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THE MECHANISM OF AFTER-BURSTS IN CEREBRAL CORTEX

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In a previous paper, a particular form of periodic, 'spontaneous' neural activity was described, which can be seen in slabs of isolated and unanaesthetized cerebral cortex (Burns, 1954*b*). The most convenient way of creating a focus of origin for this type of spontaneous activity is to give the cortical surface a few strong electrical stimuli, following which a series of discrete *after-bursts* occurs which may continue for as long as 1 hr; each burst in the series has all the properties of the surface-positive response to a single electrical stimulus (Burns, 1951). The factors which contribute to the formation of a focus for such after-bursts were investigated and it was concluded that:

(*a*) Each discharge of the cells in the network which conducts the surface-positive response (type-B cells, Burns & Grafstein, 1952) whether 'driven' or spontaneous, makes their further spontaneous discharge more probable.

(*b*) The 'spontaneous' firing of the type-B cells which follows a period of conditioning stimulation is due to different rates of recovery of resting membrane potential at the two ends of the cell, such that the deep ends of these neurones repolarize more slowly than do their superficial extremities.

It was assumed that, during recovery from a series of stimuli, current would flow between the superficial and deep ends of the neurones which had been excited; if this current flow were to exceed a certain threshold, some of the cells would be expected to discharge spontaneously. Moreover, if an after-burst occurred then the recovery process would be set back and the whole cycle of events might be repeated.

It has already been pointed out that the assumptions outlined above seem to offer a satisfactory qualitative explanation of the experimental results that have been described. For such a theory to be acceptable, however, it must go some way towards accounting for those quantitative statements which can at present be made about this form of spontaneous activity. It was, therefore, the intention of the argument and experiments reported below, to test the implications of these assumptions in greater detail.

METHODS

The methods used in the experiments with cats which are described were those outlined in a previous publication (Burns, 1954*b*).

RESULTS

The construction of a model neurone

The argument that follows is an attempt to make the hypothesis of neural activity, which has been described above, a little more precise. It is recognized that the assumptions made provide a picture of neural mechanism which is much too simple to be true. But, when more is known about the factors controlling membrane potential in the soma and dendrites of the type-B cortical neurones, it should be possible to fit the true relevant parameters into the general pattern of the argument presented here.

The nerve cell is assumed to be arbitrarily divided into two portions, a superficial and a deep-lying part with the same resting membrane potential V_0, but with different rates of depolarization and recovery such that the time-courses of all processes for the deep end of the neurone are comparatively slow. The neurone membrane is assumed to produce both action potential and negative after-potential so that recovery of resting membrane potential occurs in two phases, a rapid and a comparatively slow phase. It has already been found necessary to assume that the rapid phase of activity involves the deep end of these neurones for longer than the superficial end, in order to explain the surface-positivity during a burst response to stimulation (Burns, 1951). The argument here is, however, concerned mainly with the slower phase of the recovery of resting membrane potential. It is assumed that this phase of recovery follows an exponential time-course between the membrane potential V_1 found at the 'end' of the rapid phase of recovery, and V_0. If the neurone is re-excited at some time before repolarization to V_0 has been completed, then the value of membrane potential at the end of the second discharge is reduced still further to $V_2 < V_1$. Thus each discharge of the neurone may depress the value of V_n progressively. At the end of a series of driven discharges both superficial and deep ends of the active neurones will begin the process of slow repolarization to V_0 at different rates. Fig. 1 shows schematically the way in which a difference of potential between the two ends of the nerve cell will develop gradually, reach a peak and then decline.

The behaviour of this simple hypothetical neurone under varying conditions of stimulation and excitability is tedious to calculate. Fortunately, it is easy to construct an electronic circuit whose behaviour is controlled by similar parameters. In the circuit shown in Fig. 2*a* the potential V will be V_0 in the resting condition and is regarded as analogous to the membrane potential of a nerve cell. Imagine that the switch S is operated cyclically so that it is thrown over to position b a number of times at a fixed frequency, but wastes no time

between positions a and b. Then the potential V will decrease with successive closures of the switch to reach a new value. It is assumed that the time taken for the discharge of C_1 is short in comparison with the time spent by the switch in position b so that with each closure of the switch, the charge of C_1 is completely removed. In fact C_1 and R_1 are only inserted in the circuit to provide changes of V analogous to the rapid phase of an action potential. It has already been pointed out that we are here primarily concerned with the relatively slow negative after-potential which will be dictated by the slow recharge of C_2 through R_0 and R_2. Therefore it is assumed that $C_1 \ll C_2$ and $C_1 R_1 \ll C_2 R_2$.

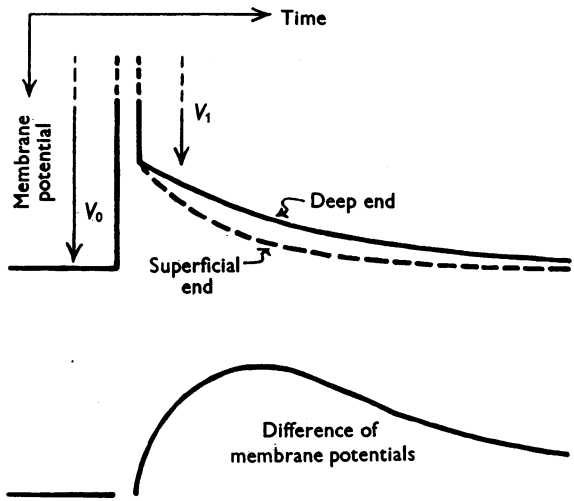

Fig. 1. Diagram drawn to illustrate the way in which different time constants for the repolarization processes at the two extremities of a neurone may lead to current flow between the two ends during recovery from activity.

Fig. 2b shows two such circuits linked by a voltmeter. It is supposed that the two switches S are ganged. After a period of n cycles of operation of these switches, V_n and v_n will return along exponential time-courses towards V_0. The voltmeter is supposed to be coupled to the switches in such a way that if $V - v$ exceeds a threshold value V_t, both switches are driven through one cycle of operation, and make contact with positions b once more. Thus the switches having been driven externally through a number of cycles may now close spontaneously several times before the resting condition of the circuit is restored.

