

THE NATURE OF PROTOPLASMIC AND NERVOUS TRANSMISSION¹

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One of the many remarkable peculiarities of the living system—perhaps the one that impresses us as the most distinctively *vital*—is the regular and rapid transmission of metabolic and functional influence between its different parts. In all higher animals tissues and organs which are widely separated and apparently unconnected except by narrow tracks and strands of protoplasm are observed to exert a profound influence upon one another's activity; and it is a familiar fact that slight changes in the surroundings may, by acting as "stimuli," instantly alter the whole behavior of the organism. Thus we poke or stir an apparently dead animal to see if it is alive. Such facts show at once that the transmissive agency, whatever its essential nature, is independent of the transport of material between the regions affected; in this general respect the transmission of physiological influence in living matter resembles the transmission of sound, light, wave-motion or electricity. And since all vital processes are dependent on chemical reactions, we may say that living matter exhibits in a high degree the power of chemical action at a distance.³ This property is not confined to special organisms, tissues or cells; apparently all forms of protoplasm transmit influence in this manner, though in varying degrees and at different rates. Its fundamental biological significance is apparent, since it is the chief means of controlling and coördinating the various separate functions and activities of the organism—a necessary condition of continued life. Transmission of this kind reaches its highest development in the nerves of higher animals; the conduction of states of nervous excitation has been the most fully studied

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³ Ostwald: "Chemische Fernwirkung," *Zeit. phys. Chem.*, **9**, 540 (1891).

phenomenon of this class, and the nature of the nerve-impulse has long been one of the traditional problems of physiology.

Nervous transmission, however, is only one specialized case of the more general process—which is perhaps best called “protoplasmic transmission.” This process is illustrated whenever the organism or one of its parts, or even a single cell, responds as a whole to a localized stimulus; some “physiological” influence is transmitted from the original point of stimulation to more or less distant regions of the living system, and either arouses these into activity or changes their already existing activity. Thus, to give a familiar illustration, if we touch or otherwise stimulate a *Paramecium* at one point, there follows instantly a temporary reversal of the ciliary stroke over the whole surface, as a result of which the animal stops and swims backward; it then turns and swims forward again in a different direction; the whole sequence of movements constituting a well-defined normal feature of its behavior, the so-called “motor reaction.” This is a typical case of stimulation; evidently the direct action of the stimulating agent is to cause some local alteration in the surface-layer of protoplasm, and in some manner this initiates a disturbance which is propagated rapidly over the whole surface and alters everywhere the activity of the motile surface-structures or cilia.

It is especially significant that this effect follows a slight change in the *surface* of the cell; since there is much evidence that alteration of the protoplasmic surface-layer forms the essential condition of many if not all cases of protoplasmic transmission. Chambers has found that when a red blood-corpuscle is touched locally by a capillary needle, the whole cell undergoes rapid dissolution; the first visible effect is the diffusion of haemoglobin into the surroundings, not only at the point of contact with the needle, but over the whole surface.¹ Evidently some physical alteration of the surface-

¹ R. Chambers: Proc. Am. Assoc. Anatomists, 1915 (abstract in Anat. Record, 10, 190 (1916); cf. also Science, 40, 625, 824; and 41, 290 for other observations.

film, associated with loss of semi-permeability, is transmitted over the cell-surface. Similarly, a leucocyte locally punctured or cut undergoes rapid disintegration. These experiments well illustrate the remarkable structural instability of many forms of protoplasm. Blood-corpuscles especially are often extremely sensitive to mechanical contact or other local change of condition; and this property is so highly developed in certain blood-cells (*e. g.*, of Crustacea), that they have received the name of "explosive corpuscles" from the suddenness and completeness of their breakdown; the platelets of mammals exhibit a similar behavior. Changes of activity produced by local physical or chemical alteration in irritable cells have also a marked tendency to spread and to involve the entire cell, so that it reacts as a whole; and there is undoubtedly a common basis for the transmission in all of these cases, although normally stimulation, unless carried to excess, has no evident destructive effects. A muscle-cell stimulated at one end undergoes contraction as a whole; it is impossible in a normal cell to localize the contractile activity, which is instantly transmitted from one end to the other. Hence such a cell exhibits the peculiar type of response called "all or none," responding either completely or not at all—a form of behavior which (we may note in passing), although highly characteristic of irritable living elements, is by no means confined to these but is found also in many inorganic systems which readily conduct chemical disturbances, *e. g.*, explosive mixtures or compounds. Another interesting instance is the transmission of a peculiar structural and chemical change over the surface of the eggs of many animals during fertilization, starting from the point of entrance of the spermatozoon. This phenomenon has recently been demonstrated with great clearness by Just in the sand-dollar egg.¹

Finally, many of the processes of so-called "physiological correlation" in animals and plants, by which growth or physiological activity in one region influences or controls similar processes in other and often distant regions, appear

¹ Just: *Biological Bulletin*, 36, 1 (1919).

to be based upon transmissions of the same essential kind. Cases of form-regulation or other structural changes due to transmitted influences are often attributed to the transport of special material substances or hormones; but this form of explanation, while it has been shown experimentally to hold true in certain cases, by no means applies to all. For example, the effect of severing a nerve-trunk near its origin is to produce highly characteristic metabolic and structural changes at the periphery; these so-called "degenerative" changes occur too rapidly to be accounted for as due to the transport of substances along the axone. Apparently the maintenance of normal structure and functional capacity in this tissue are dependent upon some influence transmitted from the nerve cells in the central nervous system; this influence is comparable with that seen in the dependence of the normal tone and nutrition of a muscle upon its innervation. The alteration in the structure of a gland-cell, following stimulation of its innervating nerve, is another instance of a similar kind. Other related cases are seen in lower animals like planarians and hydroids, where growth and formative processes in development and regeneration are normally carried out under the control or dominance of the most rapidly growing parts of the organism, usually the anterior or apical regions. Many such instances have recently been brought forward by Child, who has referred the transmission of this peculiar "trophic" influence not primarily to a transport of material between the regions concerned, but to some kind of transmitted effect or activity comparable with the nervous.¹ But evidently reference to a nervous or "neuroid" influence does not "explain" phenomena of this kind; it merely places them in the same class with the phenomenon of nervous activity which, familiar as it is, is only one special instance of a more fundamental property or mode of action which is universal in living protoplasm. There is little doubt that all of these different forms of transmission are to be regarded from the same general

