ELECTRICAL TERMINATION OF HYPOGLYCAEMIC COMA.

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PROLONGED cerebral electrostimulation of subconvulsive intensity has been employed as an experimental procedure at this hospital during the past year, and the indications for this technique in the treatment of mental disorders are being investigated. Preliminary tests in conjunction with Dr. H. Weil-Malherbe showed that electrostimulation, when applied to normoglycaemic patients under pentothal anaesthesia, caused a pronounced increase in the concentration of adrenaline-like substances in the blood during the passage of the current. The same current was therefore applied to a series of patients in hypoglycaemic coma to determine whether the effects obtained after injection of glutamic acid—and considered by Weil-Malherbe (1949) to be adrenergic in origin—could also be obtained after electrostimulation. The results of these investigations are presented in this report. The stimulating current employed for this purpose was of the " square wave " (interrupted galvanic) type, which was first applied as a cerebral stimulus by Leduc (1902) in his pioneer demonstration of electrical anaesthesia and sleep. More recently Liberson (1945) has investigated this type of current in relation to E.C.T., subsequently utilizing it in his Brief Stimulus Technique (Liberson, 1947, 1948). This latter technique is also under investigation here at the present time, the same stimulator being used for both convulsive and sub-convulsive therapies ; the results obtained with the Brief Stimulus convulsive therapy will be presented in a later report.

THE ELECTROTECHNIQUES.

Since the presentation by Hirschfeld in 1949 of his preliminary report on " Non-Convulsive Electro-Stimulation " a wide variety of important claims have been made for this procedure. Hirschfeld's technique (1949, 1950) employs a unidirectional, pulsed current of low intensity, which is applied to the head by means of small electrodes placed bitemporally about one inch above each ear. By this means he believes that he is producing a selective stimulation of the diencephalic area. For his earlier investigations Hirschfeld utilized the complex modulated current developed by Reiter (cit. Wilcox, 1948), the level of average current employed being about 5 mA for two to five minutes of stimulation time, and he reported good results with this technique in a variety of mental disorders. Since then much work has been done in America on the applications of this procedure using this type of current. More recently Hirschfeld and Bell (1951) have claimed satisfactory results using rectangular impulses of the type employed by Liberson (1947) in his Brief Stimulus Technique of E.C.T. These two types of current differ from the standard mains a.c., which is used in the " classical " Cerletti-Bini electroplexy, in that they are composed of brief, unidirectional spikes or waves, such that the total quantity of current required to produce a response is many times less. This physiological efficiency is achieved on the one hand by using pulses of duration approximately equal to the chronaxie of the cortical motor neurones and with intervals compatible with their refractory period (Liberson's technique) ; on the other hand the impulses are modulated both in frequency and in amplitude in order to obtain a greater summation of response (Reiter's technique).

Prior to these reports Riboli and Mancini (1948) investigated the neuro-vegetative effects of cerebral stimulation by means of standard alternating current of low voltage ; they noted that the resulting blood-sugar curve was similar to that following electroshock. Applying this type of stimulus to patients in hypoglycaemic coma, Riboli (1948, 1950) reported that currents of the order of 30–80 mA given for five to fifteen minutes decreased the depth of coma and frequently aroused the patients, and he presented much evidence that a rise in the blood-sugar level was the principal factor concerned. He also, however, postulated the existence of some other complementary hypothalamic mechanism in order to explain his success in those cases of prolonged coma which had failed to awaken despite administration of glucose to

the point of hyperglycaemia, but which returned rapidly to a state of consciousness following electrostimulation. More recently Hoffman and Wunsch (1950) reported similar experiments using Hirschfeld's technique with a Reiter electrostimulator, and employing a current level of the order of 3 to 4 mA of average current applied for a set time of five minutes. In their series of twelve investigations these workers reported no change in the depth of coma in only one instance ; on four occasions the patient aroused completely, and on the remaining seven occasions the coma was superseded by a state of semi-consciousness. They found no uniform correlation between the clinical response of the patient and the change in the blood-sugar level, and they concluded that diencephalic stimulation alone was the primary factor responsible, regardless of any secondary effect on the hypoglycaemia. As an extreme example they reported that one of their cases was fully aroused and talking rationally with a blood-sugar concentration as low as 7 mgm. per cent.

Apparatus.