Fig. 3 gives the wiring diagram of a model neurone built of two thyratrons. This was constructed as a simple working version of the equivalent hypothetical circuits of Fig. 2. In the resting condition the two cathode biases are adjusted so that neither valve fires spontaneously. The cathode bias of each valve is then determined by the anode potential of the other, so that if either valve

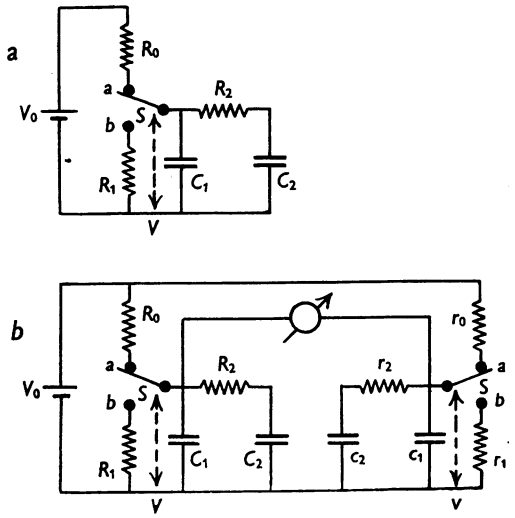

Fig. 2. Hypothetical circuits used to illustrate the assumed properties of type-B cortical neurones. For details see text.

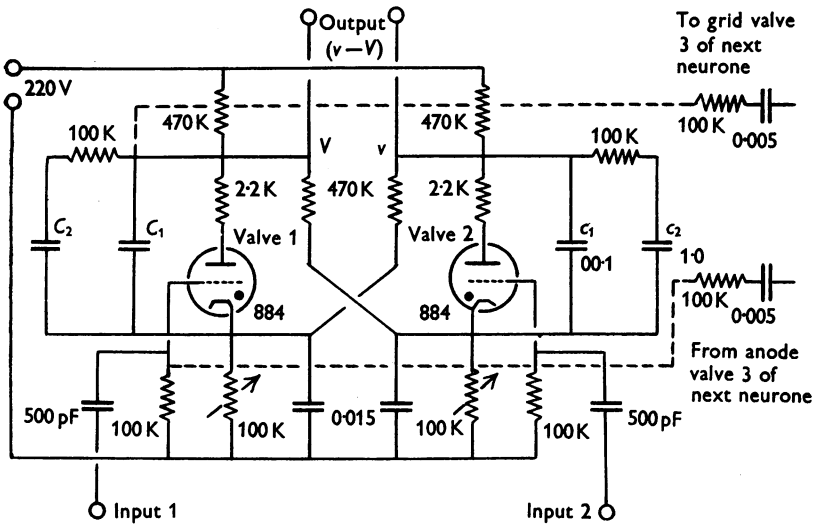

Fig. 3. A working model neurone built to the specifications of the hypothesis described in the text from two thyratron valves. For details see text.

is discharged the other must fire, provided that the resting cathode biases have not been made too great. The condensers across the cathode load were inserted in order to introduce a measurable conduction time from one end of the neurone to the other. The condensers C_1 and C_2 were made variable so that the time-constants of discharge and recovery for the two ends of the model neurone could be made the same or different. The model has been constructed to operate on a time scale some ten times faster than the biological events which it imitates in order to avoid the use of very large condensers.

Some general properties of the model neurone of Fig. 3 are as follows:

(1) The resting values of V and v (the 'membrane potentials' of the two ends of the cell) are equal to V_0 (V_0 = approximately 100 V).

(2) Excitation of either end of the neurone (through input 1 or 2) leads to discharge of both thyratrons.

(3) The response of the circuit bears an all-or-nothing relation to the strength of stimuli applied to the grids.

(4) The model has both a relative and an absolute refractory period.

(5) If $V-v$ exceeds a threshold value (determined by the cathode resistors) the circuit will fire.

The last point can be demonstrated by short-circuiting V temporarily, after which the model neurone gives a prolonged 'injury discharge'.

Experiments with a single thyratron neurone

When $C_1=c_1$ and $C_2=c_2$, the time constants of discharge and recovery are equal for both ends of the circuit. Under these circumstances the model has many of the properties of peripheral nerve or skeletal muscle fibre. Fig. 4*a* and *b* shows records of the responses of the model to single stimuli given to each end of the circuit in turn. The record shows the time-course of the potential difference between anodes $(v-V)$; in this and all subsequent records, when $(v-V)$ is positive, an upward deflexion of the record is obtained. It can be shown that if the cathode biases are increased, which decreases the excitability of the model, conduction velocity from one end of the neurone to the other is decreased. Provided comparable time constants for both ends of this circuit are the same, a period of repeated stimulation can never produce after-discharges.

When $C_1>c_1$ the behaviour of the model in response to a single stimulus is much more complicated. For the records of Fig. 5, $C_1/c_1=C_2/c_2=5$. The bipolar records of Fig. 5*a*, *b* show that the sign of the first deflexion is dependent upon the end of the circuit which is stimulated. But after the initial wave of excitation has invaded the neurone, its subsequent behaviour is largely independent of the site of stimulation. The end (valve 1) with the longer time constants fires once and then recovers resting potential relatively slowly, while the other end (valve 2) discharges a number of times depending upon the local excitability, or the magnitude of its cathode load (Fig. 5*a*, *c*).

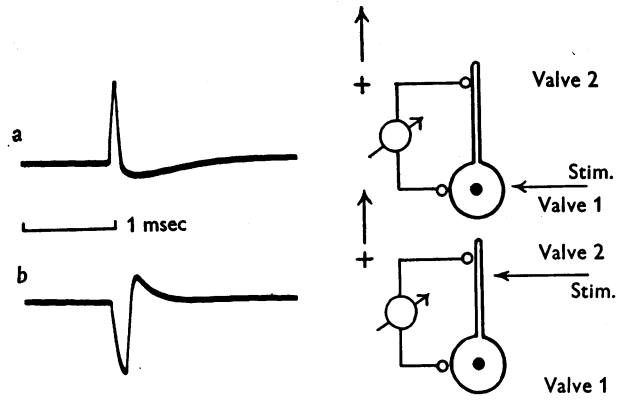

Fig. 4. The responses of the model neurone to single stimuli when comparable time constants for the two ends of the circuit are the same. $C_1/c_1 = C_2/c_2 = 1$ (Fig. 3). *a*, stimulation through input 1 (Fig. 3). *b*, stimulation through input 2 (Fig. 3). Accidental differences between the two ends of the circuit are responsible for the asymmetry of the records.

