D., *Biochem. J.*, 1952a, **51**, 311.
Idem, *J. ment. Sci.*, 1952b, **98**, 565.
Idem, *Lancet*, 1953, *i*, 974.
WYSS, O. A. M., and OBRADOR, A., *Amer. J. Physiol.*, 1937, **120**, 42.