¹ Cf. C. M. Child: "Individuality in Organisms," University of Chicago Press, 1915.

point of view, as examples of protoplasmic transmission, *i. e.*, transmission of physiological influence without accompanying transport of material—what may be called “physiological distance-action.”

It is interesting to note that inhibitory as well as excitatory influence may be thus transmitted; for example, growth in one region of an animal or plant frequently inhibits or prevents growth in adjacent regions; this influence is of great importance in the correlation of development or other morphogenetic processes, and undoubtedly plays a great part in the control and regulation of normal ontogeny and regeneration. Similarly, functional activity in one region of an organ may inhibit or prevent activity in another region of the same or a different organ; this is notably the case in the central nervous system, where the neurones innervating antagonistic muscle groups have a reciprocally inhibitory influence on one another's activity. The same kind of reciprocal influence is seen in other tissues, *e. g.*, in peristaltic movement (“myenteric law”), and apparently is usual in conducting elements like nerve-fibers.

Now it seems unlikely that a phenomenon so universal in organisms—one on which so many of their most characteristic activities depend, especially in animals—should be entirely confined to living matter; it is rather to be assumed that processes of the same essential nature are present also in non-living matter. Such a conclusion is implied by evolutionary theory, and if it is granted the question becomes: what is the general type of physico-chemical process to which protoplasmic transmission belongs, as a particular and highly specialized instance? The essential or general basis for conduction-processes of the protoplasmic type must exist in some form in inorganic processes, and our problem is to determine what type of inorganic system presents phenomena of the same fundamental kind, and under what conditions they are manifested.

In considering the physico-chemical nature of the physiological conduction-process it seems desirable to dissociate it

as completely as possible from associated and dependent processes of other kinds; and accordingly the special conducting tissue, nerve, in which this dissociation has apparently been accomplished by nature, is the one upon which most of the exact studies of protoplasmic transmission have been made. I shall therefore discuss more especially the conditions in this tissue. These conducting protoplasmic strands, which everywhere pervade the organism in higher animals, transmit excitatory, inhibitory and controlling influences with extraordinary quickness, regularity and dependability. They arise in development as outgrowths from nerve-cells, and in accordance with this mode of origin they must be regarded as possessing the general properties of irritable living protoplasm in addition to—or in correlation with—their own specialized peculiarities as conducting elements. Hence we may consider the conditions under which a nerve is stimulated and conducts stimuli as representing the fundamental conditions of protoplasmic excitation and transmission in general; and these conditions, as well as the constant features of the changes undergone by the nerve itself during transmission, have been determined in great detail by the labors of a long series of investigators. The essential generalizations established by this work may be stated thus briefly: (1) The excitation-state may be aroused or initiated by a variety of means, including mechanical, chemical, thermal, and especially electrical; a high degree of electrical sensitivity is universal in conducting tissues. (2) Once aroused the excitation-state is transmitted automatically from one region of the tissue to the next adjoining; in this manner the active state is propagated continuously along the tissue to any distance without evidence of decrease in intensity. This implies that some process associated with the local activity has the effect of initiating similar activity in adjacent regions. (3) The local process ceases when stimulation ceases, *i. e.*, it is automatically self-limiting, the tissue returning quickly to the resting state; after a brief interval of lowered excitability (refractory period) it may be again stimulated as before.

(4) The rate of transmission exhibits a wide range of variation in different tissues and organisms—from a few centimeters per second to 100 meters or more per second. Under normal conditions and at a definite temperature the rate is constant and specific for each tissue and each organism. (5) This velocity is in any single case dependent on temperature, showing a temperature-coefficient like that of most chemical reactions at ordinary temperatures ($Q_{10} = 2$ to 3); *e. g.*, in the frog's sciatic nerve the rate at 10° is *ca.* 15 meters per second, at 20° *ca.* 30, and at 30° *ca.* 60 meters per second. This fact implies a dependence of the whole transmission-process on some kind of chemical or metabolic change in the tissue. (6) Transmission may also be influenced reversibly by chemical substances; in particular it is readily decreased in rate or prevented by lipoid-solvent or lipoid-soluble substances and certain salts (especially K, Mg, Ca, Sr, etc.); also by electrically polarizing the conducting elements by an externally applied current (electrotonus). (7) It is unaccompanied by change of form, by evident change of temperature, or by optical change; but is invariably associated with a change of electrical potential in the conducting tissue, the active area becoming temporarily negative (to the galvanometer) by a P. D. of *ca.* 30 to 50 millivolts relatively to the inactive areas. This variation of potential travels at the same rate as the activation-wave, and undoubtedly forms an integral part of the latter.