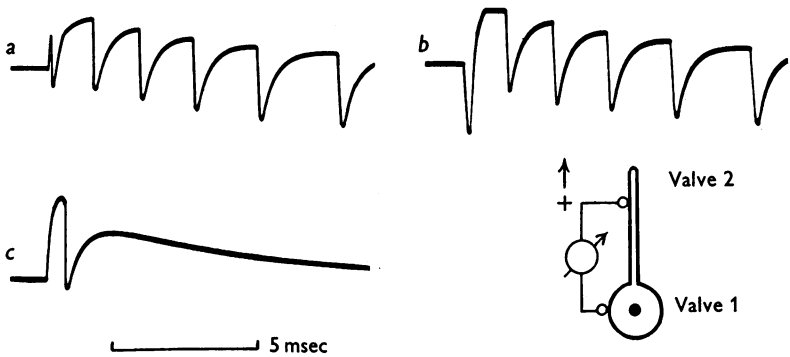

Fig. 5. The responses of the model neurone to single stimuli when the time-courses of discharge and recharge are greater for V_1 than for V_2. $C_1/c_1 = C_2/c_2 = 5$ (Fig. 3). *a*, stimulation of valve 1. *b*, stimulation of valve 2 under identical conditions. *c*, stimulation of valve 1 when cathode load of valve 2 is increased so as to increase its grid bias and decrease its excitability.

The properties of a network of model neurones

Responses to a single stimulus. The properties of a single model neurone of this sort are more relevant to the behaviour of cortical neurones during an epileptiform or paroxysmal after-discharge; a preliminary report on this subject has already been published (Burns, 1954*a*), while a more detailed interpretation of paroxysmal after-discharges will appear later. A model for the surface-positive after-bursts in isolated cortex must provide at least two model nerve-cells of the type described, since the protracted nature of the burst response is due to a process of self-re-excitation occurring in a network of type-B neurones. For this reason two thyratron neurones were joined together in such a way that excitation of either was transmitted with a delay to the

other; this miniature network will, when excited at any point, discharge repetitively until, like its biological counterpart, the refractory period of the system exceeds the circuit time. In fact the second neurone to which that of Fig. 3 was coupled consisted of a circuit identical to the left-hand half (valve 1) of Fig. 3. The coupling time constants were such as to give a circuit time for self-re-excitation of about 10 msec.

In Fig. 6 are shown responses of the model neurone when coupled to a neighbour in the way described. For the following experiments $C_1/c_1 = C_2/c_2 = 10$. A single stimulus to either end of the model caused five discharges of V_2 before self-re-excitation failed. Each discharge of V_1 is accompanied by several discharges of V_2, which we should expect from the experiments of Fig. 5. The burst responses recorded in Fig. 6 can be described as occurring in three phases, indicated in Fig. 6*c*. The first phase is one of relative mean negativity of the anode of valve 1, which for convenience will be referred to as the 'lower end' of the model neurone. This is clearly due to the fact that $C_1 > c_1$ which makes the rapid phase of 'repolarization' of the lower end of the neurone take longer than does the same phase at the other end. The mean difference of potential between the two ends of the neurone during the burst response obviously depends upon two factors:

(*a*) The relative rates of the rapid phases of repolarization following discharge at each end of the neurone.

(*b*) The relative frequencies with which the two ends of the neurone discharge, which in the experiment of Fig. 6 were in the ratio of 4 : 1 for upper : lower ends.

The second phase of the potential changes in Fig. 6 is one in which the lower end of the model neurone becomes positive relative to the upper end. This potential difference can easily be shown to depend upon the fact that the upper end of the neurone discharges more frequently than does the lower end during the burst response. Fig. 7*a–c* shows burst responses in which the excitability of valve 2 was successively decreased (by progressive increase of its cathode resistor) so that the number of discharges of valve 2 during the burst was less in Fig. 7*b* than in Fig. 7*a* and less in Fig. 7*c* than in Fig. 7*b*. It will be seen that there is a progressive increase in phase 1 and progressive decrease in phase 2 of the recorded potential. Moreover, it can be shown with the model neurone that as the burst response is shortened by decreasing the excitability of the reciprocating neurone (valve 3, Fig. 3), phase 2 of the potential declines (Fig. 7*d*).

Phase 3 of the potential changes of Fig. 6 is clearly due to the fact that $C_2 > c_2$. The effects of this phase on the behaviour of the model will be discussed in a later section where the responses to repeated stimuli are considered.

The single surface-positive burst response of the cat's cortex. Experiments with the model neurone suggest that during a surface-positive response the super-

ficial extremities of the type-B cells should fire more frequently than their deep or somatic ends. As a result of earlier experiments it was concluded that the mean discharge frequency of these cells was about 60/sec (Burns, 1951). This conclusion was reached after examination of records taken from leads on the brain's surface. Records from metal- or saline-filled micro-electrodes with their tips lying close to the somata of type-B cells (Burns, 1954*b*) give quite another

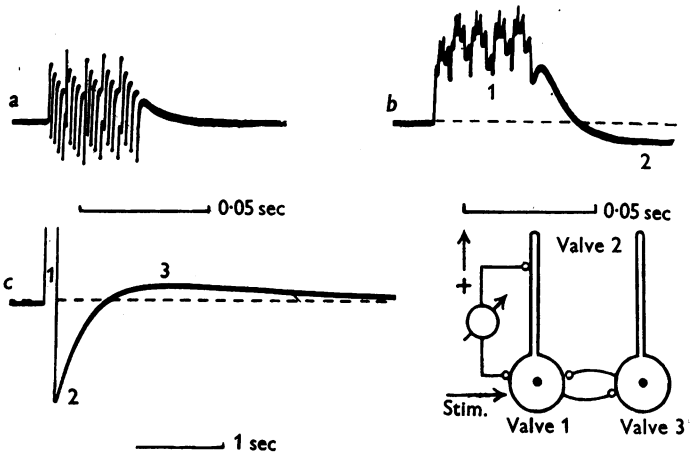

Fig. 6. The responses of one of a pair of model neurones to single stimuli recorded in various ways. $C_1/c_1 = C_2/c_2 = 10$. (Fig. 3). *a*, the response recorded undistorted. *b*, the same response recorded with the high frequency discharge of V_2 attenuated. *c*, the same as in *b* but on a slower time scale to show potential changes following the burst response. The amplification is increased between *a* and *b* and between *b* and *c*.

