a temperature of 40° C. abolished the negative variation and conduction. In the frog's sciatic a temperature of 0° C. does not block the action current and the impulse, but at − 2° to − 7° C. both are blocked. Between 8° and 35° C. little effect of changes in temperature can be seen. Herrick[25] found that between 10° and 35° C. there was no change in the negative variation, but below 10° C. the negative variation diminishes. In general a low temperature slows and prolongs the negative variation, and a high temperature causes an increase in height and a diminution in duration. In mammals a temperature of 2° or 6° C. blocks conductivity, but conduction returns on warming. The fibres going to the abductors of the larynx are blocked by cold before the adductors.

*The Electrical Phenomena of Nerves.*—The electrical phenomena of nerves were first studied accurately by Du Bois-Reymond in 1843–45. Like all protoplasm a nerve shows a difference of potential between the uninjured and the injured portions. This difference is of such a character that the injured part appears negative to the uninjured. Thus Du Bois-Reymond found that if two electrodes connected with a galvanometer be placed one on the cut end of a nerve, the other at some point on its surface, a current flows in the circuit from the uninjured surface toward the cut end and may be detected by the deflection of the galvanometer. This current is called the current of rest, or of injury, or the demarcation current of the nerve, and it may amount to 0.0035 to 0.02 volt. The amount of this current is about the same in warm- and cold-blooded animals. Besides this current, which is at its maximum between the equator and the cut end of the piece of nerve, there is a difference of potential between the two ends of a nerve, so that if the two cut surfaces of a motor nerve or a sensory nerve be connected with an electrometer there is a small axial current. In a motor nerve this axial current flows in the nerve from the peripheral to the central end, and in the sensory roots in an opposite direction.[26] The amount of this axial current is not great, but the current is constantly present, and is greater in the posterior than in the anterior roots. In the anterior it amounts to about 0.0006 of a Daniel, in the posterior roots to 0.0015 of a Daniel. The electromotive force of the nerve current of injury is said to be greater in a nerve used constantly, like the pneumogastric, than in other motor nerves. In non-medullated nerves the current is greater than in medullated. This current of rest or of injury persists for some time, becoming constantly weaker, but may be still detected several days after section when the excitability is entirely lost. Although the direction of the nerve current is ordinarily in the sense already mentioned, it may be reversed by high temperature and by desiccation. By appropriate means a nerve may be prepared which shows no current of injury. Thus if a frog's sciatic is removed from the body and placed in frog's blood containing a little calcium, the nerve after several hours is said to show no injury current whatever.[27]

It is probable that the current of injury may be increased or diminished in many different ways, but this subject has not yet been sufficiently investigated to allow us to classify the facts in any general group. Ether diminishes the current as do acids; alkalies increase the current.

The cause of the current of injury is, as its name implies, probably to be attributed to chemical or physical changes taking place in the nerve at the point of injury more rapidly than elsewhere. There are several explanations of this change. Du Bois-Reymond, who supposed the nerve to be made up of bipolar electric particles, of which the two ends were negative and the middle positive, believed it to be due to the exposure of the negative ends of the particles by the section. Hermann[28] refers it, as do most authors, to the alterations in the state or composition of the protoplasm at the injured point. The author has suggested that this change consists in the increase in size or the coagulation of the positively charged colloidal particles of the nerve brought about by the injury, thus causing a change of their surface of separation from the fluid leading to the liberation of formerly bound negative charges. It is impossible, however, at the present time to state positively what the real explanation is.

