delivered the Lumleian lectures in which he is supposed to have expounded his doctrine of the circulation of the blood; two years later the first Pharmacopæia Londinensis was issued by the college. The civil wars reduced the college to the greatest distress. Unable to pay an assessment by Parliament of five pounds per week, and its rent to St. Paul's, it was in danger of being sold by auction, when Dr. Baldwin Hamley came to the rescue, purchased house and garden himself, and with the utmost generosity presented them to his colleagues two years afterwards. Prosperity followed, for in 1653–4 the munificence of Harvey enriched the college with a museum, a "noble building of Roman architecture," stocked with valuable and curious contents, and a library of medical books, treatises on geometry, geography, astronomy, music, optics, natural history and travels. But this prosperity was not long continued. After Harvey's death in 1657, the treasury was nearly empty, lectures were suspended, large numbers of physicians were living and practising without a license within the liberty of the college, examinations were discontinued. The creation in 1664 by Sir Edward Alston of upwards of seventy honorary Fellows, both brought unlicensed practitioners under the authority of the college and replenished its coffers. But in 1665, during the great plague, most of the Fellows and officers of the college fled the city, and thieves broke in and stole the whole of the contents of the treasury chest. On September 5, 1666, the great fire consumed the whole of the college buildings; only the charters, annals, insignia, some instruments and portraits, and 140 printed books in the library were saved. The premises in Amen Corner were never rebuilt, and the college remained homeless until its new buildings in Warwick Lane, designed by Sir Christopher Wren, were opened without ceremony on May 13, 1674. This commodious and stately building occupied four sides of a quadrangle enclosing a large paved court, on the east side of which was erected at Sir John Cutler's expense a spacious anatomical theater. The other sides of the quadrangle contained the library, cœnaculum, censors' room and other public apartments. At the back of the college were the botanical garden, and in 1684 a noble library building was presented by the Marquess of Dorchester. Here the college stood for 150 years; all that remains of it now is the beautiful Spanish oak wainscoting, the gift of Hamley, which lines the Censors' Room in Pall Mall, and two colossal statues of Cutler and Charles II, which may be seen in the Guildhall Museum. At the end of 150 years the college buildings had become dilapidated, Warwick Lane was a slum, the population and fashion had moved westwards, and a more convenient situation for the Royal College of Physicians was a necessity. Mainly through the influence of Sir Henry Halford, a grant of land was obtained from the Crown at a cost of £6,000 in Pall Mall East, and on it the present college building, designed by Sir Robert Smirke, was erected and opened with great ceremony on June 25, 1825. The premises in Warwick Lane were sold for £9,000. One may regret their disappearance, and that it is no longer possible to people them with the shades of those who have made the history of medicine and of this famous college during 150 years of its life. The names of such are Mayerne, Glisson and Sydenham, exponents of clinical medicine, followed by Radcliffe, Garth, Arbuthnot, Freind, Sloane and Meade, and last but not least, William Heberden. All of these have made their mark in the history of medicine, and directly or indirectly have been associated with the history of the college. The quartercentenary of the Royal College of Physicians of London reminds us that, in spite of modern progress, we can not afford to neglect the learning of past ages.

SPECIAL ARTICLES

SUGGESTIONS REGARDING THE CAUSES OF BIOELECTRIC PHENOMENA

Bioelectric phenomena constitute a group of facts for which adequate and satisfactory explanations have hitherto been lacking. It is my purpose in this paper to point out certain significant correlations between these phenomena and the metabolic gradients which are now known to exist in organisms; and to propose an explanation of the former in terms of these gradients. The metabolic gradients were first demonstrated by Child in *Planaria;* subsequently he and his students extended the observations to include a large number of adult organisms, cells and embryos.[1] This work has shown that the anterior, oral or apical end of organisms has the highest metabolic rate and that this rate decreases along the sagittal axis. A gradient in rate of metabolism therefore exists along this axis; and to a less extent along other axis of symmetry also. This fundamental discovery has furnished a basis for the interpretation of many hitherto entirely inexplicable biological facts,[2] and I believe that it also throws light upon the nature of the bioelectric currents.