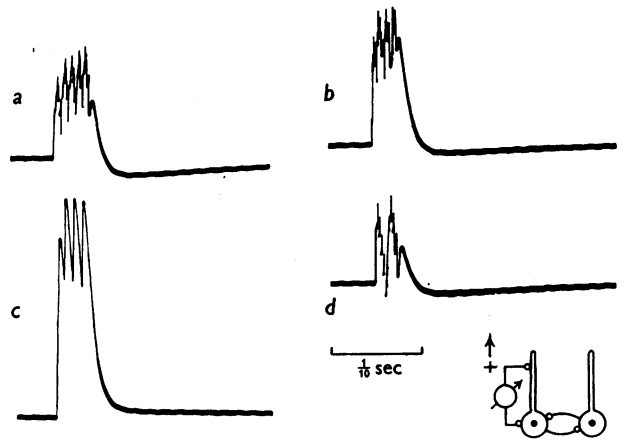

Fig. 7. The effect of variation in the excitabilities of valves 2 and 3 (Fig. 3) on the potentials during and after a burst response of two linked model neurones. The excitability of valve 2 of the 'left-hand neurone' is progressively decreased in records *a*, *b* and *c*. In record *d* the excitability of the left-hand neurone is as in *a*, but the excitability of the right-hand neurone is decreased.

impression. The data for Fig. 8 were taken from an experiment in which potentials were recorded during the burst response between a deep microelectrode and a surface lead immediately above. Such records are of a relatively slowly oscillating potential change with the spike discharge superimposed upon it. Measurements (made from records of a number of bursts recorded from a single animal) of the time interval (t) between all successive maxima of the slow oscillatory potential provided a curve relating frequency of activity ($1/t$) to the probability of its occurrence. The most probable frequency of the slow potential fluctuations was found to be 75/sec with a sharp fall of probability for frequencies greater or smaller than this (Fig. 8*b*). Analysis of the

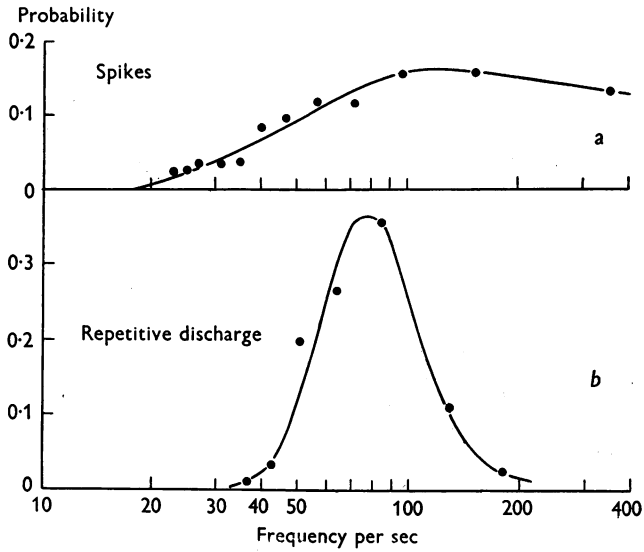

Fig. 8. The probabilities of various spike and slow-wave frequencies, during a surface-positive burst response in the cat.

frequency response of the spike discharges recorded at the same time showed the most probable frequency of spikes to be about 140/sec; there was a marked fall in probability for frequencies less than 140/sec, and a very slow fall for frequencies above this value up to 400/sec (Fig. 8*a*). Although all the available evidence suggests that the surface-positive response is the result of activity in only one type of cell-population the frequency data show that the most common event is for one slow potential oscillation of each cell to be accompanied by several spike discharges. These observations are consistent with the hypothesis made at the beginning of this paper, and deductions from this hypothesis made with the model neurone would lead us to expect two frequency components to the burst response, the one initiated by the upper end of the type-B neurones, the other due to the deep end (soma). During the burst response of the model network both the lower end and the upper end of the

model nerve cells discharge completely but at different frequencies. The records obtained with a micro-electrode from cats only show that cyclical activity of type-B neurones is occurring at two mean frequencies; there is no indication that the relatively slow oscillatory potential represents a complete discharge of the somata of these neurones. The greater part of the slow potential waves that are recorded may be a contribution from synaptic potentials (Eccles, 1953) similar to that postulated by Li & Jasper (1953) in their discussion of unit activity within the intact cerebral cortex.

So far as the phases of potential change described in Fig. 6 are concerned, the burst response of the model neurone imitates potential changes during and after the burst response of the cat's cortex in all its phases. Fig. 9 shows responses obtained from the model and from the cat which have been scaled with respect to time to look as nearly identical as possible. In the cat, however, phase 3 of the potential changes is too small to be detected after a single burst response. Only following several driven responses does phase 3 become large enough to be recorded (Fig. 10*a*). Moreover, in the cat the deep after-positivity (phase 2 of the potential changes) which follows a single burst response increases with increase of burst duration as it does in the case of the model neurone network (Fig. 7).

Responses of the model neurones to repetitive stimulation when $C_2 > c_2$ (*Fig.* 3). As would be expected, repeated excitation of the model neurones at comparatively low frequencies can lead to a series of after-bursts, whose duration depends upon the initial excitabilities of the circuit (the resting grid potentials). It is phase 3 of the potentials described in Fig. 6 which is responsible for this series of spontaneous bursts of activity. This phase of the potential changes which follow the burst response depends upon C_2 being larger than c_2; the fact that the lower end of the model neurones (valve 1) repolarizes slower than does the upper end may cause excitation to spread from the more rapidly polarizing end (valve 2) and thus trigger a burst response from the miniature network of neurones. Fig. 10*b* shows the potential changes recorded as usual from one of the model neurones during and after a short series of stimuli. At the beginning of the period of stimulation, between the burst responses the lower end of the model neurone (valve 1) becomes relatively positive to the upper end. This positivity declines as stimulation is continued and may reverse so that towards the end of the series of stimuli, between bursts the lower end becomes negative to the upper. Whatever the relative potentials of the two ends of the circuit at the end of stimulation, after the last driven burst, relative negativity of the lower end (valve 1) increases with a time-course dependent upon the ratio $C_2 : c_2$. If the relative negativity of the lower end reaches a certain level a spontaneous after-burst occurs; following this after-burst the recovery process is set back a step, begins again and, in the same manner, may lead to another spontaneous burst (Fig. 10*c*). The same series of potential changes can be