The question now arises as to the general physico-chemical nature of a transmitted activity having these characteristics. Can we characterize it more definitely than as a "molecular change"—a once favorite expression in the text-books? First of all it is important to note that the excitation-wave on reaching the terminal organ, *e. g.*, muscle, affects the latter in a manner which can be closely simulated artificially only by stimulation with the electric current, especially the interrupted current. This fact in itself suggests that what is really transmitted to the muscle is some form of electrical influence and that the stimulating effect is essentially an

electrical effect. There are various reasons for attaching chief importance to the electrical factor in the transmission-process. Sensitivity to electric currents is a universal property of living protoplasm. We find also that in its normal activity living matter gives rise to electric currents in the surroundings. Both of these fundamental discoveries date from the time of Volta and Galvani. It is therefore not surprising to find the suggestion made at different times in the history of physiology that the active region in a conducting nerve may stimulate the adjacent resting region *electrically* by means of the bio-electric current formed at the boundary between the two regions, and that transmission is due to this local electrical stimulation. The active region is negative relatively to the adjacent resting region, so that a circuit is formed between the two. Just as the action-current of one muscle may stimulate another muscle to contract, so the local action-current produced when one region of a nerve enters activity may be sufficiently intense to excite the adjacent resting regions. It is readily conceivable that in this way the excitation-state might be transmitted from active to resting regions. We know that the nerve is sensitive to weak electric currents, and also that such currents arise whenever the tissue becomes active. This general hypothesis thus seems a consistent one, and recently it has again been brought forward and attempts to test it experimentally have been made by several physiologists, including especially the late Keith Lucas, perhaps the most ingenious and exact of recent experimenters in this field. In his Croonian Lecture of 1912¹ Lucas points out that since the electric disturbance is an invariable concomitant of the excitation-wave, it is possible that the two are in reality identical, and that the disturbance of electric potential at one point in a nerve may be the actual and direct cause of the same phenomenon in a neighboring part; and he has brought forward various facts favoring this hypothesis. The majority of physiologists, however, have apparently continued to regard the electric variation as a mere by-product of the

¹ Keith Lucas: "Croonian Lecture," Proc. Roy. Soc., 85B, 507 (1912).

excitation-process and not as playing in itself any essential rôle in transmission.

Let us now briefly review the chief general facts indicating that the local bioelectric current accompanying local stimulation is the essential factor in the spread of stimulation to adjoining regions of the irritable tissue. On examining the electric current accompanying activity in a conducting tissue like nerve we find that its direction of flow and other chief characteristics—intensity, duration, rate of development—are such that the above hypothesis receives decided support. A current flows between the active region of the tissue (AA) and the adjoining regions (BB) which at the time under consideration are still in a state of rest (see Fig. 1).

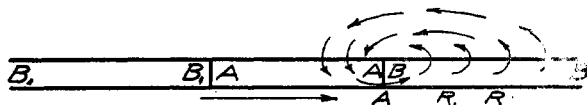


Fig. 1

In this diagram the area AA represents the region of the nerve-axone which is active, or occupied by the excitation-wave, at the instant under consideration; its length in a frog's motor nerve at 20° is about 6 cm. The wave is regarded as moving in the direction of the large arrow. The region now undergoing secondary electrical stimulation by the local action-current between regions A and B extends to the distance AR (ca. 3 cm) beyond the wave-front. The direction of the current (positive stream) in part of the local circuit is indicated by the small arrows. The region (B₁B₁) immediately behind the excitation-wave is temporarily in a refractory state.

This current is the so-called action-current; the local bioelectric circuit between regions A and B may be called the "active-resting circuit." Observation shows that the current (positive stream) of this circuit invariably *leaves* the tissue at the inactive or resting regions and *enters* it at the active region; this is what is meant by the usual statement that the active region is *negative*, or that a "negative variation" accompanies activity. Now when we study the conditions under which an external electric current led into the tissue from a battery causes stimulation, we find that stimulation always originates at the region where the positive stream of the stimulating current leaves the tissue, *i. e.*, at the negative

electrode; while at the positive electrode, where the current enters the tissue, there is the reverse effect of inhibition or decrease of irritability. This characteristic "polar" condition is found in the great majority of irritable tissues, and is known as the "law of polar stimulation;" in general, anode and cathode have opposite physiological effects upon irritable and other living systems. It is clear, therefore, that wherever in the resting region (B) the current of the bioelectric circuit has sufficient local intensity, it will have a stimulating effect, *i. e.*, will initiate a new state of activity, while at the active region itself (A) its influence will be inhibitory or will tend to cut short activity. Now the very fact which we are trying to explain is that whenever any local region (A) of a conducting tissue like nerve is made to enter excitation—by whatever means, normal or artificial—a similar state of excitation, after a brief interval, appears in the resting area (B) adjoining A and disappears from A itself; *i. e.*, a wave of excitation appears to be transmitted from A to B; B upon thus becoming active repeats this effect upon regions beyond; and in this manner a wave of activity travels along the tissue. All of the characteristics of the activity thus transmitted are those which we should expect to find if the bioelectric current were in fact the condition of transmission. It is a well-established fact that the action current of a tissue like muscle or nerve is amply capable of stimulating another portion of the same tissue. The stimulation of one muscle by the action-current of another is a simple and frequently performed experiment; if the two muscles are in close contact and one is stimulated through its nerve the other contracts, and a similar experiment can be performed, though less readily, with nerve. Thus both the observed intensity and the direction of the action-current are consistent with the hypothesis that the local bioelectric current, when it is brought into existence by stimulating one region of the conducting tissue, itself stimulates the adjoining regions. By a repetition of this effect at each active-resting boundary as soon as it is formed the state of excitation may be transmitted along the tissue

for a distance which may be indefinitely great if the tissue is normal in its condition and uniform in its properties throughout its length.

