THE ELECTRICAL ACTIVATION OF PASSIVE IRON WIRES IN NITRIC ACID

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The chief analogies between the activation of a passive iron wire by the electric current and the electrical stimulation of an irritable living tissue may be stated briefly as follows:¹

In both cases the activating or stimulating current must exceed a certain minimum as regards (1) intensity (referred to unit surface, or density), (2) duration of flow, and (3) rate of change. The polar rule also applies; to be activated the passive wire must be the cathode; if it is the anode, the effect of the current is stabilizing, *i.e.* is in the direction of passivation rather than activation; thus a passive wire (*e.g.* in 70 volumes per cent HNO_3)² polarized anodically by a constant current is more difficult to activate (*e.g.* mechanically or electrically) than an unpolarized wire under the same conditions, and transmits an activation wave more slowly.¹ Conversely, a wire polarized cathodically, by a current of "sub-threshold" density, is more readily activated and transmits activation more rapidly than an unpolarized wire.³ Interferences and facilitations of this kind are to be regarded in the physical sense as summation effects; they have thus physiological analogies in the phenomena of electrotonus.⁴ Summation of sub-threshold "stimuli," mechanical and electrical is also shown.¹ Finally, the passive wire may be activated, under appropriate conditions, by the break of an already flowing constant current (see below, p. 122).

¹ For a fuller general comparison *cf.* Lillie, R. S., *J. Gen. Physiol.*, 1920, **3**, 107, 129.

² Volumes of HNO_3 of specific gravity 1.42 in 100 volumes of solution.

³ For the effects of polarization on nerve *cf.* Bishop, G. H., and Erlanger, J., *Am. J. Physiol.*, 1926, **78**, 630.

⁴ *Cf.* Ebbecke, U., *Zur Lehre vom Elektrotonus, Ergebn. Physiol.*, 1933, **35**, 756.

Since Hermann's time the primary change in electrical stimulation has been very generally recognized to be a change of polarization. This change determines or releases the characteristic biological reaction of stimulation. Apparently, however, it is not sufficient that a certain critical change of polarization should be produced by the stimulating current; the polarized state must be reached with a certain minimal rapidity and maintained for a certain minimal time. As is well known, the minimal duration of current flow required for stimulation by a constant current of threshold intensity varies characteristically for different tissues and for the same tissue under different conditions. With stronger currents the required duration decreases as intensity increases, and various formulae have been proposed to describe the intensity-duration relationship.⁵ If polarization is the primary change in electrical stimulation, the total duration necessary for any stimulating current may be regarded as the sum of two separate durations, (1) that of the purely physical process of polarization and (2) that of the succeeding presumably electrochemical process which initiates the biological reaction. These may be characterized respectively as polarization time and activation time. In certain oscillograph records of electrical stimulation the special characteristics of the two corresponding processes can be clearly distinguished; a curve having the general form of a polarization curve is followed immediately by another showing peculiarities characteristic of the biological response.⁶

Recently the phenomena of polarization have been studied by Ebbecke⁷ in a simple physical model consisting of a pair of platinum wires immersed in an electrolyte solution and connected through a galvanometer to a rheostat and battery. With potentials lower than the decomposition potential of the solution, current flows temporarily on making and breaking the current, but not (or inappreciably) during the intervening period. Similarly, little or no current flows if the potential (within the defined range) is slowly changed. In these several respects a wire immersed in a solution acts like a condenser; and in further studies with condenser systems Ebbecke⁸ has shown that the characteristic duration-intensity curves of electrical stimulation agree well with the conception of stimulation as being determined by the charging or polarizing of surfaces with properties similar to those of imperfectly insulated condensers. This general view has been reached independently by many other investigators.⁹

⁵ For a recent full account cf. Monnier, A. M., *L'excitation électrique des tissus*, Paris, Hermann et Cie, 1934.

⁶ Cf. Bishop, G. H., *Am. J. Physiol.*, 1928, **84**, 417, Fig. 6; Schmitz, W., and Schaefer, H., 1933, *Arch. ges. Physiol.*, **233**, 229, Fig. 2.

⁷ Ebbecke, U., *Arch. ges. Physiol.*, 1926, **211**, 485.

⁸ Ebbecke, U., *Arch. ges. Physiol.*, 1927, **216**, 448.