The term metabolism is too well understood to require definition; it commonly signifies the sum of chemical processes which results in the production of new protoplasm or other organic compounds, or of energy. "Metabolic rate" simply means the rate at which these processes take place; and modern chemistry, particularly through the study of organic and other catalyzers, has taught us the supreme importance of rate in any chemical system. The metabolic rate is generally measured either by the rate at which the raw materials, particularly oxygen, for the reactions are used up; or by the rate of production of end-products, especially carbon dioxide. The extent to which a given mass of protoplasm is actually alive is determined by its metabolic rate; these chemical reactions, always building and destroying, are the very essence of the living; when they sink to a rate so low that only the most delicate means serve to detect them, the organism is practically lifeless, but when they burn intensely, the most marvelous manifestations of protoplasm, such as thought, leap forth.[3]

The following suggestions are by no means entirely new; similar ones have already been made by Waller, Child and Tashiro.[4] In collaboration with Mr. A. W. Bellamy of this laboratory, I am collecting further data upon these matters, and the complete results, together with a more extended discussion of the literature, will appear later; but a sufficient number of facts are already known to justify a preliminary statement of the relation between metabolic conditions and differences of potential found in organisms.

1. *Permanent Differences in Potential.*—In a number of cases we know both the metabolic gradient and the permanent differences of electrical potential along the antero-posterior axis. Thus Mathews[5] in 1903 discovered that the head of hydroids is electro-negative to the stem, and that anterior levels are electronegative to posterior ones. Later, Child[6] demonstrated that in these animals the head or any anterior level has a higher metabolic rate than any posterior level.[7] Hyde[8] found

1 Child, "Individuality in Organisms," Univ. of Chicago Press, 1915.

2 Child, *Jr. of Morph.*, XXVIII., p. 65; XXX., p. 1; *Roux's Archiv*, XXXVII., p. 136; Newman, *Biol. Bull.*, XXXII., p. 314, are a few examples where such interpretation has been applied.

3 Alexander and Cserna, *Biochem. Zeitsch.*, LIII., p. 106, have demonstrated that the oxygen consumption of the brain greatly exceeds that of any other part of the body.

4 Child, "Individuality in Organisms," p. 63; Tashiro, "A Chemical Sign of Life," Univ. of Chicago Press, 1917; Waller, "Signs of Life from their Electrical Aspect," London, 1903.

5 *Am. Jr. of Physiol.*, VIII., p. 294.

6 SCIENCE, XXXIX., No. 993.

7 An additional statement regarding the metabolic gradient in hydroids would seem to be required owing to the recent paper of Garcia-Banus (*Jr. Exp. Zool.*, XXVI., p. 265), who states that apical pieces of the stem of Tubularia do not regenerate oral hydranths faster than basal pieces. In the summer of 1914 at Woods Hole, while I was a student in Professor R. S. Lillie's class in physiology, I performed this experiment with the common tubularian hydroid found there, called at that time *Parypha*. I found the hydranths arising earlier on the apical pieces; the result was clear-cut and definite. The experiment has since been repeated at Woods Hole to my personal knowledge with the same result as mine. Driesch also (*Roux's Archiv*, IX., p. 130) found that oral

that the animal pole of turtle and other vertebrate eggs is electronegative to the vegetal pole, and the anterior ends of vertebrate embryos electronegative to posterior regions. Child[9] subsequently found in similar materials that the electronegative regions are also regions of high metabolic rate. Morgan and Dimon[10] reported that the anterior and posterior ends of *Lumbricus terrestris* and *Allolobophora* (*Helodrilus*) *fœtida* are electronegative to the middle. Mr. Bellamy has repeated this experiment and confirmed the result on *Helodrilus caliginosus*. In my work on the aquatic oligochætes,[11] I was able to show in a number of species that the anterior and posterior ends have a higher metabolic rate than the middle. The same state of affairs presumably exists in the terrestrial oligochætes also, although these can not be tested by the available methods for demonstrating differences in metabolic rate.