The question now arises whether this hypothesis explains the other characteristic features of the excitation-wave, and especially the high velocity which it attains in the motor nerves of warm-blooded animals. Evidently if we are to have rapid transmission by the above means the local bioelectric current must rise quickly to an effective strength and its stimulating influence must extend for a sufficient distance beyond the region immediately active. The fact is, however, that in rapidly conducting tissues like nerve the rise of the bioelectric current to its maximum at any point is very rapid, occupying about 0.001 second in the frog's motor nerve at 20°. Moreover the tissue is extremely sensitive to weak electric currents; two platinum electrodes differing in potential by 20 millivolts and placed three centimeters apart or even more will stimulate; this P. D. is less than that normally existing between the active and the resting areas of the nerve. The intensity of the normal action-current where it traverses the nerve at a point 3 centimeters distant from the active-resting boundary must be about the same as at a stimulating electrode in the above experiment, since the P. D. and the resistance of the two circuits are similar. Now it is evident that the current of the active-resting circuit is most intense near the boundary between the active and the inactive regions, for the simple reason that the local intensity of the current is determined (in accordance with Ohm's law) by the P. D. and the total resistance of the circuit, and this resistance is directly proportional to the distance between the two areas of unequal potential. Hence near the active-resting boundary the current will be relatively intense, and beyond a certain critical distance from this boundary (AR in diagram) it will be too weak to stimulate. But if the stimulating influence extends for only 3 centimeters beyond the boundary, the speed of development of the bioelectric current is great enough (and the latent period of stimulation

brief enough) to account for the actually observed rate of transmission in nerve. In the frog's sciatic nerve the time occupied by the rising phase of the bioelectric variation (*i. e.*, from zero to its full intensity of 30 to 40 millivolts) is about 0.001 second at 20°, the whole variation lasting about 0.002 second; if the current on reaching its full intensity stimulates the adjoining resting region at all points up to a distance of 3 centimeters from the active-resting boundary, stimulation will be initiated at a point 3 centimeters in advance of the active area at a time 0.001 second later than at the active area itself. The local response thus secondarily evoked is of full intensity—*i. e.*, is the same qualitatively and quantitatively as at the original active area, since the tissue reacts on the "all-or-none" principle—hence there is no change in the intensity or other characters of the excitation-wave as it progresses by a repetition of this process at each new active-resting boundary. But a transmission of 3 centimeters in 0.001 second is 30 meters in one second. This is the observed velocity of transmission at this temperature. Observations on the influence of temperature on both processes confirm this interpretation. Raising the temperature 10° doubles the rate of the bioelectric variation; at the same time it doubles the rate of propagation of the nerve-impulse. Lucas has found a constant proportionality between the rate of the local change of potential in muscle and the speed of the contraction-wave at different temperatures.¹ With a temperature-coefficient (Q_{10}) of 2, a velocity of 30 meters per second at 20° would be equivalent to one of 120 meters per second at 40°.

In general we find a close correlation between the local rate of development of the action-current in different conducting tissues and the speed of propagation of the excitation-wave.² Further it is remarkable that tissues with rapidly

¹ K. Lucas: Jour. Physiol., 39, 207 (1909).

² In Am. Jour. Physiol., 34, 484 (1914) I have given a table showing the relation between speed of transmission and local rate of development of the bioelectric variation in a large number of different tissues and organisms.

developing action currents and rapid conduction are readily stimulated by *rapidly developing* electric currents which are led into the tissue from outside, but not by slowly developing currents. Such tissues also require only a brief duration in the stimulating current of threshold intensity; the latent period of stimulation is also brief. Quickness of response is characteristic of rapidly conducting tissues, and *vice versa*. Each irritable tissue has its own characteristic "time-factor" of electrical stimulation, called "chronaxie" by Lapicque; this is best measured by the minimal duration of the stimulating current of threshold intensity, which is brief in rapidly responding and rapidly conducting tissues; and correspondingly such tissues are found to be responsive to rapidly changing but not to slowly changing currents. This correspondence between the time relations of the stimulating current and of the tissue's own action-current is highly characteristic; a rapidly conducting tissue always has a brief and rapidly developing action-current, and responds to (or is stimulated by) rapidly developing currents of brief duration. It is as if the tissue were "timed" or adapted to respond to electric currents having the special peculiarities of its own action-currents.¹ The hypothesis that transmission is due to the stimulating effects of the local action-current appears thus consistent with all of the observed characteristics both of the normal response of the tissue to electric stimulation and of its own normal electrical behavior.

Further support of this hypothesis has recently come from a quite different direction. It will be seen on reference to the diagram that any definite velocity of transmission implies that the local bioelectric current has an intensity sufficient to stimulate the resting tissue for only a certain limited distance (AR) in advance of the region already active. Beyond this limit the current will necessarily be too weak for excitation. Everywhere up to the critical point R there will be full and complete stimulation in a normal nerve, since

¹ Cf. Lapicque: Jour. de Physiol. et de Pathol. gén., 10, 601 (1908), for an account of the time-factor in electrical excitation.

under normal conditions this tissue exhibits the "all-or-none" type of response, and if it responds at all responds with full intensity. But if by any means we lower the intensity of the current traversing the nerve at the point R, *e. g.*, by decreasing the electrical conductivity of the local circuit, then activity in the area A will no longer cause stimulation at R, but the limit of the secondarily stimulated area will be shifted nearer to the active-resting boundary line (*e. g.*, to R₁). In other words, the immediate stimulating effect of any active area will then be exerted through a shorter distance; this implies that the propagation-velocity will be lowered. According to our hypothesis, this velocity should be proportional to the electrical conductivity of the circuit. Recently Mayor has shown in experiments on the nerve-ring of the marine medusa *Cassiopea* that the velocity of nervous transmission when the tissue is immersed in sea-water of different dilutions runs closely parallel with the electrical conductivity of the medium.¹ This is precisely what we should expect to find on the theory of transmission through stimulation by the local bioelectric current. The existence of such a relation is difficult to explain unless electric currents passing through the medium are an essential factor in the transmission of excitation. The further fact, which has been demonstrated in a number of instances, that stretching the nerve leaves its rate of conduction essentially unaltered,² confirms this interpretation, since it implies that stimulation is always being initiated at a certain linear distance in advance of the already active area. In any solution electrical resistance is proportional to linear distance.