*Negative Variation.*—Du Bois-Reymond[22] discovered about 1843 that if one electrode from a galvanometer be placed on the cut end of a nerve and the other on its longitudinal surface, on stimulation of the nerve the needle of the galvanometer, which had been deflected by the current of injury, receded momentarily toward zero. This electrical disturbance he called the negative variation or current of action. It has since been shown that this electrical disturbance generally or invariably accompanies the nerve impulse and is a convenient way of detecting the passing of such an impulse. The variation follows mechanical, heat, or chemical stimulation as well as electrical. It occurs in plants and muscles and secreting epithelia as well as in nerves. The variation is of such a nature that the first electrode reached by the impulse becomes negative to the other. The negative variation is biphasic, that is, a positive phase follows the negative. The negative variation travels at the same rate as the nerve impulse, and shows other parallelisms which clearly indicate its close connection with the phenomenon of conduction. Thus exposure of the nerve to carbon dioxide, ether, or chloroform is said to cause a preliminary rise in excitability and an increase in height of the negative variation, both conduction and the negative variation being later abolished;[29] a ligature abolishes both the variation and the conduction; cold lengthens the duration of the negative variation, but diminishes its height, and warmth increases the height and shortens the duration. These facts so clearly establish the parallelism between the negative variation or action current and the nerve impulse that by most physiologists the electrical disturbance is regarded as an invariable concomitant of the nerve impulse. Others hold a different opinion, however. Cases are on record in which the cooled muscle of a frog has contracted, following a stimulus not accompanied by a negative variation; and in other instances the negative variation may be detected without muscle contraction. Steinach found in warmed frogs tetanus produced with the secondary coil 43 cm. from the primary, while the negative variation first appeared when the secondary coil was at a distance of 39 cm. Boruttau believes that in the one case the muscle is a little more sensitive than the electrometer, and in the other the latter is more sensitive than the muscle. The size of the negative variation is proportional, as a rule, to that of the current of injury, and up to a certain point a larger stimulus causes a larger negative variation and a larger muscle contraction. The negative variation is increased by catelectrotonus and diminished by anelectrotonus. A negative variation occurs also in the tetanus due to natural stimulation of the nerves of strychnine frogs. The cause of the negative variation and its relation to conduction will be discussed on page 232.

*Electrotonus.*—If two electrodes from a battery are placed upon a nerve, a nerve impulse is generated at the cathode or negative electrode when the current is made, and at the anode or positive electrode when the current is broken, provided the current be fairly strong. While the current flows through the nerve no impulses are as a rule generated, but nevertheless a change in irritability is brought about in the nerve. This change of irritability and conductivity in the region of the electrodes has been carefully investigated by Pflüger and is called electrotonus.[30] The irritability of the nerve is increased in the neighborhood of the cathode during the passage of the current and diminished in the neighborhood of the anode; after the current is broken the anodic region undergoes a rise in irritability and the cathodic region a fall. These changes may be demonstrated by stimulating the nerve in the region of the cathode or anode with stimuli just strong enough in the normal nerve to cause muscle contraction, when if applied to the cathodic region an increased muscle contraction is obtained; if applied to the anodic region no response follows. If the current is strong and continued for some time the cathodic region also becomes less irritable. The strength of current necessary to produce electrotonic effects is very small, 0.0001–0.00001 milliampère may suffice. Sensory nerves show the same phenomena of electrotonus as motor, although Zirhelle thought that both the anode and the cathode diminished excitability in the former. Exceptions to the general statement that irritability is increased by the cathode and diminished by the anode have been noted by several observers, *i.e.*, Budge, Schiff, Valentine, and others. Irritability may increase (though very rarely) in anelectrotonus, and Nasse has observed several cases of the total reversal of the law. The cause of these rare exceptions is not yet clear.





Although the constant current only changes excitability but does not ordinarily excite during the passage of the current, yet in some cases a tetanus of the muscle is observed during the passage of the current, or after it is broken.[39] This tetanus, called Ritter's tetanus, arises from the cathode if it occurs during the passage of the current, and from the anode if it occurs after the current is broken. This tetanus may be artificially produced at will if the excitability of the nerve is increased by cooling, by drying, or by the osmotic extraction of water. This tetanus demonstrates the fact that the changes going on in the nerve during the passing of the current are of the same nature as those which produce the impulse. The current really stimulates throughout its passing, only the changes produced after the current is once applied are too gradual to cause a muscle contraction. If, however, the excitability of the nerve is already artificially raised (that is, if the instability of the nerve substance is artificially increased), the change is sufficiently abrupt to generate nerve impulses so that a number of muscle contractions take place during the passage of the current. It is necessary to bear these facts in mind, since the law of electrical excitation is ordinarily stated in the way mentioned—*i.e.*, that excitation occurs only at the make and break of the current.