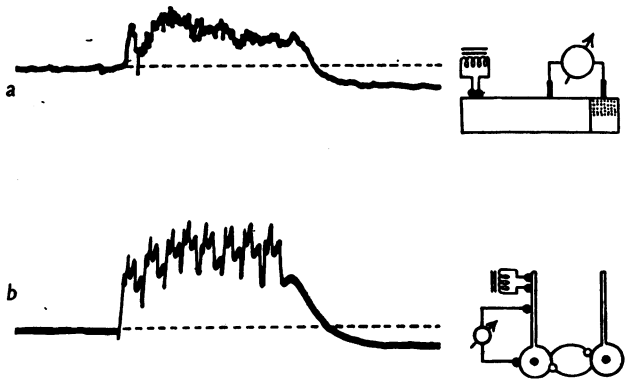

Fig. 9. To show the similarity between the burst responses of the cat's cerebral cortex and the model neurones. *a*, record of the response to a single stimulus of the cat's isolated cerebral cortex. *b*, the response of one of a pair of linked model neurones to a single stimulus.

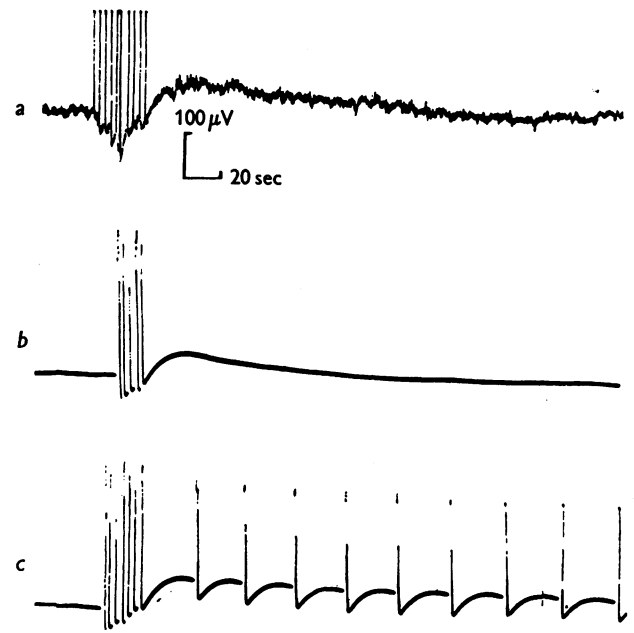

Fig. 10. Records of slow potential during and after repeated stimulation. *a*, recorded from the cat in response to 10 stimuli at 3 sec intervals. The recording electrodes were 10 mm from the stimulated point and consisted of a non-polarizable wick electrode on the brain's surface and a deep micro-saline electrode 1·5 mm beneath. *b* and *c*, the responses of one of a pair of model neurones to 5 and 7 stimuli respectively, recorded as in Fig. 6*c*.

demonstrated in the cat's cortex (Fig. 10*a*)—the deep positivity between the driven bursts and the deep negativity which follows the series of conditioning stimuli and which may, if great enough, be accompanied by after-bursts (Burns, 1954*b*). The record of radial potential changes in the cat (Fig. 10*a*) was obtained from a cortical point far from the stimulating electrodes. In this way one can be sure that the potential changes recorded are due to the type-B cells alone, whereas near the stimulated point many other types of cell must be excited by the stimulating current.

If the excitabilities of the valves of the model were made great, then a few stimuli were sufficient to set the circuit into an infinite series of spontaneous bursts, although in the earlier resting state the circuit had been quite stable. But if the various excitabilities were reduced somewhat, then the relations between the parameters of stimulation and the number of after-bursts produced were very similar to those already described for after-bursts in the cat's isolated cortex (Burns, 1954*b*). In Fig. 11 are shown the relations between stimulus strength, number of stimuli, frequency of stimuli and number of after-bursts produced in the model neurones. These curves are similar in form to those already determined for the cat's brain (Burns, 1954*b*). The first part of the curves, relating number of stimuli or strength of stimuli to number of after-bursts, are approximately linear for both model and cat. With a fixed number of conditioning stimuli in the case of both cat and model there is an optimal frequency of stimulation for the production of after-bursts which is approximately the reciprocal of the duration of the burst response to a single stimulus (Fig. 11*c*). At frequencies of stimulation in excess of the optimum, the model network, like its feline counterpart, does not respond to every stimulus with a burst response (Burns, 1954*b*).

In the cat, a series of after-bursts frequently starts after a latent period which is often longer than the intervals of time between the first few after-bursts. The same phenomenon can be seen with the model neurones where the latency of the first after-burst is clearly due to the time taken for the relative negativity of the lower end of the circuit (valve 1) to build up to the threshold value at which valve 2 is triggered and the first burst response is caused (Fig. 10*c*). The time required for threshold potential to be reached depends upon the level of potential found at the end of the last driven burst in the conditioning series. When the end of the period of conditioning stimulation leaves the lower ends of the neurones relatively positive, there is a long latency; a lesser degree of deep-positivity at the end of conditioning leads to relatively short latencies before after-bursts begin.

Estimation of the time constants of repolarization in the cat. Most phenomena in the cat that lend themselves to quantitative study are not dependent on the relative rates of repolarization of the two ends of the neurones alone; they will also depend upon the relative excitabilities of the membrane at each end of the

cell. The information provided in Fig. 8 suggests that, on the average, a type-B neurone discharges 4 or 5 times for each depolarization of its somatic end. Valve 2 of the model neurone will discharge 4 or 5 times more frequently than valve 1 (see Fig. 5) if C_1/c_1 is of the order of 10. It seems probable then that the ratio of the time constants for the rapid phase of repolarization of the two ends of type-B cells is also of this order.