⁹ Cf. Lapique, L., *L'excitabilité en fonction du temps*, Paris, Presses universitaires de France, 1926; Monnier, A. M., see footnote 5; Bishop, G. H., *Am. J. Physiol.*, 1928, **85**, 417; Ebbecke, U., see footnote 4; Hill, A.V., *Chemical wave transmission in nerve*, Cambridge University Press, 1932.

If in Ebbecke's model we replace the platinum wires by passive iron wires (with HNO_3 as electrolyte) the physical conditions remain essentially unchanged until a certain upper limit of potential is reached; then the cathodal wire is activated, and the characteristic electromotor variation and other features of activation are shown. As already described,¹ the reaction of the wire varies in its special features and time relations according to a number of conditions, including the kind of wire, concentration of acid, temperature, and presence of other substances. In more concentrated HNO_3 (above 55 v. per cent) it resembles the response of irritable living tissues in being temporary and automatically reversed; the wire shows a darkening and effervescence lasting for a brief period (varying from a fraction of a second to several seconds) followed by a return to the passive state. In acid of this concentration the passive state is a stable one (analogous to a physiological "resting" state) while the active state is unstable or temporary and maintainable only intermittently,—hence the tendency to automatic rhythm shown under certain conditions.¹⁰ This characteristic behavior is based on the fact that two chemically opposed processes are concerned in the reaction cycle of activation. The first is the reduction which breaks down the passivating film; this effect is associated with automatic transmission by local circuits (activation phase); the second is the oxidation which reforms the film (repassivation or recovery phase). After repassivation secondary changes in the film proceed for some time longer, occupying the so called relative refractory period.¹¹

Certain characteristic features of electrical activation depend on the relative rates or intensities of these two opposed processes. A current of a certain intensity and duration will activate a wire in nitric acid of a certain concentration (e.g., 60 v. per cent) but not in more concentrated (e.g., 70 v. per cent) acid. Since the same quantity of current traverses the surface of the wire in both cases, it is evident that some factor opposing activation is present, which is effective in the stronger but not in the weaker acid. This factor is the oxidizing action of the HNO_3 which increases with concentration. By increasing the current the wire can be activated in the stronger acid; reduction then becomes temporarily more rapid than oxidation and the film is disrupted sufficiently to activate the whole wire. The all-or-none characteristic, so conspicuous in fully recovered wires, depends on the automatic transmission by local circuits; such transmission always plays a part in any case of activation, which may be initiated in a small local area and yet involve the whole wire.

Such experiments show that the iron wire in nitric acid represents a system where activation, an effect of reduction, is opposed by a counter-process, oxidation, whose effect increases with the external concentration of acid; this counter-process acts by forming an insoluble oxide which is deposited as an impermeable surface film. In strong acid the process of repassivation is automatically initiated

¹⁰ Lillie, R. S., *J. Gen. Physiol.*, 1929, **13**, 1.

¹¹ Lillie, R. S., *J. Gen. Physiol.*, 1931, **14**, 349.

at any region as soon as that region becomes active and therefore anodal.¹² The system possesses in fact the general properties ascribed by Blair¹³ to his recent mathematico-physical model of excitation, in which the excitatory process is automatically opposed by a counter-process proportional to the state of excitation.

Another peculiarity shown by both the passive wire and the living tissue is that the readiness with which either system responds to any activating agent varies in a characteristic manner during a certain interval of time ("refractory period") immediately following a response. Responsiveness is slight or absent at first and then increases progressively to a maximum corresponding to the normal equilibrium or resting state of the system. In both systems "absolute" and "relative" refractory periods are present^{1,11} and the temperature coefficients of recovery are similar.¹⁴ During its relative phase the wire requires for activation a stronger or more prolonged current than when fully recovered, and the transmission of activation is slower.¹⁴ It is therefore necessary, in studying experimentally the intensity-duration relationship in passive wires, to make all observations either in fully recovered wires, or in partially recovered wires at equal intervals between successive activations. The wires used must be uniform in composition, since the rate of recovery varies greatly in different kinds of iron, and temperature must be constant.