The explanation of these electrotonic changes of irritability is not difficult on the colloidal hypothesis already sketched. The primary effect of the current is to cause a disturbance in the even distribution of the ions in the nerve. Positive ions predominate in numbers near the anode, negative ions near the cathode. These ions bring about a change in the state of the colloids. Near the anode the positive ions increase the stabilitly of the protoplasmic hydrosol, the colloidal particles are here increasing in numbers and increasing their total surface; near the cathode, on the other hand, the colloidal particles, owing to the presence of negative ions, are diminishing in numbers, increasing in size, and diminishing the surface of contact. The stability of the hydrosol is being reduced near the cathode, and, in accordance with the general law stated farther on, excitability varies inversely with the stability of the protoplasmic hydrosol. If this change is abrupt, so great a contraction of surface of the particles takes place that an impulse is generated strong enough to reach the muscle and cause muscle contraction. If the change is gradual, as it is after the first application, the change is not strong enough at any moment to cause an impulse large enough to reach the muscle. Stimulation takes place at the anode on opening, and excitability is increased here owing to the fact that on breaking the current the positive ions accumulated here in excess diffuse into the region formerly occupied by the cathode, and the negative ions from the cathodic region by diffusion reach the anode. There is thus produced in the neighborhood of the anode a diminished positivity or an increased negativity. The equilibrium of the solution is at once upset, the positive colloidal particles suddenly diminish in numbers and surface and increase in size owing to this diminution of positive ions, and this generates, as always, a nerve impulse which may continue, causing tetanus. Thus the rise in irritability near the anode is explained. Similarly in the region of the cathode, on breaking the current there is a sudden diminution of the negativity of this region and an increase in positivity due to the diffusion into this region of the positive ions from the anode. The result is that a sudden increase in number and surface of the particles results and conductivity and irritability are accordingly reduced. In other words, a process of solution is occurring near the anode and of gelation near the cathode during the passing of the current; after breaking the current the reverse of these processes occurs. It may be stated that these changes, although not visible in nerves, may be readily seen in infusoria and other forms of protoplasm, and the change in state of the protoplasm is of an opposite character at the two poles, liquefaction generally occurring on the anodic side.

Besides the changes in irritability of the nerve produced by the current, there are changes in its electrical behavior at the same time. Polarization takes place, so that on breaking the current a reverse current in the opposite direction may be observed. This polarizing current often reverses itself, running first in one direction and then in the other. This reversal is less pronounced in nerve than in muscle and is absent in dead muscle. These facts show that the polarization current is due not only to a physical polarization taking place at the limiting membranes of the nerve, but also to a change in state of the protoplasm. The polarization current may take place in the same direction as the original current, particularly after heavy currents of very brief duration.

While a constant current passes through a nerve electrical disturbances may be seen on both sides of the electrodes. If electrodes connected with a galvanometer are applied on the anodic side, it will be found that each point nearer the electrode is positive to that farther away, and if on the cathodic side negative to that farther away. We thus get physical electrotonic currents. These currents are due in large part, if not altogether, to the polarization taking place at the boundary of the axis-cylinder process, causing a spread of the current along the nerve.[31] They are, however, not altogether explicable on this hypothesis, for they disappear in dead and disintegrating nerves; they are greatly reduced by etherizing the nerve; and they are suppressed if the nerve be ligatured between the polarization current and the galvanometer electrodes. The currents are more powerful near the electrodes and their intensity is greater on the side of the anode than on that of the cathode. The anelectrotonic current may have an electromotive force of 0.5 of a Daniell, while the catalectrotonic current has but 0.05 Daniell. These currents are sufficiently strong to stimulate other nerves in contact with those stimulated. They exist in non-medulated as well as medullated nerves. They may be reproduced on artificial nerve models called core-conductors, consisting of a wire surrounded by a solution of an electrolyte. The suppression of the current by ether may be due to a diminution of polarization owing to an alteration of permeability of the axis-cylinder wall.