The stimulator employed in these investigations was constructed by the writer, and was designed to give a constant current output similar to that used by Liberson (1947), i.e., unidirectional, rectangular pulses of brief duration. The pulse duration is variable between 300 microseconds and 2 milliseconds, and a choice of two frequencies is available, namely 50 and 100 p.p.s., by using either half-wave or full-wave rectification of the a.c. mains on the pulse-forming circuit. As a standard practice the higher repetition rate is used, since Liberson (1945) has demonstrated that this is nearer the optimal frequency for cerebral excitation. Similarly, for subconvulsive application the shortest available pulse duration of 300 microseconds is currently employed by the author, since this entails the minimal expenditure of current quantity. These conditions fix the pulse interval at 9·7 milliseconds and give a mark : space ratio of 1 : 32. In theory, therefore, when the average current flowing is equivalent to 1 mA of continuous d.c., the pulse peak current will be 32 mA. In actual fact oscillographic calibration determined that under the above conditions of frequency and pulse duration the ratio of the peak current to the average current as indicated by a milliammeter in the output circuit was 35 : 1. The discrepancy between this figure and the value calculated theoretically is due to a combination of errors from the following sources :-

(i) Imperfections in the wave form : The theoretical value is calculated on the assumption that the impulses are pure rectangles and does not take into account their times of rise and decay, whereas the oscillographic analysis of the wave form determined that, although the increment was in fact negligible for pulses of all durations the decrement was of the order of 30 microseconds for a pulse duration of 300 microseconds.

(ii) Variations in the frequency of alternation of the mains, upon which the repetition rate depends.

(iii) A d.c. milliammeter in the output circuit may not give an exact measure of the continuous d.c. equivalent of a pulsed current. It was determined, however, that this index was valid as a relative measure of intensity, i.e., doubling the peak current did in fact double the average value indicated. In this manner a straight-line representation of this relationship was plotted for each value of the pulse duration at each frequency.

In the subsequent text and in the tables the current level will be indicated by the average value as measured with a d.c. milliammeter, unless the pulse peak is specifically stated.

The same apparatus is also equipped with glissando and timing devices to enable it to cover the whole range of the stimulatory therapies, convulsive, subconvulsive and combined. These details, however, are irrelevant to the present purpose. In the preliminary trials of the subconvulsive technique circular stainless steel electrodes 2 cm. in diameter were used, but it soon became apparent that either prolonged or frequently repeated applications of the current gave rise to burning of the underlying skin. Subsequently larger electrodes 3 cm. in diameter, also of stainless steel, have been employed and no further complication of this type has been encountered.

Methods.

The subjects of this investigation were fourteen schizophrenic patients selected at random from those receiving insulin-coma therapy. Six of these were male and

eight were female, with ages ranging from 20 to 49 years. In addition clinical results alone obtained in three other female patients are also reported. The insulin was given intramuscularly and the dosage was individually adjusted to produce hypoglycaemic coma three to four hours after the injection; it varied from 42 to 208 units. In judging the presence of coma the criteria given by Küppers and quoted by Sargant and Slater (1948) were employed, i.e., the loss of all purposive responses to auditory, visual and painful stimuli. The patients were allowed to remain in coma for at least twenty minutes before stimulation was commenced. The stimulating current was applied bitemporally through electrodes of 3 cm. diameter placed one inch above each ear, and with two exceptions the stimulation was maintained for an arbitrary period of five minutes; on the other two occasions this period was extended to ten minutes. A repetition rate of 100 pulses per second with a pulse duration of 300 microseconds was employed in every case. A gag or rubber airway was inserted between the teeth to prevent possible injury to the tongue by the trismus induced by the current. In the first few investigations the current was increased gradually at the onset until the tonic muscular contractions induced began noticeably to impede the respiratory movements and was then adjusted to allow freedom of respirations. This level was most frequently found to occur when the average current flowing was as low as 1 d.c. milliampere, equivalent to a peak current of 35 mA. Subsequently, when it appeared desirable to use higher currents, it was found necessary to modify the technique by raising the initial intensity more rapidly to about 4 mA and then reducing it after fifteen seconds to the required level. This almost invariably produced a total cessation of respirations during the initial induction, but, on reducing the current, respirations were resumed at a greater intensity of stimulation by this method than could be attained with the former technique. During the period of stimulation there were generalized tonic contractions, sometimes moderate restlessness, and the respirations, when resumed, were shallow but forceful, noisy and greatly increased in rate. With continued stimulation, however, there was a tendency for the motor response to diminish and the respirations to become more peaceful, and, when the current was discontinued, even those patients who remained in coma appeared more flaccid, relaxed and quiet. Those who returned to consciousness did so rapidly, and usually without passing through the transition stage of noise and restlessness which characteristically follows a nasal feed.