Since activation depends on the reduction of the oxide film, it is to be assumed that a certain minimal P.D. between the cathodal wire (or the initiatory local region in such a wire) and the adjacent layer of solution must be reached in order to activate. This is the decomposition potential characteristic of the system; electrons then pass from the metal to the reducible oxide molecules at its surface and reduction occurs. This potential is not reached instantaneously when the circuit is closed but rises to the required level progressively, following a curve similar to the charging curve of a condenser. After the establishment of this critical potential, current flows continuously between the metal and the electrolyte, and the equivalents reduced are proportional to the Faradays passed. It seems clear that in the living system also a chemical reaction is initiated at the surface of the irritable element after the polarizing current has flowed for a certain time, and that this reaction directly or indirectly alters the plasma membrane, apparently increasing its permeability. To regard this reaction as an electrolysis might be unjustifiable, unless the protoplasmic surface is equivalent to an electrode surface. It is, however, well known that a thin electrically polarized membrane separating two solutions may be the seat of chemical reaction when a current

¹² It should be remembered that in the iron wire this condition holds only in strong acid (>55 v. per cent); in weak acid the passive state is one of unstable equilibrium, and activity once initiated continues until the metal is completely dissolved.

¹³ Blair, H. A., *J. Gen. Physiol.*, 1932, **15**, 709, 731.

¹⁴ Lillie, R. S., *J. Gen. Physiol.*, 1925, **7**, 473. Cf. p. 500.

is passed; this is the phenomenon of electrostenolysis, which has been recently reinvestigated with an improved apparatus by E. S. Fetcher¹⁵ in this University. He has shown that while oxidation and reduction occur when a current is passed through a thin membrane (*e.g.*, of cellulose acetate) interposed between solutions containing oxidizable or reducible substances (provided there is a sufficient fall of potential between the two faces), there is this characteristic difference between the membrane and a metallic electrode, that in electrostenolysis (*e.g.*, in the oxidation of Fe^{++} to Fe^{+++}) the ratio of Faradays passed to equivalents oxidized is not unity but is typically of the order of some hundred to one. Allowing for this difference we may consider the conditions at a membrane and at an electrode as comparable; the two are alike in the respect that in both cases the chemical effect depends on the passage of current across a surface polarized to a sufficient potential. This similarity leads us to expect that the general quantitative conditions of electrical activation will be similar in the living tissue—where the primary effect of stimulation appears to be a chemical reaction at a membrane—and in the iron wire model. The electrostenolysis model is no doubt far simpler than the actual conditions in living tissues, but the same is evidently true of all physical (or conceptual) models of vital processes.

Intensity-Duration Relation in Passive Iron

When a constant current is passed between two passive iron wires immersed in a bath of nitric acid the chief general factors determining whether or not activation will occur are: (1) E. M. F. of current; this must usually be of the order of 1 volt or more for a regular effect; (2) density of current (*i.e.*, amperes per unit area of wire); (3) duration of flow; (4) concentration of acid; (5) temperature; and (6) interval since the previous activation of the same wire (*i.e.*, duration of recovery period). There are also factors depending on the special properties of the iron used; accidental peculiarities in the mosaic structure of the surface are a source of variation, since activation of the whole wire may result from a small local effect which is propagated; thus if any region has a greater than average susceptibility to reduction, the readiness with which the whole wire responds to an electric current is increased. Such local nuclei may be so small that in wires kept in dilute (*e.g.*, 10 v. per cent) HNO_3 a kinetic or statistical factor seems to enter, shown in a tendency to irregular spontaneous activation.¹¹ In single experiments such accidental factors may be of importance in determining the critical or "threshold" level (of

¹⁵ Fetcher, E. S., Ph.D. dissertation, A quantitative study of electrostenolysis, University of Chicago, 1934, shortly to be published.

intensity or duration) at which activation occurs; it is probably largely for this reason that reproducibility of behavior is found to be less perfect in iron wires than in living nerves or muscles under well controlled conditions.

Experiments have been carried out as follows:

In these experiments pure iron wire (the so called Armco brand) *ca.* 2 mm. in diameter was used.¹⁶ Two lengths of wire (anode and cathode in the experiment) are bent to an appropriate shape and attached to movable keys (*e.g.*, the Harvard cross-circuit type) supported on stands on either side of the vessel containing the acid; usually this was a flat-bottomed "finger bowl," 10 cm. in diameter and containing 300 cc. of acid. The wires were coated with paraffin¹⁷ except at their free ends which were straight and bare for equal lengths (usually 5 or 6 cm.); these were immersed (after passivation in strong HNO_3) horizontal and parallel to each other in the acid about 4 cm. apart. The area of metal exposed to the acid¹⁸ and the distance between the wires were thus constant during a series of experiments. Such an exposed length of wire remains permanently passive in strong nitric acid if undisturbed; on activation it shows a single brief reaction, with darkening and effervescence lasting, in 70 v. per cent HNO_3 at 20° , for about 1 second.