If transmission is thus essentially a case of secondary electrical stimulation, the problem of transmission resolves itself into the more fundamental problem of how the electric current produces its stimulating effects in protoplasm. The

¹ A. G. Mayor: *Am. Jour. Physiol.*, **42**, 469 (1917) and **44**, 591 (1917).

² Cf. Carlson: "Evidence of the Fluidity of the Conducting Substance in Nerve," *Am. Jour. Physiol.*, **13**, 351 (1905), and **27**, 323 (1911); also McClendon: *Proc. Nat. Acad. Sci.*, **3**, 703 (1917).

primary effect of the current must be a chemical one, since vital processes are chemical processes; and, if so, protoplasmic transmission must be referred to the chemical effects produced in the irritable element by the local bioelectric current, especially at its points of exit and entrance, since it is here that the stimulating effects originate. Now there is much evidence that the bioelectric current itself is primarily the index or expression of some change in the physical and chemical state of the *surface-layer* of protoplasm. As we have seen, a change in the physical properties and permeability of the protoplasmic surface-film appears to be a general accompaniment of stimulation; and there is clear evidence that the electromotor variation also accompanying stimulation is a direct consequence of this surface-change. Any change in the chemical composition or physical properties of the cell-surface will necessarily alter the potential-difference of the double electrical layer between protoplasm and medium; and we find in fact that any injurious modification of the surface-layer of the living protoplasm (like poisoning or mechanical injury) alters its electrical potential in the same manner and to the same degree as the normal process of stimulation; *i. e.*, it produces a characteristic local change of potential, the altered region becoming negative relatively to the unaltered regions by a P. D. of 40 or 50 millivolts. The local current arising between stimulated and resting areas appears to be the index or result of a similar local change of potential, due to a temporary alteration of the surface-film at the active area; and this current, by means of the chemical changes which it produces in the adjoining portions of the film, produces there an alteration of a similar kind, and so the effect spreads. Since there is evidence of a temporary loss of semi-permeability in many irritable tissues during stimulation,¹ it seems probable that this alteration consists in a more or less complete temporary disruption or disintegration of the surface-film. The precise nature of the critical or initiatory chemical change

¹ I have summarized this evidence in several places; cf. *Am. Jour. Physiol.*, 28, 197 (1911) and 37, 356 (1915).

induced where the current passes from cell-surface to medium (the region where stimulation originates) is not definitely known at present; but the general evidence already available indicates clearly that stimulation is primarily the result of the chemical and structural changes which the current there induces in the surface-film. Nernst has shown that electrical stimulation depends upon the polarization-effects produced by the current at the semi-permeable surfaces of the irritable tissue;¹ and the chemical effects immediately following this change of polarization appear to form the first step in the stimulation-process proper. The next succeeding step in the process is apparently an extensive alteration or dissolution of the film, followed by its reconstitution as the tissue returns to the resting state.

We return now to the question whether transmission-effects of this general type—through the chemical effects produced by the currents of local electrical circuits—exist also in inorganic systems, and, if so, in what respects such systems resemble living systems.

In point of fact, self-propagating chemical effects due to local circuits are a frequent phenomenon in certain types of inorganic system which, though apparently widely different from protoplasm, are in certain fundamental respects closely related, namely, metals in contact with electrolyte solutions. The most familiar instance is the rusting of iron in water or a salt solution. According to the "local action" theory of corrosion, original with Faraday and de la Rive and now generally accepted, the chemical effect is due to local electric currents formed between adjoining areas of the metallic surface which differ in composition or physical state. Processes of electrolysis at the electrode-areas of these local circuits are the direct cause of the chemical change. The surface of ordinary iron is typically non-homogeneous, with areas of greater and less solution-tension; the regions of higher solution-tension form local anodes where the iron cations enter solution; there they react with carbonate and hydroxyl ions

¹ Cf. Nernst: *Arch. ges. Physiol.*, 122, 275 (1908).

to form a rust deposit. This local deposit spreads or grows because when once formed it acts as a local cathode and promotes the solution of iron from the unruled areas in its vicinity. This effect is greatest at the boundary of the rusted area because there the intensity of the local current is greatest. There is in fact a kind of autocatalytic action, the rate of rust-formation increasing as the periphery of the rust spot extends.

The spread of chemical influence over the surface of the metal is in this case a gradual one, and can scarcely be regarded as an adequate model for the rapid chemical transmissions found in living protoplasm. We can, however, easily conceive of possible conditions under which the spread might be rapid. If we could find a metallic surface covered with a thin film of unstable material which is readily and rapidly altered or removed by local electrolysis, we should expect it to show chemical transmission-phenomena which would be rapid in rate and would extend wherever the film extended. Take, for example, a metal (*e. g.*, iron) covered by a thin continuous film of readily reduced oxide; wherever such a film were locally interrupted we should have side by side a free metallic area and an oxide-covered area; in any electrolyte solution these areas would form a local electrical couple with the metallic area anode and the film-covered area cathode. But since the chemical influence at the cathode is of a reducing nature, the film would be at once removed by reduction wherever the intensity of the local circuit was sufficient. The free metallic area would thus be automatically and rapidly extended, since the same conditions would be repeated at every boundary-region between film-covered and metallic areas. Now this is precisely the situation found in passive iron immersed in an electrolyte solution and also in many other cases which I shall not now consider, of which mercury in hydrogen peroxide is perhaps the most interesting; and it can hardly be an accident that this system shows phenomena of activation and transmission which in a surprising number of particulars resemble closely the conditions found in irritable

protoplasmic systems like nerve. In both cases we are dealing with film-covered systems which are susceptible to the polar influence of the electric current, as well as to mechanical and other influences. And since the changes occurring during the transmission of activation in passive iron are relatively simple and well understood, we may expect that their study will throw light upon the general physico-chemical nature of the changes underlying transmission in living protoplasm.¹