*Indefatigability of Nerve.*—Nerves are not supposed to be fatigued by the act of conduction. Bowditch[32] curarized frogs, thus blocking the nerve impulse and protecting the muscle from fatigue. The nerve was then stimulated by induction shocks continuously for six hours; at the end of that time the curare was excreted and the muscles began to contract. A similar experiment was tried by Maschek, who blocked the impulse by ether, and by Bernstein,[33] who blocked the impulse by the anode and with the same results. These facts indicate that nerve conduction is not accompanied by metabolic changes.

*Metabolism of Nerve.*—The only evidences of metabolism in nerve are the changes produced in it by cutting it off from its nerve-cell connection and Waller's observations on carbon-dioxide formation. No heat is produced by nerve conduction. Electrothermic contacts sensitive to 0.001° C. show no indication of heat production.[34] Similarly all attempts to show that carbon dioxide or acid are produced have been fruitless. Waller says that after exposures for a brief interval to carbonic anhydride

nerve irritability is increased and the size of negative variation is increased. The same result is obtained if the nerve is tetanized; so Waller concludes that carbonic anhydride is produced during tetanization. As many other factors affect the negative variation in the same way, we cannot conclude from this observation that the conduction of the nerve impulse is accompanied by a metabolic change, leading to carbonic-anhydride formation.

*The Action of Anæsthetics.*—The anæsthetics, chloroform, ether, carbon dioxide, and alcohol all temporarily annihilate nerve conduction, although some observers state that a preliminary rise in excitability is their first effect. If not exposed too long to the action of the anæsthetic the nerve will recover; but if too large an amount is used, or if the exposure is too long, irritability and conductivity appear to be permanently lost. Chloroform is much more active than ether and the nerve recovers from it with much greater slowness. This may be due to its being less volatile than ether and hence escaping less readily from the nerve or to its having a more powerful action. The most probable explanation of the action of the anæsthetics is that they dissolve the lecithoproteids or colloids of the nerve. Mayer[35] and Overton[36] have pointed out the parallelism of the anæsthetic action to the fat-dissolving powers of the anæsthetics. The nerve is particularly rich in lecithin compounds, and it is not improbable that the anæsthetics act upon them. The dissolving action of these substances may be easily seen in blood corpuscles, the eggs of many marine forms and other organisms, so that it is probable that they act on nerve protoplasm in the same manner. There is, hence, nothing peculiar about the action of the anæsthetics. They produce the same kind of a change in protoplasm as do positive ions, the positive electrode, or warmth. They put the nerve in a condition of anelectrotonus. They are particularly valuable because they are so soluble in protoplasm, so volatile, and effective in such small amounts.

*General Summary.*—We are now in a position to see how far the foregoing facts enable us to understand the processes in the nerve which are represented in the nerve impulse. There have been several hypotheses thus far proposed to explain these phenomena. One of the earliest was that of Du Bois-Reymond. In this theory the nerve substance is supposed to be composed of bipolar electrical particles negative at each end and positive in the middle. The current of rest is obtained by connecting the middle or positive surface with the cut end or negative surface. As each portion of a magnet shows the polarity of the whole magnet, so each portion of a nerve shows the polarity of the whole nerve. The nerve impulse is simply a turning of these particles on their axes, so that the negative ends turn toward the surface. This will explain the action current.

Hermann believed that these particles did not pre-exist, but that the current of injury was due to catabolic changes taking place at the cut surface. This became negative to the rest in consequence of these chemical changes. A similar change occurred during conduction, and this change in each part of the nerve caused the part just following it to be put in a position of catelectrotonus. On this theory the negative variation stimulated each part of the nerve in turn and was itself regenerated by the change which it brought about.

Becquerel supposed that there were numerous electro-capillary couples in the nerve which gave rise to electric currents, each couple, consisting of two different liquids, being separated by a capillary opening or by an organic membrane. D'Arsonval, who has developed this theory, supposed the electrical phenomena to be due to modification of the surface of separation of the two liquids similar to the electrical phenomena shown by the capillary electrometer.