The keys supporting the wires were connected through a tube rheostat (for varying the potential) and pole-changer to a storage battery of four to six cells with a total E.M.F. of 6–9 volts. In each series of experiments currents of known E.M.F. (led to the wires from the rheostat) and known durations were passed through the circuit containing the passive wires. At any given E.M.F. it is found that the current must flow for more than a certain minimal length of time in order to activate the cathodal wire. For obtaining brief durations of current (from 0.5 to 30σ) a Lucas pendulum (vibrating spring interruptor) was used; this was calibrated by a ballistic galvanometer in the Physical Laboratory. It was found that for the greater part of its excursion the curve of vibration of such a spring corresponds closely to a sine curve. In a number of experiments the vibration rate of the spring was decreased by attaching weights; the time range could

¹⁶ The wire used in my previous study on rhythmical reactions (*J. Gen. Physiol.*, 1929, **13**, 1). It contains 99.8 per cent iron and less than 0.2 per cent carbon, according to analyses furnished by the manufacturers.

¹⁷ A wire unprotected by paraffin shows irregular action where it passes from the solution into the air.

¹⁸ A thin layer of wire is dissolved away at each activation and allowance must be made for this. At intervals during a series it is often necessary to repair the paraffin coating at its boundary with the bare wire; otherwise acid enters between paraffin and metal and sets up irregular or rhythmical action.

thus be lengthened to *ca.* 90σ . For still longer durations of current, up to 1.3 seconds, the spring of the Lucas apparatus was removed and the two keys (respectively opening the cross-circuit between the passive wires and breaking the battery circuit) were actuated by a rigid arm attached to a uniformly rotating axis with a period of 20 seconds, operated by an electric motor and gearing.

In any typical series of experiments the least duration of current was determined at which each wire, with the rheostat placed at a known potential, showed regular activation. Conditions of temperature, concentration of acid, length and thickness of the exposed wire, and duration of recovery period (interval since the previous activation of the same wire) were kept uniform. In most cases the current was passed between the wires at regular intervals of 30 seconds, the pole-changer being reversed after each current; the interval between successive "stimulations" of the same wire was then exactly 1 minute. In 70 v. per cent HNO_3 (at 20°) recovery is almost complete after this interval. The threshold condition for each wire, with each potential used, is given by the least duration at which the wire responds to the current every time in several successive trials. If the duration is decreased still further (*e.g.*, from 7σ to 5.7σ in some of the experiments summarized in Table I), it frequently happens that the wire responds regularly at every *alternate* passage of the current, *i.e.* with a recovery period of 2 minutes but not of 1 minute, indicating a slight increase in responsiveness during the second minute of recovery. Conversely, if the recovery period is shortened, *e.g.* to $\frac{1}{2}$ or $\frac{1}{3}$ minute, the required duration of the activating current is correspondingly increased. The course of the recovery curve can thus be followed (*cf.* Table III).

A typical example of a series of determinations carried out in this manner is given in Table I.

The third column of Table I gives for both wires the product of the intensity (taken as proportional to voltage) into the least effective duration of current (it); the fourth column gives the product of the intensity into the square root of the duration ($i\sqrt{t}$), in accordance with Nernst's well known formula. It will be noted that the Nernst product shows for the first five or six determinations a fair approach to constancy; afterwards it falls off, and with the weaker and more prolonged currents (omitting Experiment 9) the direct product, it , is more nearly constant. This behavior has been found typical in a large number of experiments. When the current is still further decreased activation tends to be delayed so that both products increase again; with further decrease the response becomes irregular or fails. Values corresponding to the physiological concepts of rheobase and chronaxie can be estimated from the course of the intensity-duration

TABLE I

Six storage cells; temperature 21°; 70 v. per cent HNO₃. Length of exposed portions of wire 6 cm. Recovery interval 1 minute.