A patient was considered to have aroused from coma if he responded purposively when spoken to, for example, by opening his eyes or by a turning of the head in the direction of the voice. In actual fact this response was usually verbal and was often a rational and coherent reply. Nevertheless, it frequently occurred that a patient, although apparently fully conscious, was still unable to drink. These cases invariably returned rapidly to a state of coma. On this basis the clinical responses to electrostimulation have been divided into three categories according to the degree of return of the patient to consciousness during the subsequent fifteen minutes. The three categories are defined as follows:-

1. Complete response: The patient aroused sufficiently to drink from a cup enough glucose to remain awake. Denoted by + in the table of results.

2. Partial response: The patient responded to questions but was not able to drink sufficiently to prevent a return to coma. Denoted by (+) in the table.

3. Remained in coma: No purposive response to auditory, visual or painful stimuli for fifteen minutes after the current was switched off. At the end of this period these cases were roused by tube-feed in the usual manner. Denoted by — in the table.

For each investigation five specimens of capillary blood were obtained from the lobe of the ear and blood-sugar estimations were carried out on these by Nelson's method. The specimens were taken at the following intervals: Ten minutes and again immediately before the onset of stimulation, then immediately after, five minutes after, and finally ten minutes after switching off the current. In a few experiments a specimen was taken during the period of stimulation, about three minutes after the onset, and on these occasions the sample normally taken five minutes after stimulation was generally omitted. In cases that aroused sufficiently to drink glucose the last blood sample was omitted if more than five minutes had elapsed since the patient started to drink. Without this precaution false results might easily have been obtained.

The possibility was considered that positive results obtained by the electrostimulation might be due, not to any direct action of the current on the brain centres, but indirectly through the stimulation of pain receptors in the skin and subcutaneous tissues, even though the patient is not conscious of the pain. Control tests, designed to minimize the passage of the current through the brain, were therefore carried out on the same patients on different days by placing both electrodes on the same side of the head, and repeating the investigations under otherwise identical conditions of current intensity and duration. In this manner the localization of the stimulus, i.e., the skin sensitivity, was adequately controlled; on the other hand, the possibility that a not inconsiderable proportion of the current did in fact penetrate the cranium cannot be eliminated. Because of this, little import can be attached to any similarity of result in the two series; on the other hand, any significant difference between the two will indicate a central action of the current in the test experiments. The two sets of conditions adopted will be defined for future reference as follows:

(*a*) Transcerebral stimulation (test series), using bitemporal electrodes one inch above each ear. Denoted by a " B " in the tables.

(*b*) Unilateral stimulation (control series), by applying both electrodes one inch apart to the same temporal region. Denoted by a " U " in the tables.

Results.

In a preliminary series of patients specimens of venous blood were withdrawn at various intervals before, during and after electrostimulation, and estimations of the blood-sugar content and of the concentration of the catechol amines (combined adrenaline and noradrenaline) were carried out. The latter estimations were performed by a method developed in this hospital by Weil-Malherbe and Bone (1952) and the results have been reported by them. In the same communication these authors also reported that owing to an error of technique the blood-sugar estimations performed on these specimens subsequently proved to be unreliable. This series, therefore, will not be included here except to mention that there were two cases of complete response, six cases of partial response, and that on a further six occasions the patients remained in coma. The current levels used in this series were in general low, the majority of patients receiving 1 mA for five minutes.

A second series of patients was subsequently investigated and the clinical and biochemical results obtained in this group are shown in Cases 1–14 in Table I, in which each patient is represented by a number and each investigation by the following letter. Cases 15–17 were the only three patients in the preliminary series to receive the control tests and the clinical results only are therefore included. The results reported in Table I will be analysed from three different aspects: firstly, the clinical effects alone; secondly, a comparison of the test with the control series on the basis of the blood-sugar curves; and thirdly, the correlation of the clinical effects with the biochemical changes.