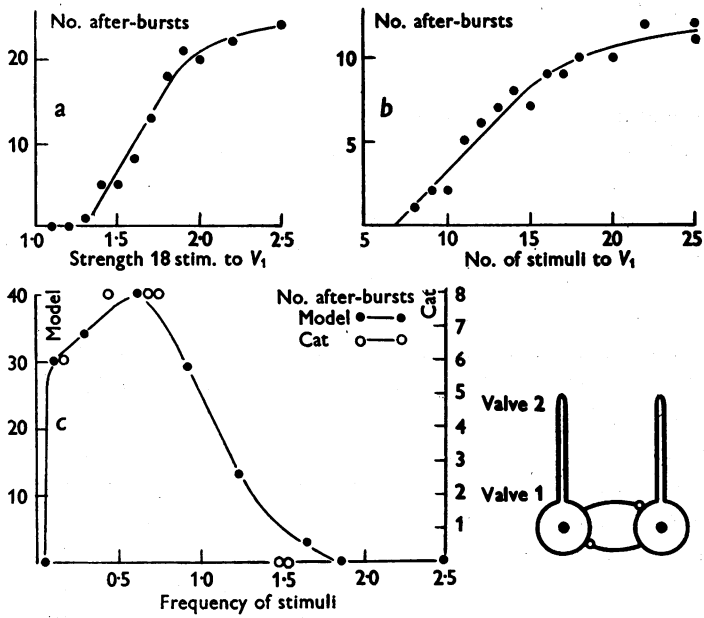

Fig. 11. The relations between the parameters of stimulation and the number of after-bursts in the network of model neurones. *a*, the number of after-bursts produced by 18 stimuli (at a frequency of 0·26 sec^{-1}) of varying strength (volts). *b*, the number of after-bursts produced by various numbers of stimuli of constant strength and frequency 0·1 sec^{-1}. *c*, the number of after-bursts produced by 20 stimuli of varying frequency in the model-neurone network. The open circles give the same relations for the cat's type-B neurones. In both cases time is measured in units of burst duration.

A rough estimate can be made of the absolute values of the relatively slow time constants of repolarization in the cat's type-B neurones. After a number of conditioning stimuli, the lower ends of the type-B neurones slowly develop a transient negativity in relation to the superficial ends. We have supposed that when no after-bursts occur this after-potential (P) runs a time course of the form:

$$P = P_1 - P_2 = Ae^{-t/a} - Be^{-t/b},$$

where A and B are constants which determine the value of P_0, the potential gradient found immediately after the last driven burst. The values of A and B will be dependent upon the number, frequency and magnitude of the conditioning stimuli. a and b are the time constants of the slow phase of repolarization for the deep and superficial ends of the type-B cells, respectively. It is

supposed that the values of a and b are altered relatively little by the nature of the conditioning stimulation. The equation for P implies that provided $a \gg b$, the terminal portion of the graph relating ln P to t should be rectilinear (see Fig. 12*a*). By extrapolation of the rectilinear part of this curve back towards $t=0$ we should obtain the line (line 2 of Fig. 12*a*) $\ln P_1 = \ln A - t/a$ from which a value for a can be estimated. A plot of $\ln (P_1 - P) = \ln P_2 = \ln B - t/b$ provides an estimate of b (see Fig. 12*b*). This procedure was checked with data from the model neurone network and found to give correct values for a and b.

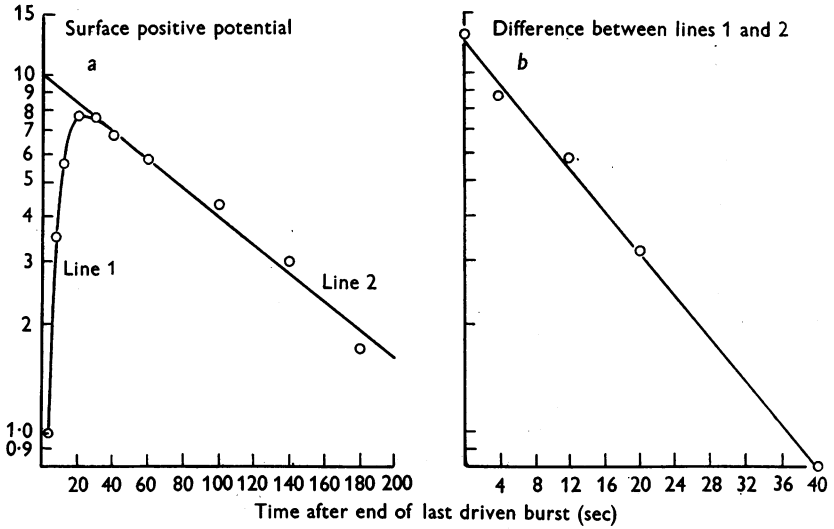

Fig. 12. Graphical determination of the repolarization rates for the upper and lower ends of type-B neurones. *a*, the points plotted represent measurements of radial potential (arbitrary units) at various times after the end of the last of 10 responses to stimulation in the cat. The measurements are from the record of Fig. 10*a*. Lines 1 and 2 were fitted to the experimental data by eye and describe $P = f(t)$. Line 2 is of the form $\ln P_1 = \ln A - t/a$. *b*, a plot of $\ln (P_1 - P)$ measured from Fig. 12*a*. The line drawn by eye is of form $\ln (P_1 - P) = \ln B - t/b$. See text for further explanation. In this experiment $a = 110$ sec, $b = 14{\cdot}5$ sec.

Such an analysis can be made of the radial potential changes between a superficial and deep electrode recorded from the cat's cortex (Fig. 10*a*) after a number of conditioning stimuli has been given, and is shown in Fig. 12. In this case, the pair of electrodes used for recording the radial potential gradient were placed remote from the stimulated point in order to ensure that the potential changes recorded were due only to type-B cells. (Close to the stimulated point, many other cell systems must be excited together with the type-B cells). Fig. 12*a* shows the results of such an experiment. From such experiments it was concluded that a was of the order of 100 sec^{-1} and b was approximately 15 sec^{-1}. Thus in the cat it appears that the upper end of the type-B neurones repolarizes some 7 times faster than does the lower extremity, during the final stage of repolarization.