E.M.F. of activating current (per cent of total rheostat potential)	Least effective duration of current (σ)		i		$i\sqrt{i}$	
	Wire A	Wire B	Wire A	Wire B	Wire A	Wire B
(1) 90	7.0	7.5	630	685	238.5	243
(2) 80	9.2	9.5	736	760	244.0	248
(3) 70	11.3	12.0	791	840	235	242
(4) 60	12.7	15.1	762	906	213	234
(5) 50	16.6	19.0	830	950	205	218
(6) 40	22.8	27.0	912	1080	190	208
(7) 30	30.1	33.3	903	1002	165	173
(8) 25	40.8	53.4	1020	1445	160	183
(9) 20	ca. 92.0	ca. 92.0	1840	1840	192	192

FIG. 1. Intensity-duration curves for wires A and B of Table I. Ordinates, voltages in percentage units; abscissae, durations of current in σ .

curve (Fig. 1); their precise magnitudes vary with the conditions of the experiment (concentration of acid, area of wire, resistance of circuit, etc). In the above series the rheobase for wire B would be approximately 1.5 volts and the chronaxie 30σ ; the former value is clearly an arbitrary one, determined by the steepness of the potential fall between the wires under the special conditions of the circuit.¹⁹ The potential between active and passive wires in 70 v. per cent acid, as measured with a voltmeter, is *ca.* 0.7 volt; this is greater than the decomposition potential of passive iron, as is shown by the automatic transmission of activation waves.

Extrapolation of the intensity-duration curves in Fig. 1 indicates a rheobase of between 15 and 20 (in the percentage units of Table I) for the two wires, wire A being consistently somewhat more responsive than wire B. Since, as already pointed out, the two opposing factors assumed in Blair's¹³ discussion of electrical stimulation are actually present in the iron wire system, it is of interest to plot the data in accordance with his formula²⁰

$$\log \frac{V}{V - R} = Kt + C$$

(where V is applied voltage, R voltage of rheobase, t duration of current, and K and C constants). On semilogarithmic paper the data fall with fair accuracy along a straight line when the rheobase is taken as either 17.5 or 15. Wire A shows a somewhat better fit with $R = 15$, wire B with $R = 17.5$ (Fig. 2).

The precise value of the constants under the conditions of these experiments has no special significance, but it is a matter of general interest that the form of the intensity-duration curve is so closely similar to that found in irritable tissues. In a large number of similar

¹⁹ The P.D. between the wires, with constantly flowing current, would be proportional to the ratio of the resistance of this part of the circuit to the total resistance.

²⁰ Hill, A. V.,⁹ p. 59, reaches a similar formula, $\log (1 - \frac{R}{C}) = Kt$, from consideration of a condenser type of model, and shows that it conforms accurately to recent data of Rushton on frog's nerve (Rushton, W. A. H., *J. Physiol.*, 1932, **75**, 445).

experiments the Nernst formula has been found to give a good agreement with observation for currents of brief duration (from 2σ to 12 or 15σ); but with longer durations the agreement is less satisfactory (*cf.* Tables I and II). Ebbecke⁸ has shown that the process of simple polarization by a constant current, as illustrated by the charging of a

FIG. 2. Semilogarithmic diagrams showing linear relation of $\log \frac{V}{V-R}$ to durations. V , voltage in percentage units of Table I; R , rheobase, taken as 15 for wire A, as 17.5 for wire B; t , durations of current in σ .

condenser, conforms approximately to Nernst's square root formula within a considerable range of potentials, but that above and below this range it has no application. In the case of the iron wire an agreement with the Nernst formula might be expected with the briefer and stronger currents, in which it seems likely that a relatively large fraction of the total duration of current flow is occupied by the process of polarization. After polarization has reached the critical

level required, activation would occur rapidly or instantaneously with strong currents; while with weaker currents the flow of current would continue for a relatively longer time before an activating degree of reduction is attained. During this second period, following the preliminary polarization, the degree of reduction may be regarded as proportional to the product it , as required by Faraday's law of electrolysis. We may thus account for the falling off of the Nernst product $i\sqrt{t}$ with the longer and weaker currents and also for the approach to constancy in the product it during a certain limited range of longer durations. As already pointed out, if the current is still further weakened, the opposing oxidative action of the HNO_3 prevents the