Clinical Effects.

The clinical results of forty-four investigations are reported in Table I, and these may be subdivided according to the degree of clinical response as follows:

	Transcerebral stimulation. (Number of cases.)	Unilateral stimulation. (Number of cases.)
Complete response	8	3
Partial response	9	3
Remained in coma	8	13

It can be seen immediately that when transcerebral stimulation was employed approximately one-third of the responses occurred in each category. The current level varied in these investigations between 1 and 4 mA, which was maintained for an arbitrary period of five minutes on all except two occasions (Cases 2c and 3b) when the time was doubled. So it would not be unreasonable to suppose that the positive results occurred in response to the higher intensities of stimulation and vice versa. To take these varied conditions into account the clinical effects have been further subdivided on the basis of the current levels used, and for each category of response the mean quantity of current applied has been calculated. This is shown

in Table II, from which it can be noted that those who did not respond to transcerebral stimulation did in fact receive a greater average quantity of current than those who aroused.

The numbers in each category are small, especially in the control series, but it would appear from this that the clinical effects obtained were not solely a function of the current quantity administered. With regard to the unilateral method of

TABLE I.—*Effects of Cerebral Electrostimulation during Hypoglycaemic Coma.*

Case.	Age and sex.	Duration of coma (mins.).	Current (mA).	Duration of stimulation (mins.).	Electrode position.	Blood sugar (mgm. per cent). 10 minutes before stim.	Immediately before stim.	During stim. (3 mins.).	Immediately after stim.	5 minutes after stim.	10 minutes after stim.	Clinical result.
1a	30 M.	40	3	5	B	13	11	9	..	14	9	−
1b		45	3	5	B	12	15	..	31	38	..	+
1c		45	3	5	U	1	6	..	7	18	..	+
2a	31 M.	45	1½	5	B	5	6	..	19	21	7	−
2b		45	1½	5	U	6	7	..	11	15	7	−
2c		35	1½	10	B	10	9	18	22	17	14	(+)
3a	49 M.	30	3	5	B	20	19	..	25	29	27	−
3b		30	4	10	B	18	19	..	27	26	21	−
4a	23 M.	30	3	5	B	11	10	..	29	52	..	+
4b		35	3	5	U	17	21	..	45	39	30	(+)
5a	31 M.	40	2½	5	B	5	6	..	22	25	..	+
5b		35	2½	5	U	5	6	..	9	19	18	(+)
6a	26 M.	40	3	5	B	11	10	..	15	26	25	(+)
6b		35	3	5	U	20	21	..	34	27	25	(+)
7a	20 F.	30	2	5	B	8	10	..	27	42	..	+
7b		35	2	5	B	7	7	5	13	..	18	(+)
7c		35	2	5	U	6	6	8	5	..	6	−
8a	37 F.	40	2	5	B	18	18	..	25	29	..	+
8b		50	2½	5	B	5	4	7	24	..	19	+
8c		40	2½	5	U	7	7	7	9	..	8	−
9a	31 F.	30	2½	5	B	12	13	..	21	25	20	−
9b		45	2½	5	U	10	11	..	18	16	13	−
9c		30	2½	5	B	8	10	..	14	18	16	−
9d		50	2½	5	U	6	8	..	8	8	7	−
10a	38 F.	50	2½	5	B	1	2	..	19	24	11	−
10b		45	2½	5	U	6	5	..	8	13	8	−
10c		35	3	5	B	2	3	..	12	20	13	(+)
10d		40	3	5	U	10	11	..	15	15	11	−
11a	42 F.	30	2	5	B	18	20	..	31	..	..	+
11b		30	2	5	U	18	20	..	26	..	..	+
11c		25	2	5	B	11	13	..	24	33	24	(+)
11d		30	2	5	U	5	5	..	17	14	11	−
12a	30 F.	25	3	5	B	7	5	..	18	25	15	−
12b		30	3	5	U	9	10	..	19	20	9	−
13a	30 F.	25	2½	5	B	12	13	..	27	32	28	(+)
13b		30	2½	5	U	27	29	..	37	39	36	+
14a	22 F.	20	2½	5	B	5	6	..	19	40	36	(+)
14b		25	2½	5	U	8	9	..	16	23	13	−
15a	34 F.	60	1	5	B	..	..	..	..	..	..	(+)
15b		30	1	5	U	..	..	..	..	..	..	−
16a	37 F.	30	2	5	B	..	..	..	..	..	..	(+)
16b		45	2	5	U	..	..	..	..	..	..	−
17a	46 F.	35	1	5	B	..	..	..	..	..	..	+
17b		35	1	5	U	..	..	..	..	..	..	−

B = Bitemporal electrodes.
U = Unilateral electrodes.