DISCUSSION

The experiments described in this paper were undertaken in order to define the implications of a hypothesis concerning the function of some neurones in the cerebral cortex. It had been suggested that the known properties of type-B cells of the cat's cerebral cortex (Burns & Grafstein, 1952) could be explained if it were assumed that the deeper or somatic end of each neurone of the network repolarized after activity more slowly than did the pial extremity (Burns, 1954*b*). The repolarization of both ends of the neurone was supposed to occur in two phases, a rapid and a relatively slow phase, both of which followed a logarithmic time course. The time constants of all processes of discharge and recharge were assumed to be slower for the lower end of the neurones than for the upper end.

It would certainly prove impossible with contemporary techniques to test these assumptions directly. It is difficult enough to insert an intracellular electrode into the soma of any cortical neurone on account of the mobility of the brain, but there is no hope at all of getting such an electrode into the dendritic ramifications of such cells. Consequently the validity of the hypothesis must be judged on its ability to explain or predict other details of the behaviour of type-B cells. With this in mind, an electronic model neurone was constructed and given parameters governing its behaviour similar to those assumed for these cells in the cat's cortex. The fact that such a model behaves in a manner which is qualitatively similar to the behaviour of type-B neurones is, of course, in no way a logical justification for adoption of the hypothesis. The model was, after all, constructed to specifications which 'forced' it to behave rather like a neurone. The model neurone should properly be regarded as a calculating machine which allows one to estimate rapidly and painlessly some of the more detailed implications of the simple assumptions about biological function which have been incorporated in its structure. Tests with this model have shown that the hypothesis provides an adequate and semi-quantitative explanation of the following properties of type-B cells:

(1) *The burst response to a single stimulus* (involving a period of repetitive discharge due to a process of self-re-excitation within the cell network) is one in which the cortical surface becomes positive to inactive areas.

(2) During the burst response a relatively slowly changing and oscillatory potential with a mean frequency of about 75/sec can be recorded, although the most probable frequency of discharge of the individual type-B cell is around 140/sec and many cells can be found discharging at higher frequencies up to 400/sec.

(3) At the end of the single burst response, recovering cortex becomes temporarily surface-negative.

(4) This surface-negativity then degenerates slowly and is ultimately replaced by a just measurable surface-positivity.

(5) *Repeated stimulation* producing a series of driven burst responses may lead to the occurrence of a series of spontaneous after-bursts, the generation of which depends upon:

(6) The development after stimulation of a relative mean negativity of the deeper end of the type-B cells.

(7) During the initial stage of repeated stimulation at relatively high frequencies ($> 0{\cdot}3$ sec^{-1}) the deep ends of these cells become positive to the superficial ends between the driven bursts.

(8) Short periods of relatively high frequency stimulation can lead to a series of after-bursts which begins after a latent period which sometimes exceeds the interval between the first few bursts in the series.

(9) The general form of the relation between the parameters of conditioning stimulation and the number of after-bursts produced can be predicted.

All of those properties of the type-B cell network which have so far been studied can be predicted by argument from the hypothesis made at the beginning of this paper. Moreover, the assumptions made enable one to offer a simple explanation of the observed phenomena. It seems reasonable to conclude therefore that after each discharge of the type-B neurones the somatic end of the cell with its dendritic ramifications repolarizes much more slowly than does the process which extends towards the brain's surface. It is not possible at present to make this statement much more precise. The experiments reported above do, however, give some idea of the order of magnitude of the recovery rates involved in repolarization. After each discharge of a type-B cell it seems that the first phase of recovery toward resting membrane potential takes place some 10 times more rapidly at the superficial end of the neurone than at the deeper end. The second phase of recovery occurs with time constants of the order of 15 sec^{-1} and 100 sec^{-1} for the upper and lower ends of the neurone respectively.

An after-discharge may be broadly defined as a repetitive response to a single stimulus. After-discharges have been observed in many other parts of the central and peripheral nervous systems, and it seems reasonable to ask whether the presence of different repolarization rates for different parts of the same electrically excitable cell may not offer an explanation in some of these cases. The repetitive after-discharge of eserinized skeletal muscle fibres in response to a single motor-nerve volley is clearly due to the abnormal persistence of liberated acetylcholine (Brown, Dale & Feldberg, 1936). The somewhat similar after-discharge of skeletal muscle in the initial stage of exposure to decamethonium iodide is caused by the inability of the end-plate membrane to repolarize fully (Burns & Paton, 1951). Both these examples of after-discharge in the peripheral nervous system could be regarded as extreme cases of differen-

tial repolarization, in which the end-plate region is prevented from repolarizing as rapidly as does the neighbouring membrane of the muscle fibre. The well-known after-discharges demonstrable in practically all the electrically excitable cells of the peripheral nervous system in the presence of veratrine (Krayer & Acheson, 1946) are of particular interest. It has been shown repeatedly (Graham & Gasser, 1931; Feng 1941; Kuffler, 1945) that veratrine prolongs and exaggerates the negative after-potential of peripheral nerve and of skeletal muscle fibres. This fact implies that veratrine slows the recovery of resting membrane potential after an action potential in these tissues. Moreover, it has been shown (Wible, 1924) that the application of the alkaloid to one part only of a stretch of nerve or muscle fibre will cause an after-discharge in response to a single stimulus delivered to the untreated part of the cells. In these circumstances repolarization of the veratrinized area must occur much more slowly than does repolarization in the neighbouring normal tissue, and the nerve or muscle cells may imitate on a faster time-scale events in type-B cells of the cerebral cortex. This differential repolarization rate of locally veratrinized cells must contribute to their tendency to after-discharge, although it is probably not the only significant mechanism. Peripheral nerve which has been uniformly soaked in solutions of veratrine will also give after-discharges in response to single stimuli (Feng, 1941) and unless it is assumed that the veratrine does not obtain equal access to all parts of the nerve fibre, the mechanism of differential repolarization cannot contribute to the after-discharge. It would be interesting to know whether the local application of veratrine was more effective in producing after-discharges than was complete and prolonged immersion of a nerve trunk in a veratrine solution of the same concentration.