In these cases the regions of high metabolic rate are always permanently electronegative to regions of lower metabolic rate. This fact suggests the hypothesis that the metabolic differences are directly responsible for the differences in potential and that the latter are, therefore, of chemical origin. This is also the opinion of Child, and R. S. Lillie has recently come to a similar conclusion.[12] I am also in accord with R. S. Lillie regarding the chemical process which is at the bottom of these differences in potential,—namely, that it is an oxidation and reduction phenomenon. In considering this matter, one must remember that when one states that a given region is electronegative, one means electronegative with respect to the galvanometer, exactly as one says that the zinc pole of a cell is the negative pole; actually the zinc pole is positive to the carbon or copper pole, and similarly the regions of high metabolic rate are in reality electropositive to regions of lower metabolic rate. If one considers now the familiar "action at a distance" experiment of chemistry, in which the oxidation is carried out in one beaker, and the reduction in another, one finds the electrical conditions thus produced to be identical with those observable in organisms. The current runs in the galvanometer from the reduction beaker to the oxidation beaker, and in the bridge of salt solution from the oxidation beaker to the reduction beaker. The region of oxidation is thus, as also in the region of high metabolic rate in the organism, electronegative galvanometrically, actually electropositive. We have abundant evidence that the metabolic gradient runs parallel to the rate of oxidation. In the organism, however, oxidation and reduction are not separated as in our experiment, but there in all probability, the electric difference of potential is due to difference in rate of oxidation at difference levels,—in other words, to a concentration cell with respect to oxidation.

2. *The Current of Injury.*—It has long been known that any cut or injured surface is electronegative (galvanometrically as explained above) to intact surfaces. In this laboratory we have frequently observed that such injured surfaces always have a higher metabolic rate

hydranths appear earlier on apical than on basal pieces. In animals so lowly organized as the hydroids, where the metabolic gradient is well marked only near the apical end, practically lacking near the base, and very plastic and readily alterable by external factors, it is easy to select conditions under which the basal pieces will regenerate hydranths as fast as or faster than the oral ones; such conditions are: using long pieces, taking pieces from the more basal regions of the stem instead of from the apical regions, using basal pieces near the place where a branch is about to form, slight depressing conditions, etc. (the mere fact that pieces do well in the laboratory is not evidence that no depression existed; in fact, depressed pieces are more likely to survive than vigorous ones). Since Garcia-Banus mentions none of these factors in his paper, not even stating *whether his apical pieces are near the original hydranth or not*, it is presumable that he failed to control or eliminate them, and that this explains why he was unable to obtain the same results as other investigators.

[8] *Am. Jr. of Physiol.*, XII., p. 241.

[9] This work is largely unpublished. See, however, on amphibian embryos, Child, *Roux's Archiv*, XXXVII., p. 135.

[10] *Jr. Exp. Zool.*, I., p. 331.

[11] *Jr. Exp. Zool.*, XX., p. 99.

[12] *Biol. Bull.*, XXXIII., p. 181 ff.

than uninjured regions, as determined by our methods; and further that this increase in metabolic rate is the result of the stimulation of cutting, since it does not occur if the cutting is done under anesthesia. We have also shown that this alteration of metabolic rate as the consequence of injury occurs not only at the cut surface but involves adjacent uninjured regions also, in proportion to their distance from the cut. Tashiro[13] has further found that injury invariably increases the carbon dioxide output of living material, and he believes this reaction to injury to be an infallible sign that the material is living.

In the text-books of physiology, explanations of the current of injury are usually based upon supposed alterations of membranes, concentrations of electrolytes, etc., at the cut surfaces,—that is, the cut place is supposed to cause the phenomenon. But our observations show that the change in metabolic rate occurs not only at the cut surface but for some distance away from it; and an experiment of Bose[14] demonstrates that the region of electronegativity also exists not merely at the site of injury but for a considerable distance away, diminishing in fact with distance. Here again the current runs parallel with the metabolic conditions at and near the injured regions. Bose concluded that the actual injury to the cells is not directly the cause of the electronegativity but that the stimulation due to the injury produces the electric change; and this stimulation, like many others, is transmitted with a decrement to surrounding regions. Injury is thus a form of stimulation and our experiments and those of Tashiro show that the stimulation of injury produces in the organism an increase in metabolic rate. Hence, as in the preceding case, we may suggest that the current of injury arises through the fact that the site of injury and adjacent regions are regions of increased metabolic rate and thus are electronegative to intact regions, where the rate is lower.