\+ = Aroused completely.
(+) = Coma terminated temporarily.
− = Remained in coma.

https://doi.org/10.1192/bjp.99.414.112 Published online by Cambridge University Press

TABLE II.—*Distribution of Clinical Results in Relation to Current Level.*

Current.	Transcerebral stimulation. Complete response.	Partial response.	Remained in coma.	Unilateral stimulation. Complete response.	Partial response.	Remained in coma.
4 mA	0	0	1*	0	0	0
3 mA	2	2	3	1	2	2
2½ mA	2	2	3	1	1	5
2 mA	3	3	0	1	0	3
1½ mA	0	1*	1	0	0	1
1 mA	1	1	0	0	0	2
	8	9	8	3	3	13
Mean quantity mA (mins.)	11·25	11·67	16·25	12·50	14·17	10·77

* Stimulation maintained for ten minutes.

stimulation it has already been admitted that this is not a perfect form of control, since a proportion of the current must inevitably penetrate the cranium. This is one possible explanation for the three instances (16 per cent.) of complete response and the further three partial responses obtained in this series. However, it is clearly not possible to draw an accurate comparison between the test and the control experiments on the basis of the clinical responses alone, since this does not take into account differences in the depth of coma at the time of commencement of stimulation.

The effect of electrostimulation on the depth of coma was both rapid and transient and this is well shown by the following clinical observations: In a total of twenty-three positive results (complete and partial) the longest interval between the discontinuation of the current and the appearance of a purposive response was six minutes. On four occasions the patient responded verbally immediately after the current was switched off, and on the remaining eighteen occasions this interval varied between one and five minutes, the majority responding towards the latter end of this period. Furthermore, in every case of partial response the subject was showing signs of a deepening sopor within approximately ten minutes of the cessation of stimulation. These results are very similar to those reported to follow the intravenous injection of glutamic acid (Mayer-Gross and Walker, 1947; Weil-Malherbe, 1949) and of adrenaline (Weil-Malherbe, 1949).

Glycaemic Effects.

Table I shows that in every investigation except one (Case 1a) of the test series there was a substantial increase in the blood-sugar concentration after transcerebral stimulation. The smallest overall rise in these investigations was an increase of 8 mgm. per cent. above the mean initial level (Case 3b), while the greatest was 41 mgm. per cent. (Case 4a), the average rise for the whole series (including Case 1a) being 17·5 mgm. per cent., standard error 2·0. In the one exception reported in Case 1a this increase did not take place and the concentration remained unchanged. The probable explanation for this will be discussed later. The blood-sugar curves in the control series show a similar variability of response, the increase after unilateral stimulation ranging from virtually none in Cases 7c, 8c and 9d to the substantial rise of 26 mgm. per cent. above the mean initial level encountered in Case 4b, the average for this series being 9·4 mgm. per cent., standard error 1·6. A statistical test was therefore applied to the two series of values to determine the significance of these differences.

Now for every control investigation performed a test investigation had also been carried out on the same patient under identical conditions of stimulation and blood-sugar analysis. In order to take this pairing of values into account the few random investigations were omitted from the test of statistical significance. The analytical results then represent sixteen pairs of blood-sugar curves, in each pair of which both members were performed under these similar conditions. In three cases (9, 10, 11) two pairs of curves were contributed by each individual, while the other ten pairs were each contributed by a different individual. The test of significance was then based on the variance of the differences in the increases of blood-sugar concentration in each pair of results. The sixteen pairs of analytical results are reproduced in

TABLE III.—*Glycaemic Effects of Transcerebral and Unilateral Electrostimulation during Hypoglycaemia.*