Loeb has suggested that conduction is due to a change in state of the colloids, but has furnished no evidence in support of this view. The author believes that the facts indicate the truth of this hypothesis and suggests the following more specific theory:

The protoplasm of the nerve is essentially a colloidal solution. The colloidal particles are proteid in nature and in all likelihood are lecithin proteids resembling the sheaths of the red blood corpuscles, as is indicated by the especial richness of the nerves in lecithin. These particles are of different sizes and are electropositive. They continually change their state of aggregation, being easily precipitated or brought into solution and easily coalescing with their neighbors or breaking up into a large number of smaller particles. Through these changes the surface separating each particle from the surrounding fluid augments or diminishes. When two particles coalesce the total surface is reduced; when one particle separates into two the total surface of separation is increased. Around each particle there are induced in the water electrical changes of an opposite sign. It will be seen that any change in the surface of separation must necessarily produce an electrical disturbance exactly in the same manner as do the movements of the capillary electrometer, and in this respect my suggestion harmonizes entirely with that of D'Arsonval.

Stimulation, whatever its character, whether mechanical, chemical, thermal, or electrical, brings about a change in the state of division of these colloidal particles. It produces either one of two effects, *i.e.*, a coalescence of the particles (gelation), or an increase in number of the particles (solution). According as a stimulus produces one or the other of these effects we say that it excites the nerve or anæsthetizes it. It may fairly be questioned which effect is the excitation and which the anæsthetization. This question may be answered, I believe, by the exciting action of drying the nerve and of applying cold. Both of these processes excite or generate nerve impulses. Since they can hardly be supposed to increase the solubility of the colloids, we may confidently assume that they congeal or precipitate the colloids, and hence that excitation is due to a diminution in the number of colloidal particles and a reduction in their total surfaces; and conversely, anæsthetization or inhibition is due to the reverse process. All the exciting agencies may be interpreted in this way. Thus mechanical shock which disturbs the hydrosol brings about such a condition of temporary coagulation or rigidity of the nerve protoplasm throwing the particles together. This interpretation is strengthened by Mrs. Andrews' observations on the effect of shock on the choano-flagellates, where the rigidity of the previously fluid protoplasm can be easily demonstrated, and by my own observations on other forms of protoplasm, notably eggs. Cold, as will be seen, diminishes the stability of the protoplasmic solution or hydrosol, while warmth increases it; negative ions precipitate positive colloidal solutions and they excite the nerve; excitation takes place at the cathode or negative electrode, where positive colloidal particles will be precipitated; the extraction of water acts in the same manner as cold. In fact all the phenomena of excitation are readily understood on this hypothesis. Similarly the action of all anæsthetizing agents becomes clear. Positive colloidal solutions are rendered more permanent by positive ions, and these annihilate nerve excitability; warmth of moderate amount increases the stability of nearly all solutions, and this diminishes excitability; ether and the anæsthetics dissolve the protoplasm of eggs and other cells and destroy irritability; the anode, which holds positive colloids in solution, abolishes excitability. We may sum up our conclusions in the general law that nerve excitability varies inversely with the stability of the protoplasmic hydrosol. The less stable the hydrosol, the more irritable the nerve. Irritability will be lost when the nerve is stable, either in the condition of solution or in that of total gelation. The rise in irritability at the anode on opening the current is due to the fact that, as already explained, by the action of the current the particles are greatly divided; and after the current is broken the diffusion outward of the positive ions reduces the stability of the hydrosol here and it returns back toward the normal. The electrotonic effects are due to the solution being made more stable near the anode and less stable near the cathode.





As readily as the facts of excitation are understood on this hypothesis, so many of the facts of the electrical phenomena of nerves may be explained. The electrical disturbances are the result of the alterations in the surface of separation of particles and liquid. Whenever these particles coalesce, a portion of the negative charges, formerly induced about each particle, are set free. The portion of the nerve where this is occurring becomes temporarily electronegative to the rest of the nerve. Thus the current of injury is due to the coalescence of particles at the injured end. This is always negative to the uninjured part.

If this is true, the exposure of the end of the nerve to acids or anæsthetics should diminish the current of injury, whereas alkalies should increase it. Such I have found to be the case. The current of action is the result of the progressive precipitation of the colloids and a progressive setting free of negative charges. It is, however, impossible within the limits of this article to discuss the bearing of this hypothesis on all the numerous electrical phenomena of nerves. It may be stated, however, that a warmed or etherized portion of a nerve is electropositive; a cooled portion electronegative to the normal nerve.