3. *The Current of Action.*—Whenever any living material is "stimulated," the stimulated region becomes *ipso facto* a region of electronegativity with respect to non-stimulated areas. In order to analyze this universal phenomenon, it is necessary to know what the nature of stimulation is. Physiologists are still very far from a solution of this difficult and fundamental problem. I venture to suggest, however, that everything that we know about stimulation indicates that increase in metabolic rate is its principal characteristic. Thus the oxygen consumption increases, the carbon dioxide output increases, the production of synthesized materials and of waste products is accelerated, the energy produced is augmented.[15] Tashiro,[16] for instance, after testing various kinds of plant and animal tissues, says: "In all cases stimulation causes an increase in carbon dioxide. We could never find any response unaccompanied by an outburst in carbon dioxide."

Every cell carries on a specific kind of metabolism, resulting in specific end products. As far as we know, each cell is always producing these whether it is in a stimulated condition or not, and the rate at which it does this is a measure of the degree to which it is alive. Thus Tashiro finds that all living substances give off carbon dioxide, and the rate of this output runs parallel to other manifestations of life, as relative irritability, rapidity of response, rate of conduction, etc. Let us consider very briefly the three chief active tissues of the body,—gland, muscle and nerve. In any particular kind of gland cell, barring special experimental or pathological conditions, there are in general the same kinds of granules to be found at all times. As far as one can determine, the rate of formation and discharge of granules alone is variable,—not their content. The essential effect of stimulating the gland cell through its nerve is an increase

[13] A chemical sign of life.

[14] "Comparative Electro-physiology," 1907, pp. 154 ff. Bose has a great deal of interesting experimentation on the bioelectric currents but unfortunately it is often very difficult to grasp his exact meaning.

[15] These statements can be verified in any of the recent text-books of physiology as Bayliss, Howell, Stewart, etc.

[16] *Loc. cit.*, p. 99.

in the rate of production of its secretion. As is well known, this stimulatory increase in secretory products is always accompanied by large increases in the amount of oxygen consumed, CO_2 produced and heat evolved. In the case of muscle, the amount of lactic acid produced furnishes a certain criterion of the metabolic rate of the muscle. In the resting state, the lactic acid content is small; after the stimulation of injury and after contraction, it is greatly increased. And although molecular oxygen does not appear to be consumed in this process, the production of lactic acid from carbohydrates is nevertheless chemically an oxidation. In nerve, where it was long believed that no increase in metabolism occurred during the passage of the impulse, it is now known, thanks to the researches of Tashiro,[17] that a relatively great increase in carbon dioxide output is associated with the process. He also presents some evidence that the oxygen consumption is likewise accelerated, during the conduction. In this connection it may be mentioned that Alexander and Revesz[18] found that the oxygen consumption and the carbon dioxide elimination of the brain are increased when the retina is stimulated by light. In nervous, as in other tissues, the difference between the resting and the stimulated state is then largely quantitative. Further significant facts are that the rate of the passage of the current of action along the nerve bears a direct relation to the known irritability of the nerve and the rate at which it conducts the impulse; and as Tashiro's work shows that these factors are also directly related to rate of carbon dioxide production (more irritable nerves in the resting state giving off more of the gas than the less irritable ones), it becomes obvious that metabolic condition is the primary factor in the causation of the current of action.