Case.	Electrode position.	Blood sugar (mgm. per cent.). Mean before stimulation.	Maximum after stimulation.	Increase x_1 and x_2.	Difference $x_1 - x_2$.
1b	B	14	38	24	10
1c	U	4	18	14	
2a	B	6	21	15	7
2b	U	7	15	8	
4a	B	11	52	41	15
4b	U	19	45	26	
5a	B	6	25	19	6
5b	U	6	19	13	
6a	B	11	26	15	2
6b	U	21	34	13	
7b	B	7	18	11	9
7c	U	6	8	2	
8b	B	5	24	19	17
8c	U	7	9	2	
9a	B	13	25	12	5
9b	U	11	18	7	
9c	B	9	18	9	8
9d	U	7	8	1	
10a	B	2	24	22	15
10b	U	6	13	7	
10c	B	3	20	17	13
10d	U	11	15	4	
11a	B	19	31	12	5
11b	U	19	26	7	
11c	B	12	33	21	9
11d	U	5	17	12	
12a	B	6	25	19	9
12b	U	10	20	10	
13a	B	13	32	19	8
13b	U	28	39	11	
14a	B	6	40	34	20
14b	U	9	23	14	

B = Bitemporal electrodes. U = Unilateral electrodes.

Table III, which records only the mean initial values of the blood-sugar levels before stimulation and the highest concentration attained after it. From these figures the increases (x_1 and x_2) have been calculated and hence the differences of increase ($x_1 - x_2$) for each pair. The absence of minus signs in this last column shows immediately that in every pair transcerebral stimulation (x_1) resulted in a greater rise than unilateral stimulation (x_2), and by applying the test to these figures it is shown that these differences are highly significant ($t = 8{\cdot}08$; $P < 0{\cdot}01$). This implies that stimulation of pain receptors in the skin and subcutaneous tissues is not the only mechanism responsible for the blood-sugar rise following transcerebral stimulation, although it cannot be eliminated as a contributory cause. The greater effect of the transcerebral as opposed to the unilateral stimulus must be due to a direct central action of the current in the former case.

Correlation of Clinical with Glycaemic Effects.

Adding together for the moment all the positive clinical responses, complete and partial, we then have two broad groups of cases, viz., those that remained in coma and those that did not. By comparing these two groups on the basis of the highest blood-sugar values obtained on each occasion during or after stimulation by either method, the results may be presented as follows :

Highest value of blood sugar (mgm. per cent.).	Coma terminated. (Number of cases.)	Remained in coma. (Number of cases.)
17 and below	0	8
18 to 29 inc.	10	10
30 and above	10	0

https://doi.org/10.1192/bjp.99.414.112 Published online by Cambridge University Press

It is seen that (*a*) when the blood-sugar concentration rose above 18 mgm. per cent. termination of the coma resulted on twenty out of thirty occasions, and (*b*) on no occasion did the coma persist if the blood sugar rose to 30 mgm. per cent. or above. According to the criteria of coma which were adopted—and which have been defined in the description of the methods employed—this does not necessarily imply a return to full consciousness, and it has previously been remarked that many of these cases were still unable to drink and that a few were not even able to respond verbally. Therefore, to determine if any similar relationship existed between the blood-sugar level and the later stages of recovery, as evidenced by an ability to drink, the complete and the partial positive responses were now compared on the basis of the highest blood-sugar values obtained on each occasion. It was then found that there was no significant difference between the two series, but that the blood-sugar values were similarly distributed for both degrees of clinical response. This implies that the return of consciousness at the higher levels is a more individual process than the termination of the state of coma as defined here.

To demonstrate the rate of change of the blood-sugar concentration following electrostimulation the means of each of the vertical columns of blood-sugar values shown in Table I have been calculated for both the test and the control investigations separately. The results then represent the mean blood-sugar curves obtained in each group and these are shown in Table IV. This demonstrates :

TABLE IV.—*Mean Blood-sugar Concentrations in Test and Control Investigations.*

	Blood sugar (mgm. per cent.).				
	10 mins. before.	Immed. before.	Immed. after.	5 min. after.	10 min. after.
Transcerebral stimulation :					
Mean . . .	9·95	10·41	22·10	28·21	18·93
Standard error .	1·13	1·15	1·24	2·19	1·93
Unilateral stimulation :					
Mean . . .	10·07	11·38	17·75	20·46	14·43
Standard error .	1·72	1·82	2·98	2·63	2·52

(*a*) The rapidity of the increase in the blood-sugar concentration. In both groups the rate of rise was at a maximum during or immediately after the passage of the current.