It has long been known that iron exposed temporarily to strong nitric acid or other favorable oxidizing agent assumes the so-called passive state, in which it is remarkably resistant to chemical change; *e. g.*, such iron will no longer react with dilute nitric acid, in which ordinary iron dissolves rapidly. But if a piece of passive iron, *e. g.*, a wire, immersed in dilute nitric acid be touched with a piece of ordinary or active iron or a base metal like zinc, or if it be bent or scratched with a piece of glass, or made the cathode in an electric current of moderate intensity, it is at once rendered active and reacts vigorously with the acid until dissolved. The whole metal is not activated simultaneously, but the active state is observed to spread rapidly from the original point of activation over the whole metal; this process of spreading can best be observed in a wire dipped in acid and held suspended in the air and then touched below with a piece of active iron or zinc; the passage of the active state along the metal can be readily followed by the eye, each successive region as it becomes active turning dark (from formation of lower oxide) and effervescing in the adhering acid. Under these conditions the rate of transmission is only a few centimeters per second; but if the wire is activated while it is completely immersed in the acid, the transmission over its whole length is so rapid as to appear almost instantaneous, the rate being often some hundred centimeters per second. This difference of velocity depends on the difference in the electrical resistance of the

¹ For a more detailed account of this and other parallels with living irritable elements, cf. *Science*, 48, 51 (1918); 50, 259, 416 (1919).

circuit between the passive and active areas under the two conditions, this resistance being high when the metal is in air, with only a thin layer of electrolyte adhering; the intensity of the local current then falls off rapidly with increase of distance from the active-passive boundary line, and is sufficient to reduce the film only in its immediate neighborhood. But when the wire is immersed in a large volume of electrolyte the conductivity is high and the transmission correspondingly rapid. There is thus a relation between the electrical conductivity of the circuit and the speed of transmission; just as in protoplasmic transmission.

I shall now describe briefly the more important resemblances between the conditions of activation and transmission in the two systems under comparison; the case of protoplasmic transmission will then appear in a clearer light and its specific peculiarities can be considered to better advantage.

In the first place, both systems may be activated either mechanically, chemically or electrically, and both give the same kind of transmitted effect whatever the method employed for activation. A passive wire is activated by jarring, bending or scraping, by contact with reducing substances, or by being made the cathode in an electrical circuit; similarly an irritable tissue is activated or stimulated by mechanical treatment, by various chemical substances, and by an electric current at one of its poles (the cathode). The electric current is most effective in activating either protoplasm or passive iron when it rises suddenly or rapidly to its full strength; when its intensity is increased gradually, *i. e.*, from zero or subliminal to a strength more than sufficient for activation with a sudden closure, no effect follows, the system apparently undergoing under these conditions some compensatory change which keeps it inactive. In both cases a single "stimulus" may be ineffective, while a succession of stimuli will call forth activation; this phenomenon of "summation" is especially characteristic of living irritable systems. Again, the character and intensity of the response in any instance are typically constant and independent of the nature of the

activating agent; *i. e.*, activation is either complete or absent, a type of behavior called "all-or-none" in physiology, where it is well known to be highly characteristic of irritable and rapidly conducting elements like muscle-cells or nerve-fibers. In both the inorganic and the living systems the activation-wave travels at a velocity which varies under different conditions and has a high temperature-coefficient; in the motor nerves of the more active animals it is usually several hundred centimeters per second, reaching in warm-blooded animals velocities of more than a hundred meters per second; in passive iron velocities of some hundred centimeters per second are usual, although exact measurements under different conditions still remain to be made. The passage of the activation-wave may be blocked in both systems by locally altering the electrical polarization of the surface (a phenomenon known in living tissues as electrotonus), or by certain other means like mechanical constriction or anesthetization in nerve, or by the contact of a noble metal in passive iron; in these cases also the local change in electrical conditions is probably the essential factor in the effect. A fundamental resemblance is that in both systems the passage of the activation-wave is associated with a local variation of electrical potential, which is readily demonstrated as the active-inactive circuit accompanying the wave passes the electrodes of a galvanometer connected with the conducting tissue or wire. The so-called "positive after-variation" in nerve, in which the active region of the tissue becomes temporarily more positive than normally on returning to the resting state, is also simulated by the passive wire, which is more positive (cathodal) immediately after spontaneous repassivation than later. And finally, what is perhaps the most striking resemblance of all, both tissue and metal on returning to the resting or passive state after temporary activation always exhibit a certain period of delay (called the "refractory period" in irritable tissues) before they recover their former condition of sensitivity and conductivity.