The evidence then clearly indicates that each cell is always carrying on a specific kind of metabolism and that stimulation consists essentially in the temporary acceleration of the rate of metabolism. From this point of view regarding the nature of stimulation, the current of action is readily explicable. Any stimulated region is a region whose metabolic rate has been temporarily increased by the stimulation, and as in the preceding cases, it must necessarily form with non-stimulated regions of lower rate a concentration cell with respect to rate of metabolism. It must therefore be electronegative to such non-stimulated regions. The various kinds of bioelectric currents are thus conceived as referable to the same cause, differences in metabolic rate; and they are, apparently, merely the consequence of such differences, and of no significance in themselves.

This explanation of the current of action has been long held by Waller (*loc. cit.*), who on scanty and indirect evidence and in the face of skepticism from other physiologists maintained that the metabolism of nerves is the same as that of other protoplasm, that the current of action is due to sudden increase in their rate of metabolism, and that this current is merely a sign of that metabolic change. Waller's idea has received strong confirmation through Tashiro's work.

Certain interesting corollaries follow if this conception of the nature of stimulation is true. Thus if an increase in metabolic rate is the essential feature of stimulation, it follows that any organ or cell whose rate of metabolism is already sufficiently high will function without stimulation—in other words, it will be automatic. Some physiologists deny that there are any truly automatic organs, but surely the facts that are known about the heart, the medullary centers, and the digestive tract sufficiently prove that automaticity is a real phenomenon. Consider, for instance, the embryonic heart, which in all known cases, has a beat of myogenic origin. The metabolic rate of this young muscle tissue is in all probability so high that it contracts in the absence of stimulation from without. Later, as the rate falls with age, the aid of the nervous system must be evoked to keep the apparatus going. The nervous system is, indeed, the automatic structure *par excellence* of the body and,

[17] *Loc. cit.*, Chaps. II. and III., also p. 53.

[18] *Biochem. Zeitsch.*, XLIV., p. 95.

as our conception demands, it is characterized by an exceedingly high rate of metabolism. This is demonstrated not only by its blood supply, its great susceptibility to lack of oxygen, to anesthesia, to cyanide and other poisons, but also by direct measurements of its rate of oxygen consumption. Thus, Alexander and Cserna[19] find that the oxygen consumption of the brain is vastly greater than that of equal weights of any other organs, and MacArthur and Jones[20] that the cerebrum and cerebellum respire faster than any other parts of the central nervous system, the rate decreasing gradually from these parts posteriorly. The nervous system by virtue of its intrinsically high metabolic rate is able to control other parts of the body, and to increase their metabolic rates by sending impulses along the nerves.

It should be mentioned that stimulation is characterized not only by the acceleration of the metabolic processes but also by other changes, which may well be the consequences of this acceleration, such as alteration of the colloidal state (probably in the direction of liquefaction), increase in permeability, and other effects.

4. *Galvanotaxis.*—The metabolic gradient also furnishes us with a logical explanation of the phenomena of galvanotaxis. It is well known that many animals when placed in an electric current will turn their anterior ends toward the cathode and travel to the cathode, maintaining such an orientation. Now as I pointed out in the first section of this paper, the anterior ends of a variety of organisms have been shown to have a higher metabolic rate than other parts of the body and to be electropositive (internally) to other parts. Since then the anterior end is positively charged or at least possesses the properties of an anode, it must when placed in the current be directed toward the cathode and it will tend to travel towards the cathode like any other positively charged material. Animals on the same basis might also travel backwards to the anode. Galvanotaxis is then a real taxis, or forced orientation, in the sense of Loeb. A crucial test of this hypothesis can be made upon the oligochaete worms, where, as we know from experiment, there are two regions of high metabolic rate and of electropositivity, —namely, the anterior and posterior ends. These animals should then when placed in a current bend themselves into a U-shape, head and posterior end directed towards the cathode, and middle towards the anode, and travel to the anode maintaining such a posture. This is exactly what they do as first pointed out by Moore and Kellogg[21] and since confirmed by Mr. Bellamy.