(*b*) The transience of the blood-sugar rise, which attained its peak about five minutes after the end of the stimulation and then declined rapidly in the ensuing five minutes.

(*c*) The magnitude of the rise. Transcerebral stimulation approximately trebled the blood-sugar concentration and unilateral stimulation doubled it.

These changes, therefore, appear to parallel closely the clinical course of events as already described, viz., the abrupt termination of the coma within six minutes after switching off the current, the brief period of consciousness or sopor, and finally, if glucose is not administered, the rapid return to coma ten to fifteen minutes after the end of the stimulation.

DISCUSSION.

The results have shown that transcerebral electrostimulation during hypoglycaemic coma causes a rapid and transient rise of the blood-sugar level, and that this is closely correlated with the clinical effect. These observations are in agreement with the facts reported by Riboli (1950), but conflict with the conclusions of Hoffman and Wunsch (1950), who found no such correlation. It has also been shown that the increase in the blood-sugar level is the result, predominantly at any rate, of a direct action of the current on the brain centres, since there is a highly significant difference when this central action is largely eliminated by unilateral application of the electrodes. These results are paralleled closely by those of Weil-Malherbe and Bone (1952), who reported that transcerebral stimulation by the author's method also causes a sharp rise in the concentration of the circulating catechol amines (combined adrenaline and noradrenaline), and that this is also correlated with the clinical response. The latter investigations were performed at this hospital using the technique of electrostimulation that is reported here, and on four occasions the two sets of

estimations were carried out simultaneously on the same patients (Cases 7b, 7c, 8b, 8c). The brisk increase of blood adrenaline was found by these investigators to reach its peak during the passage of the current and to fall immediately afterwards. It therefore precedes by a few minutes the hyperglycaemic response reported here.. Weil-Malherbe and Bone also observed that the five applications of unilateral stimulation investigated by them did not result in any change in the blood-adrenaline level. These five control tests are also included in Table I of this paper, the clinical results only being recorded in three cases (15b, 16b, 17b), while in the other two cases (7c, 8c) the blood-sugar values are also given. It is interesting to note that on the latter occasions there was also no change in the blood-sugar level, while on all five occasions the patient remained in coma. The intercorrelation between blood adrenaline, blood sugar and clinical effect in response to electrostimulation is therefore good.

So far there is no reason to doubt that the glycaemic response is adrenergic in origin; nor is there any necessity to postulate the existence of a secondary mechanism, other than glycaemic, to account for the clinical effects. If this exists it must manifest itself in a quantitative, not a qualitative, discrepancy. It has been seen that in the present investigations a blood-sugar concentration of 18 mgm. per cent. was the absolute base line and 30 mgm. per cent. the maximal base line for the termination of coma. No case aroused below the former level, but 100 per cent. of positive responses occurred above the latter, but here the evidence is less conclusive, for the interpretation depends entirely upon appreciation of the level at which termination of the coma would occur in the absence of electrostimulation but with an identical rate of increase of the blood-sugar level, a point on which agreement has not yet been reached. On the one hand, Mayer-Gross and Walker (1945) reported experiments indicating that a blood-sugar concentration above 30 mgm. per cent. was necessary before sufficient glucose was available to the cortical cells for the restoration of consciousness. Accordingly, when after intravenous injection of glutamic acid consciousness was restored below 30 mgm. per cent. of blood sugar, a complementary mechanism was postulated by them (Mayer-Gross and Walker, 1947). On the other hand, Weil-Malherbe (1949), reporting similar results, concluded and has since confirmed (Weil-Malherbe and Bone, 1952) that the mechanism is adrenergic. He was also able by intravenous injection of adrenaline to duplicate in every respect the clinical and glycaemic effects of glutamic acid. Since electrostimulation has similar effects to glutamic acid and has also been shown to mobilize an adrenergic mechanism, the same conclusions are applicable.