The conduction of the nerve impulse may be understood on this hypothesis as follows: Each precipitation of colloidal particles sets free by the accompanying reduction in surface negative charges formerly induced in the water about each particle; these charges at once precipitate the next layer of particles, and so on. Thus the negative variation successively stimulates each following segment of the nerve, as Hermann supposed, and it is regenerated by the change which it itself has produced. The sheath and peculiar structure of the nerve probably, as Boruttau supposes, plays an important part in the electrical phenomena of polarization and stimulation, and possibly in determining the speed of transmission, but the change in the protoplasm itself is the most important factor in conduction. Finally, it should in all fairness be stated that among the difficulties or exceptions to this hypothesis are the statements that the anæsthetics bring about a preliminary rise in irritability, and that conductivity and excitability may vary somewhat independently of each other. Whether these facts can be harmonized with the explanation already offered remains for the present unknown. *Albert P. Mathews.*

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**NERVES, PATHOLOGICAL CHANGES IN.** See *Neurone, etc.*

**NERVE TISSUE, HISTOLOGY OF.**—According to the fundamental conception of neurology the entire nervous system, central as well as peripheral, has been regarded as composed of morphological units, the neurones, held together by the supporting tissues, the neuroglia. The term neurone was suggested by Waldeyer in 1891, and was accorded almost universally an international acceptance by anatomists, physiologists, pathologists, and clinicians. The term neura, proposed by Rauber, and neurodendron by Kölliker, to designate the same unit, have not met with similar favor. More recent investigations, however (Apáthy, Bethe), have thrown some doubt upon the neurone doctrine as formerly held. The neurone consists of a cell body, dendritic processes, and an axis-cylinder process (axone with its terminal ramifications). As the neurone does not consist only of the cell body, but also has processes, some of which are of extreme length, it is impossible to see the entire neurone in the majority of cases. As a matter of convenience, therefore, the description of the neurone may fall under two headings—the nerve cells or nerve-cell bodies, and the nerve fibres.

The Nerve Cell.—The essential part of a neurone originating the nerve impulse is the cell body. Nerve cells or ganglion cells, as they are generally called, occur in groups known as ganglia in the cerebrospinal system, the sympathetic system, and in the organs of special sense. While variable in size, they are among the largest cells in the body, often, as in some of the ganglion cells in the anterior horns of the spinal cord, reaching a size of from 90 to 135 $\mu$, the cells of Betz in the paracentral lobule being especially large. Many nerve cells, however, are much smaller in size, the cells of the granular layer of the cerebellum being only from 4 to 8 $\mu$ in diameter.

Study of the morphology of the neurones requires the consideration of their external peculiarities as well as of their internal architecture. The former are best revealed by the methods of Golgi and Ehrlich, and the latter by the methods of Nissl and Held.

*Morphology of the Nerve Cells.*—Nerve cells vary greatly in shape. Starting originally as spherical cells, some may retain this shape as in the spinal, Gasserian, or other ganglia; others may become ellipsoidal, as in the spinal cord, pyriform as the cells of Purkinje in the cerebellum, pyramidal as the cells in the gray matter of the cerebrum, or stellated as the multipolar ganglion cells of the spinal cord. The most conspicuous peculiarity of the nerve cells is the branching. This may take place only on one side leading to a prolongation of the protoplasm into a single pole, such cells being known as unipolar nerve cells; when the protoplasm is prolonged into two, usually opposite, poles, the cells are appropriately designated as bipolar; when the protoplasm extends in several directions multipolar cells are formed. Each polar prolongation is continued to form a nerve-cell process. Of such processes two kinds are recognized, the branched *protoplasmic processes* and the *axis-cylinder process*.

The branched protoplasmic processes, now usually called the *dendrites*, form prolongations of the protoplasm from the cell body, hence the old name of protoplasmic process. They are always broader and thicker at their origin, becoming gradually narrower as they divide,