TABLE II
Conditions Similar to Those of Table I. Three Storage Cells

E.M.F. of activating current	Least effective duration (σ) of current in HNO_3 of			$i\sqrt{t}$		
	80 v. per cent	70 v. per cent	60 v. per cent	80 v. per cent	70 v. per cent	60 v. per cent
<i>per cent</i>						
87.5	6.3	3.1	1.9- 2.3	219	154	122-134
75	8.4	4.3- 4.6	2.7- 3.1	217.5	155-160	124-132
62.5	9.6	6.7- 7.2	4.7- 5.5	194	162-167	135-141
50	12.6	9.3- 9.7	7.2- 7.6	175	152-156	134-138
37.5	17.6	13.9-14.4	ca. 9.6	158	140-142.5	ca. 116
25	(No activa- tion)	1 second or more	18.5-19.5			ca. 105

disruption of the film from ever reaching a stage sufficient to start an activation wave. The region of sub-threshold intensities is then reached, the upper limit of which is determined by the conditions (concentration of acid, etc.) already defined.

Influence of Concentration of HNO_3

For brief durations of activating current the product $i\sqrt{t}$ may be taken as a measure of the resistance of the system to activation. This product shows a characteristic increase with increase in the concentration of acid, as shown by Table II. In these experiments wires were activated, under otherwise uniform conditions, in HNO_3 of the three concentrations, 60, 70, and 80 volumes per cent.

For durations of less than 10σ the average values of $i\sqrt{t}$ in the three concentrations of HNO_3 are approximately: for 80 v. per cent, 210; for 70 v. per cent, 160; for 60 v. per cent, 130. Since the conductivities increase with concentration of acid, the differences in responsiveness are somewhat greater than these figures represent. The interpretation of these results has already been indicated; increasing the concentration of HNO_3 increases the intensity of the oxidative or passivating action which opposes activation.

Influence of Duration of Recovery

In the experiments of Tables I and II the interval between the successive activations of each wire (the period of "recovery") was uniformly 1 minute. The relation between the duration of the re-

TABLE III

Exposed lengths of wire 6 cm. 70 v. per cent HNO_3 . Temperature 21° . Voltage of activating current constant throughout (four storage cells; 5.7 volts).

Interval since previous activation	Minimal duration of activating current (σ)
<i>sec.</i>	
120	12.7
60	13.8
30	25.2
20	39.0

covery period and the readiness of activation by a current of constant intensity is shown in the experiments of Table III. In these experiments the intervals between the successive activations of each wire were varied between 20 seconds and 2 minutes.

With 20 seconds of recovery the critical duration for activation is three times as long as with 2 minutes; after this interval recovery may be regarded as complete. Since the time occupied by the polarization process is presumably constant in all experiments, we may infer that the critical degree of reduction required for activation is several times greater in a wire exposed to the current immediately after activation than in the same wire after complete recovery. The most probable assumption is that the oxide film is relatively thick immediately after repassivation, and later becomes thinned to a constant thickness

(possibly monomolecular) by the solvent action of the acid.¹¹ In this progressive change of the system from a resistant state to a state of maximum alterability (corresponding to an equilibrium or "resting" state) there is an evident parallel with the change in an irritable tissue during the relative refractory period. In both cases the change in responsiveness is to be ascribed to a change in the properties of the surface layer. In the living system some structural or chemical change in the plasma membrane depending on metabolism is apparently involved, but its precise nature is unknown.

Influence of Surface-Active Substances

The presence of surface-active compounds also decreases the responsiveness of the iron wire to the electric current and correspond-

TABLE IV

Conditions as before. HNO_3 70 v. per cent. Temperature 21° . E.M.F. 6 volts.

Concentration of amyl alcohol	Minimal duration of activating current (σ)
<i>vols. per cent</i>	
0 (control)	7.2
0.25	8-9.6
0.5	10.5-12.1
0.75	13.8-16
1.0	21.2
1.5	24.0-25.7
2	ca. 24.0

ingly decreases the rate of transmission; the latter effect is especially marked during the early part of the relative refractory period. For example, in steel wires immersed in 70 v. per cent HNO_3 containing 0.5 v. per cent amyl alcohol the speed of transmission, after 3 minutes recovery, was found to be only 30 per cent of that shown by the control wire in pure 70 v. per cent HNO_3 . Such compounds also delay and may even entirely prevent the automatic repassivation. Changes in surface conditions, dependent on adsorption of the compound, undoubtedly underlie all such effects. In general, the effectiveness of such compounds increases with their surface activity. So far, however, no conditions have been found under which a surface-

active compound entirely prevents (although it may greatly delay) the transmission of an activation wave. In this respect the parallel with narcosis is incomplete.