The conclusion of Weil-Malherbe that an adrenergic mechanism is responsible for the decreased depth of coma following injection of glutamic acid is regarded by Hoffman and Wunsch (1950) as supporting " the relative unimportance of the blood-sugar level " which they found after electrostimulation. It is probable, as Weil-Malherbe (1949) in fact pointed out, that the adrenaline, when liberated, may also operate through auxiliary mechanisms which enhance the effect of the blood-sugar rise, but it was not suggested that the latter was unimportant, and it is improbable that the two can be dissociated. It is difficult, therefore, to understand how electrostimulation could terminate hypoglycaemic coma without producing a significant increase in the blood-sugar concentration, since the absence of such a rise is indicative that the current did in fact not penetrate the cranium. It may also be mentioned *en passant* that the absence of any significant rise in the blood-sugar curves of two patients who received pentothal and electrostimulation only, which Hoffman and Wunsch (1950) record as controls, is not surprising, since Piette (1950) has shown that previous administration of pentothal prevents the hyperglycaemic response which otherwise occurs following E.C.T.

Riboli (1948) was forced to postulate the existence of a complementary mechanism in order to explain his clinical successes in certain cases of prolonged coma. These had previously failed to arouse despite intravenous administration of glucose to the point of hyperglycaemia and injection of adrenaline, strychnine and vitamin B_1, but they returned rapidly to a state of consciousness following a short period (3–10 minutes) of electrostimulation. The writer can neither confirm nor deny this, since his experience is limited to only one such case. The patient in question failed to arouse completely after her tube-feed, but remained in a state of light coma. She received an intravenous injection of glucose and injections of vitamin B complex and of adrenaline, but without effect. Fifteen minutes later her blood-sugar concentration was estimated and was found to be 324 mgm. per cent. Electrostimulation

was then commenced, two-and-a-half hours after the onset of coma, and was maintained at an intensity ranging from 2 to 4 mA for a total period of nine minutes during the ensuing twenty minutes (2 + 2 + 5 minutes), but this also failed to rouse the patient. Half-an-hour later she received a further intravenous injection of glucose, after which she slowly returned to consciousness, but she remained confused for the rest of the day. This one case, therefore, does not confirm the findings of Riboli (1948, 1950) on similar occasions; others, however, may do so and no opinion on this point can be expressed at present.

One final point demanding explanation is the exceptional result reported in Case 1a of Table I. This was the only occasion on which transcerebral stimulation failed to cause an appreciable rise in the blood-sugar level, and the concentration on this occasion remained unchanged. This raises an issue which concerns every form of electrical stimulation of the brain through the intact coverings, and particularly to patients during insulin coma, namely that the amount of current actually flowing through the brain is always an unknown quantity, since the majority of the applied current passes through the low-resistance extracranial shunt network composed of the skin and subcutaneous tissues. This by-pass has been variously measured in animals and cadavers and estimated in man at between 85 and 99 per cent. of the total applied current (Fleming *et al.*, 1939; Golla *et al.*, 1940; Smitt and Wegener, 1944; Bollea and Manfredi, 1947; Hayes, 1950). With the degree of sweating which occurs in hypoglycaemic coma this by-pass may become an even greater and more variable quantity by the further addition of an extracutaneous conductor. This appears to be the only probable explanation for the results obtained in Case 1a, and confirmation might have been obtained by measurement of the interelectrode impedance. This, however, was not recorded and the matter must remain in doubt. In subsequent investigations the patient's head was first well towelled and similar results did not occur.

Summary.

1. Cerebral electrostimulation of subconvulsive intensity has been applied to patients during hypoglycaemic coma. The current employed was composed of brief, unidirectional " square waves " and is described in detail.

2. Transcerebral stimulation frequently roused the patient from coma, but the final outcome still depended upon the administration of glucose.

3. Transcerebral stimulation caused a rapid and transient rise of the blood-sugar level, which was correlated with the clinical response in time and intensity.

4. This increase in the blood-sugar concentration is largely attributable to a direct action of the current on the brain centres, since it was significantly lower when the central passage of the current was reduced by unilateral application of the electrodes.

5. The results obtained are similar to those which have been reported to follow the injection of glutamic acid and of adrenaline during hypoglycaemic coma.

6. One case of " irreversible " coma was treated by electrostimulation in the presence of hyperglycaemia and was not roused by the current.

7. The opinion is expressed that the clinical effects of the electrostimulation may be attributed primarily to the changes in the blood-sugar concentration.

8. No opinion can be expressed at present concerning the value of this procedure in cases of " irreversible " coma with hyperglycaemia and further material in this field is awaited.

I am indebted to the Physician Superintendent, Dr. R. Ström-Olsen, and to Dr. D. W. Liddell for providing the clinical material, and to Dr. H. Weil-Malherbe for the biochemical investigations.

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