This last phenomenon should be described more fully,

since it is perhaps the clearest indication of all that the fundamental conditions of activation and transmission are the same in the protoplasmic system and its metallic model. In every irritable tissue excitation is immediately followed by a brief period of inexcitability, the so-called refractory period; the duration of this is brief in rapidly responding tissues like nerve and voluntary muscle (where it lasts only a few thousandths of a second), and relatively prolonged in "slow" tissues like heart-muscle (about one-third of a second), or involuntary muscle and certain special sensory elements (*e. g.*, photoreceptors in mollusca), where it may last for several seconds or even minutes. Each nerve-impulse as it passes along a nerve is thus followed by a trail or wake of temporary inexcitability. The refractory period evidently represents an interval during which certain processes of restoration or recovery (probably associated with chemical and structural resynthesis) are at work; it has a number of features in common with fatigue and may be regarded as a temporary or evanescent instance of this phenomenon.¹

Normally a nerve or muscle returns automatically to the resting state after stimulation, and after the refractory interval can be again stimulated as before. Now in a passive wire immersed in strong HNO_3 there is a similar automatic return of passivity, so that the activation-reaction which sweeps over the surface when the wire is touched with zinc is only local and temporary, like the excitation-wave in nerve or muscle. The remarkable fact from the physiological point of view is that the metal immediately after the return of passivity is entirely refractory to reactivation as a whole, and recovers its full power of transmission only by degrees, and the more slowly the stronger the acid. In acid of 60 volumes percent (of HNO_3 sp. gr. 1.42) complete recovery usually requires one or two minutes (varying somewhat with temperature and other conditions); at first the activation-wave is transmitted slowly and for only a short distance, like

¹ An account of the refractory period in nerve is contained in the recent book by Keith Lucas: "Conduction of the Nervous Impulse," London, 1917.

the transmission-wave in a fatigued or anaesthetized nerve which conducts with a "decrement;" by degrees the distance through which it travels (as well as its speed) becomes greater and greater, until eventually rapid transmission through an indefinite distance becomes again possible.

Now passivity in iron is almost certainly due to the presence of a thin film of oxide or oxygen compound which adheres closely to the surface of the metal; this film gives the passive iron the properties of a cathodal or noble metal, with a potential about 0.7 volt higher (in dilute HNO_3) than the normal or active iron. The spontaneous return of passivity in strong acid indicates therefore the deposition of a fresh film of oxide, and this must occur first at the local anodal regions of the metal, since, as is well known, making an active metal anodal has a strong passivating influence. Each region traversed by the activation-wave becomes temporarily anodal as it becomes active, and is therefore subject to the oxidizing influence resident at every anode; this influence, added to that of the HNO_3 , at once reinduces passivity. We thus understand why the local activation is temporary and is at once transmitted to the adjoining passive areas of the metal, which, as already pointed out, are cathodal; being cathodal they are immediately activated by reduction and then at once become anodal, upon which they are automatically repassivated in the manner just indicated. The refractory or non-transmissive condition just described indicates that the newly formed passivating film is in a different physical or chemical condition from an older film; it is less readily removed by cathodic reduction; hence transmission is imperfect or absent. Possibly the film is too thick when first formed—the reflecting power of the surface is then less than later—or its physical condition is otherwise unfavorable to rapid change. The essential condition for transmission is that the film should be readily and rapidly removed by cathodic reduction; and from general considerations it seems probable that the condition which it reaches eventually, when sensitivity is completely restored, is one in which its molecules are

closely packed, similarly oriented, and in a layer of about one molecule in thickness. The film is in fact similar to an adsorption-film, which, as the work of Langmuir and others has shown, is in many cases of this order of thickness.¹ On this view, the period of recovery represents a period during which all of the surface oxide molecules, except those directly attached to the metallic iron, are dissolved away by the outer acid, and the remaining molecules are uniformly distributed over the surface in a layer one molecule thick. The film is then in a condition favorable for rapid transmission.

Now in the irritable protoplasmic system (*e. g.*, nerve axone) it seems probable that closely analogous conditions exist. During activation the surface-film (which apparently consists largely of some unstable readily reducible material) is rapidly altered, possibly in large part disintegrated or removed; during the succeeding refractory period it is restored and recovers its original constitution and physical properties.² I am inclined to believe—and in this I acknowledge my obligations to Langmuir's work—that the material which is thus altered and replaced during protoplasmic excitation is spread out in a very thin layer, possibly not more than one molecule thick, separating the protoplasm from the surrounding medium. This film consists of some chemically reactive water-insoluble material, probably chiefly lipid. Just what chemical changes it undergoes during excitation is difficult to say at present. In its reconstitution or redistribution during the recovery phase oxidation-processes appear to be especially important, since all processes of recovery and reconstruction in protoplasm are favored by the presence of oxygen.

¹ I. Langmuir: Jour. Am. Chem. Soc., 39, 1848 (1917).

² These processes occur under the influence of the local bioelectric circuit between the active and the adjoining inactive areas of the nerve. Immediately before becoming active any given area (which is at this time a resting, *i. e.*, positive, area) is traversed by a bioelectric current passing in the direction *from protoplasm to medium* (positive stream); when the area becomes active (and hence negative) this direction is immediately reversed. To this reversal in its direction (shown in the "diphasic" character of the galvanometer curve), corresponds a reversal in the chemical effect of the current at the area in question.

We have assumed throughout our comparison that the electric current can effect chemical changes, especially oxidations and reductions, at the cell-surface in essentially the same manner as at the surface of a metallic electrode, and in fact we have ascribed to the protoplasmic surface-film all of the essential properties of an electrode. Can such a point of view be justified? Usually it is assumed that electrolysis is a phenomenon confined to the region of contact between a metallic electrode and the electrolyte solution adjoining, and that a combination of metallic and electrolytic conductors is necessary both for electrolysis and for the production of electric currents by chemical action.

There must, however, be something insufficient about this manner of regarding the phenomena in question. The conditions in living matter prove that metallic conductors are not essential either to the production of chemical change by the current, or to the production of a current by chemical change, since it is a fact that the electric current alters profoundly the chemical processes in the living system, and also that the living system during its activity produces electric currents which traverse the surroundings. We have seen that different areas of the protoplasmic surface, *e. g.*, of a nerve-fiber, give rise to local circuits whenever they differ in their activity or in their physiological state, just as do two differently constituted areas of a metallic surface; and we have also seen that these currents are intense enough to stimulate other irritable systems of the same kind.