5. *Other Electric Phenomena.*—Since regions of high metabolic rate are electropositive (internally) to regions of lower metabolic rate, it follows that if any region can be made electropositive by running a current through it, that region must then have its metabolic processes accelerated and must thereby be stimulated, must become more irritable. That this is true is a familiar fact in electrophysiology. A constant current stimulates at the cathode when the current is made—that is, the region around the cathode becomes positively charged (or possibly becomes an anode in some other way), and hence has a higher metabolic rate, and serves as the source of the response. Similarly on the break of the current, the area of stimulation is that surrounding the anode, it having been shown that on the break the anode is really temporarily a cathode. Electrotonus is the same phenomenon. After prolonged passage of the electric current through a tissue, a large region around the cathode becomes excessively irritable because it is full of positively charged particles,[22] and a large region around the

19 *Biochem. Zeitsch.*, LIII., p. 106.

20 *Jr. of Biol. Chem.*, XXXII., p. 259.

21 *Biol. Bull.*, XXX., p. 131.

22 I do not wish to be understood as stating positively that the electrical sign of various parts of the organism is actually due to their containing free particles of that sign. This seems the most convenient way of putting the matter but the facts in themselves do not serve to determine whether the charge is on the inside or on the surface or indeed what condition is responsible for it. The facts of electrotonus would seem to favor the idea that the charged particles are inside.

anode loses its irritability because it is negatively charged.

A detailed report of the experiments which we are conducting on galvanotaxis and electrical gradients in organisms will, of course, appear elsewhere.

L. H. Hyman

Hull Zoological Laboratory,
University of Chicago

THE AMERICAN MATHEMATICAL SOCIETY

The two-hundredth regular meeting of the society was held at Columbia University on Saturday, October 26, 1918. War conditions were reflected in an attendance of only eleven members. Professor E. W. Brown, of Yale University, presided at the morning session, and Professor O. E. Glenn, of the University of Pennsylvania, at the afternoon session. The following new members were elected: Professor R. A. Arms, Juniata College; Professor M. D. Earle, Furman University; Professor Ernest Flammer, Queen's University; Professor Gillie A. Larew, Randolph-Macon Woman's College; Dr. Flora E. LeStourgeon, University of Chicago; Professor John Matheson, Queen's University; Mr. F. R. Morris, University of California; Professor Susan M. Rambo, Smith College; Dr. W. G. Simon, Adelbert College. One application for membership was received.

A list of nominations for officers and other members of the Council was prepared and ordered printed on the ballot for the annual election in December. A committee was appointed to audit the accounts of the Treasurer for the current year. A committee was also formed to collect funds for a suitable memorial to the late Professor Maxime Bôcher, of Harvard University, who was president of the society in 1909–1910.

The following papers were read at this meeting:

J. E. McAtee: "The transformation of a regular group into its conjoint."

E. W. Chittenden: "On the Heine-Borel property in the theory of abstract sets."

G. A. Larew: "Necessary conditions for the problem of Mayer in the calculus of variations."

D. M. Y. Sommerville: "Quadratic systems of circles in non-euclidean geometry."

M. B. Porter: "Derivativeless continuous functions."

G. H. Hallett, Jr.: "Concerning the definition of a simple continuous arc."

R. L. Moore: "A characterization of Jordan regions by properties having no reference to their boundaries."

R. L. Moore: "Concerning simple continuous curves."

Edward Kasner: "Fields of force and Monge equations."

It was decided to hold the annual meeting of the society at Chicago in the Christmas holidays. No eastern meeting will be held at that season. But members attending the Baltimore meeting of the American Association are invited to read their papers before Section A, after registering titles and abstracts with the Secretary of the Society for record in the report of the Chicago meeting.

The southwestern section will not hold its Thanksgiving meeting this year. The February, 1919, meeting of the society will also be omitted. A regular meeting will be held in New York on April 26. The official list of officers and members will not be published in 1919.

F. N. Cole,
Secretary

SCIENCE

A Weekly Journal devoted to the Advancement of Science, publishing the official notices and proceedings of the American Association for the Advancement of Science

Published every Friday by

THE SCIENCE PRESS

LANCASTER, PA. GARRISON, N. Y.
NEW YORK, N. Y.

Entered in the post-office at Lancaster, Pa., as second class matter