After-discharges occurring as a part of spinal reflexes have usually been explained by using the hypothesis of self-re-excitation (Forbes, Davis & Lambert, 1930; Lorente de Nó, 1933). No very convincing proof has ever been given of the functional existence of self-re-exciting chains of neurones in the cord, but there seems little reason to doubt the validity of this assumption. Although differential repolarization rates may be a property of interneurones, there is certainly no reason to believe that the soma of the anterior horn cell repolarizes much more slowly than does its axon (Brock, Coombs & Eccles, 1952). In the presence of strychnine, however, the behaviour of the motoneurone is quite different and it seems that differential repolarization may play an important part in the maintenance of after-discharges. Brooks & Fuortes (1952) found that the proximal end of apparently resting ventral roots became negative to the distal parts in the presence of strychnine. They believed that depolarization of the anterior horn cell soma was one of the actions of this drug. On the other hand, Bremer (1953) reports that strychnine increases and prolongs the ventral root potential. He found that the discharge rhythm of the anterior horn cells could be 'reset' by an interpolated stimulus, that it could be

slowed or stopped by anelectrotonus of the cord and could be augmented by calelectrotonus (Bremer, 1941). It looks as though much of the behaviour of motor-nuclei under the influence of strychnine could be explained by assuming that the drug delays the repolarization of the anterior horn cell soma.

In the case of the superior cervical ganglion, the after-discharges produced by high-frequency preganglionic stimulation cannot depend upon self-re-exciting chains of neurones (Bronk, 1939). It is difficult to believe that these after-discharges lasting some 20 sec are maintained by the persistence of acetylcholine, since a low frequency of postganglionic discharge maintained by perfusing the ganglion with weak acetylcholine solution is temporarily stopped by a burst of tetanic stimulation of the preganglionic trunk. MacIntosh & Emmelin (personal communication), using contraction of the nictitating membrane as a measure of postganglionic discharge from the eserinized ganglion, found after-discharges in some preparations lasting 10 min. Following the period of tetanic stimulation of the preganglionic trunk there is a latent period after which the contraction of the test muscle builds up to a maximum. The contraction of the nictitating membrane was due to ganglionic activity since cooling of the postganglionic trunk abolished the after-discharge. The after-discharge was unaffected by an injection of D-tubocurarine subsequent to the conditioning tetanus and therefore could not have been maintained by the persistence of acetylcholine. It seems possible that this particular form of after-discharge may be due to differential repolarization rates for the soma and axon of the postganglionic neurones. It would be interesting to know the effects upon these after-discharges of polarizing currents.

The paroxysmal after-discharges which follow repeated and strong stimulation of the cerebral cortex (Adrian, 1936) are almost certainly maintained by differential repolarization rates of the excited cells (Burns, 1954*a*). They usually begin after a latent period of inactivity following the conditioning stimuli. They are accompanied by a relatively persistent surface-positivity at the focus of origin (Goldring & O'Leary, 1950) and can be stopped by surface-negative polarization. Surface-positive polarization can create a focus for paroxysmal discharge. A more detailed investigation of this form of after-discharge will be reported at a later date.

While there is not much direct evidence to suggest that differential repolarization plays an important part in physiological processes outside the brain, its existence in the cerebral cortex raises interesting questions in relation to the problem of the spontaneous activity of cortical cells. It has frequently been suggested that some cells in the cerebral cortex can discharge spontaneously without being driven by afferent impulses (Gerard, 1936; Bremer, 1949). Experiments with neurologically isolated cortex do not provide a clear answer to this problem. Activity has been reported in the acute and chronically isolated cortex of both man and animals (Kristiansen & Courtois, 1949; Echlin,

Arnett & Zoll, 1952; Henry & Scoville, 1952). The activity usually takes the form of bursts which look very similar to the surface-positive bursts described by Burns (1951, 1954*b*). The existence of 'normal rhythms' of exceptionally low voltage described by Kristiansen & Courtois is more doubtful; it is very difficult to be sure that these potential fluctuations are not picked up by the recording electrodes from sources outside the isolated area. In our own acute experiments, exploration with a micro-electrode has never revealed discharge of any units within the unstimulated isolated grey matter, other than the activity of type-B cells when they are involved in after-bursts. Unfortunately, the traumatic effects of the surgery used to isolate an area of cortex cannot be estimated and no conclusive arguments about spontaneous activity can be built on the available evidence. In the undisturbed brain type-B cells *may* have the power of spontaneous discharge, and the lack of truly spontaneous discharge seen in our own experiments may be the unwanted consequence of the necessary manipulation of the brain. Whatever are the properties of these cells in the undisturbed state we can state with confidence that in the resting state they lie close to the margin of instability. Moreover, if a group of these cells discharges once then it is very liable to discharge a second time. It is easy to set the excitabilities of the linked model neurones to such a value that although the system is perfectly stable, one or a few stimuli will set the model network into an endless series of after-bursts. If spontaneous discharge is the ultimate fate of an undisturbed type-B cell, deprived of all afferent stimulation, then the mechanism of differential repolarization that has been described must be responsible for the maintenance of subsequent spontaneous activity. We have no evidence that any other cell system in isolated cerebral cortex can so easily be brought into an unstable state.

The network of type-B cells that has been described clearly provides a system by which a few biological stimuli arriving at any given point in the cerebral cortex can effect the excitability of cells at any other remote point within the system for a period of many minutes. Many neurophysiologists have sought mechanisms that might play a part in elementary learning phenomena, in the study of similar long-lasting facilitations. Although facilitation may play an important role in the initial stages of development of some more permanent change in the central nervous system, those forms of facilitation so far studied have always seemed disappointingly transient. Adrian (1936), speaking of the facilitations of paroxysmal or epileptiform after-bursts said 'There is no evidence that they can ever become complex enough or permanent enough to be the basis of a learnt reaction'. The relatively unstable cell system described in this and previous papers can theoretically be set into perpetual activity, but the mechanisms involved make the activity itself unstable and any factors which interrupt activity will cause the permanent dissolution of any pre-existing pattern of excitability within the network of type-B cells.

SUMMARY

1. It has been proposed (Burns, 1954*b*) that the 'spontaneous' firing (or series of after-bursts) of type-B cells in isolated cerebral cortex of the cat, which follows a period of conditioning stimulation, is due to different rates of recovery of resting membrane potential at the two ends of the cell, such that the deep ends of these neurones repolarize more slowly than do their superficial extremities.

2. The implications of these assumptions have been tested in as quantitative a fashion as possible.

3. For this purpose experiments were carried out with an electronic calculating machine or network of model neurones constructed to the specifications of the hypothesis.

4. The behaviour of the model network proved similar to that of type-B neurones in the cat, in every way that has been tested.

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