Now it is well known that the electric current produces no chemical change in the interior of an electrolyte solution during its flow; the chemical changes which occur are confined to the region where electricity passes between electrode and solution, *i. e.*, to the surface-layer of the electrode and the adjacent layer of solution. When, however, a current is passed through living matter the case is entirely different; chemical effects are produced not only at the electrodes but throughout the entire mass of protoplasm. In its general physico-chemical constitution protoplasm is essentially a colloidal or emulsion system containing electrolytes and freely

partitioned by semi-permeable membranes and other thin films; and we must conclude that the chemical effects produced by the current depend upon this partitioned or film-pervaded structure of the system, since they are absent in homogeneous solutions. We know further that the passage of a current changes the electrical polarization between the opposite faces of any partition which interferes with ionic movement; and the case of electrolysis at metallic electrodes shows that when the P. D. across a boundary-surface reaches a critical value there is a transfer of electricity associated with chemical change. Apparently what is essential to produce this latter effect is that there should be a sufficient fall of potential across a short distance. The thin surface-films in living protoplasm, not only at the general cell-surface but also within the interior of the protoplasmic system, may be assumed to act in a similar manner. Any change in the P. D. across such a partition must effect displacements of electrons in the chemical substances forming the film or in immediate contact with it, and these displacements will, if sufficient, lead to chemical reactions which secondarily alter the character of the film. Chemical and structural changes in these films may thus occur comparable with those induced in the surface-films of passive iron when the metal is made cathode; and if such changes are accompanied by increased permeability or breakdown (like the changes in the passivating films) they may lead to self-propagating waves of chemical and structural alteration similar to those occurring in the metallic system. It thus seems probable, judging from the far-reaching nature of the chemical changes produced in a highly irritable cell, *e. g.*, a muscle-cell, by a slight local stimulus, that in such a case an extensive system of colloidal films or partitions pervading the entire protoplasm is broken down or altered by the rapid propagation of a wave of decomposition originating at the cell-surface. It is as if a heap of passive iron filings immersed in nitric acid were activated; at every film-covered surface a chemical decomposition occurs resulting in the temporary destruction of the film; the film is then reconstituted and the system resumes its previous condition.

Presumably in muscle the accompanying changes of surface-tension in the colloidal structural elements composing the fibrils form the direct mechanical condition of the contraction. We may thus understand why conditions that stabilize the protoplasmic surface-films, like cold, anaesthetics, and certain salts, prevent the propagation of these waves of alteration and hence render the living system irresponsive to stimulation.¹

There can be little doubt that the electrically controlled chemical reactions in protoplasm are surface-reactions; and, as in other instances of such control, what is needed to initiate these reactions is the conveyance of electricity (positive or negative, according to conditions) into the surface-layer of reactive material from the adjacent electrolyte solution or the other phase contiguous to the reacting layer. In the ordinary case of electrolysis at a platinum electrode this electricity is furnished to the reacting molecules in the surface-layer from the metal, which is connected with some external source of potential. In the case of a chemically alterable colloidal surface-film in a protoplasmic system the electricity is presumably derived from the molecules of chemical substances, *e. g.*, oxygen combined as peroxide, which are in contact with the film. In principle the two cases are not different, as we can readily see if we imagine (for example) the length of metal connecting the oxidizing and reducing surfaces (or electrode-areas) in an oxidation-reduction cell to be progressively reduced until it becomes zero; in such a case the substances whose reaction gives the current would be in direct contact; the reaction and the accompanying electrical transfer would occur as before, although there would be no external evidence of the latter. Similarly two chemical reactions with oppositely directed electron-transfers may occur at different areas of a thin surface-film separating adjacent solutions, in such a manner as to create an electrical circuit between the two areas, provided the potential is sufficient and the electrical resistance not too high. In a system

¹ In a recent article on the theory of anaesthesia, *Biological Bulletin*, 30, 311 (1916); I have reviewed the evidence indicating that anaesthetics act in this manner (*cf. pp. 332 seq.*).

of the structure of protoplasm, pervaded by thin films of reactive material, the electrical transmission of chemical influence to a distance is thus theoretically possible, just as it is in a system consisting of a solution containing reactive substances at different regions which are connected through a metallic conductor so as to form a circuit.

There is no difficulty about the conduction of electricity through the general mass of protoplasm or through the surrounding medium; both contain salts and are good conductors of the second class. The critical question is: can conduction take place across the protoplasmic surface-films in association with processes of electrolysis, *i. e.*, chemical change depending on electrical transfer between the interacting molecules under the influence of an externally imposed E. M. F? The foregoing considerations show that if this is possible in the layer of molecules in contact with the surface of a metallic electrode, there is no theoretical reason for denying its possibility at a sufficiently thin layer of chemically reactive material interposed between two electrolyte solutions.

Physiological distance-action thus becomes a special case of chemical distance-action in a system where the reaction-surfaces, instead of being metallic surfaces, consist of thin films of chemically alterable organic material. We must assume this material to be water-insoluble, if we are to account for the characteristic immiscibility of living protoplasm with water and the general stability of protoplasmic structures in their predominantly aqueous media; and since all forms of protoplasm are rich in water-insoluble constituents, the lipoids, we are led to ascribe a physiological rôle of fundamental importance to these substances. They apparently furnish the essential material for the alterable surface-films whose properties we have been considering. The properties of proteins seem less adapted than those of lipoids to fulfil this rôle. The investigation of the properties and the conditions of formation and disintegration of surface-films in general and of lipid films in particular becomes thus a matter of fundamental physiological interest.¹

¹ For a discussion of the parallels between the behavior of protoplasmic surface-films and the surface-film of passive iron, cf. *Science*, 50, 259, 416 (1919).