Table IV illustrates the manner in which the minimal duration of an activating current is prolonged by the addition of amyl alcohol.

Since the amyl alcohol is rapidly oxidized under these conditions the delay in activation is to be attributed chiefly to the caproic acid which is formed. Butyric acid added to nitric acid acts similarly, although less effectively in equivalent concentrations. These effects are completely reversible on returning the wire to pure nitric acid. Acetic acid has little or no effect, even in much higher concentrations.

Activation by Break of Constant Current

When a constant current flowing through an irritable tissue is interrupted there is a stimulation (the "break" response) having all the characteristics (such as polar reversal) of stimulation by a polarization current. The polarized surfaces are those of the plasma membranes of the irritable elements, and the circuit is completed through the protoplasm and the interstitial fluids. An analogous activation on break of a constant current is also readily demonstrated in the passive iron wire, but only under somewhat special conditions. If we employ the usual arrangement, consisting of a battery of several storage cells connected through a key to a tube rheostat from which wires lead to the two passive wires in 70 v. per cent HNO_3 , we observe in closing the circuit, with a P. D. of 1 to 2 volts, the usual immediate activation of the cathodal wire followed by the automatic return to the passive state. On opening the circuit, however, nothing happens in the anodal wire, although it is now the cathode of the reversed polarization current; under these conditions the intensity and duration of this current are insufficient for activation. If we increase the polarizing potential, by moving the contact further along the rheostat, we increase correspondingly the resistance to the polarization current through the rheostat wire, and also increase the "anelectrotonic" stabilization of the anodal wire; both these conditions are unfavorable to activation by the polarization current and none occurs. The passive wire can, however, be made sufficiently "sensitive" to respond

to the polarization current by decreasing the concentration of the nitric acid, but if this is done another difficulty enters. In acid of less than 50 v. per cent concentration the activated wire does not undergo spontaneous repassivation, but remains continually active. Hence if it is in the same circuit with another passive wire, the latter, being cathode, is automatically activated by the current of the couple formed by the two wires, unless other conditions are present to prevent. For example, the anodal wire may be kept passive by anodal polarization, with sufficient intensity of current; but although this wire at once becomes active when the polarizing current is broken, this activation is an effect not of the polarization current but of the current of the couple formed by the two wires. In general, when one of two passive wires, immersed in nitric acid and connected with each other through a low resistance, is activated directly, *e.g.* by scratching with glass or touching with zinc the other wire immediately becomes active also ("distance action" effect).¹⁴

This difficulty can be removed by substituting a platinum electrode for one of the passive iron wires and making this electrode the cathode of the polarizing current. Wire and electrode are immersed in 25 v. per cent (or weaker) HNO_3 . During the flow of the polarizing current the passive wire remains bright and unchanged, with oxygen bubbles forming on its surface. Then, on breaking the current, the wire, being now the cathode of the polarization current, is at once activated. A simple arrangement suitable for demonstration consists of two dry cells connected through a pole-changer to the keys supporting the passive wire and the platinum electrode; connected also to these keys is a dial resistance forming an adjustable shunt. With a moderate resistance (of 1 to 100 ohms) in the shunt the iron wire (as anode) remains passive while the battery circuit is closed. On breaking the circuit the wire is instantly activated. The necessary conditions are that the polarization potential should be sufficient and that the resistance to the polarization current should not be too high. If the shunt resistance is too low the current through the nitric acid between the platinum and the wire does not polarize the latter sufficiently, while if it is too high the polarization current is too weak to be effective.

GENERAL DISCUSSION

It seems clear that the various resemblances of behavior between the passive iron wire and the irritable living system (cell or axon) are to be referred to one special structural feature common to both systems, namely the presence of a thin, impermeable, electrically polarizable and chemically alterable surface layer or film. In both systems some critical chemical (or electrochemical) reaction occurs when the polarization of this layer is altered sufficiently (in one direction) and maintained at the altered level for a certain time. During this time an electric current passes across the surface; the flow of this current is attended with chemical decomposition and structural change in the film; as a result the system as a whole is activated.

In the iron wire in strong nitric acid the essential chemical events associated with the transmission of an activation wave are a reduction followed immediately by an oxidation; the former reaction disrupts the film, the latter restores it. Two reactions, opposed in their chemical character and physical effect, are thus identifiable in this system; and the facts of electrical activation cannot be understood without taking both reactions into account. Cathodal reduction, on which activation depends, is resisted by the oxidative action of the surrounding nitric acid; this action increases with concentration; and correspondingly the required intensity and duration of the activating current also increase. A further constant condition is that any region of the iron surface as it becomes active becomes also anodal; the resulting anodal oxidation is an additional factor opposing activation and tending to bring the reaction to rest. Under certain conditions this local anodal action may be sufficiently intense to prevent the active state from spreading; thus small active areas made by scratching a passive wire are repaired automatically (*i.e.*, repassivated) without giving rise to activation waves.^{1, 10, 14} In general we must conceive the process of activation in strong acid as always occurring against the resistance of a counter-reaction, which develops coincidentally with the activation and tends to restore the passive state. This is why the local reaction of activation is automatically self-limiting; one electrochemical reaction reverses or repairs the changes

produced by the other. The contrasted character of anodal and cathodal reactions is obviously the basis of the law of polar activation in the passive iron system, as well as of the phenomena of interference and reinforcement, resembling electrotonus, mentioned at the beginning of this paper.

Conditions of a closely analogous kind appear to exist in the irritable living system, although we must be on our guard against pushing the analogy too far,²¹ since every model, including a mathematical one, is at best an approximation, and certain inconsistencies are inevitable. Nevertheless, the general resemblances seem to imply that when we stimulate electrically the living irritable system (*e.g.*, muscle cell or nerve axon), the critical electrically controlled reactions—which we picture as occurring in the thin polarized layer of protoplasm immediately inside the cell boundary—are similarly contrasted in their general chemical character at the regions where the current enters and leaves the cell. If we regard the cell surface as an electrode surface and the protoplasmic layer immediately inside this surface as the solution in contact with the electrode, we should expect, on general electrochemical principles, that a current (positive stream) passing from cell surface to protoplasm would have an oxidizing action on the adjacent protoplasmic molecules; while at the regions where the direction of current is reversed the electrochemical effect would be reducing.²² From this point of view the general electrochemical conditions would be similar in the protoplasmic system and in the passive iron model, regions of reduction corresponding to those where activation is initiated, and regions of oxidation to those where activation is arrested and the resting state restored. The general physical conception of an activation wave, disregarding the details of the chemical changes involved, would thus be the same for both systems. Other characteristic physiological conditions, such as

²¹ Hill has recently issued a warning against this, and I am in sympathy with the general tenor of his remarks—with certain reservations as to detail (*cf.* Hill, A. V.,⁹ p. 47).

²² The conditions in electrostenolysis are similar, oxidation occurring at the surface of the membrane facing the cathode; *i.e.*, where the positive stream passes from membrane to solution.

the importance of oxygen and of anodal polarization²³ in the recovery of nerve, lend support to this view.

This is perhaps as much as can be said with any justification at present; and it would be premature to interpret the facts of nerve metabolism during activity, so far determined, in terms of the alternating reduction and oxidation of special compounds present in the surface film of the excited area.

SUMMARY

1. The relation between the E. M. F. and the minimal duration of an activating current has been determined for passive iron wires in nitric acid under varying conditions of concentration of acid, duration of recovery period, and presence of surface-action compounds.

2. The characteristic intensity-duration curves resemble those of irritable living tissues with moderate speeds of response to stimulation (with chronaxies of the order of 10 to 30 σ).

3. The intensity of the current required for activation, as well as its minimal effective duration for a given intensity, increases rapidly with increase in the concentration of HNO₃.

4. The responsiveness of the iron wire to brief currents is low immediately after activation and returns progressively to the original level during the immediately following period, at first rapidly and then slowly, following a time curve resembling the corresponding curve of living tissues during the relative refractory period.

5. Surface-active compounds decrease reversibly, to a degree dependent on concentration, the responsiveness of iron wires to brief currents.

6. Conditions are described under which the iron wire is activated by the break of an already flowing constant current.

²³ Woronzow, D. S., *Arch. ges. Physiol.*, 1924, **203**, 300.