gether many kinds of scientific workers and have always tended toward the end we are here considering. In a broader way the annual meetings of the association contribute in the same direction. By combining its meetings with those of many of the special societies the American Association has brought together probably the largest gatherings of all kinds of scientists that have ever occurred. The salutary influence of these conventions, where workers in widely different fields have opportunity to become mutually acquainted, can not, I think, be overestimated.

With their continued increase in size and complexity the annual meetings of the American Association are becoming a serious financial problem. Locally raised funds are generally very inadequate and dues and registration fees are purposely kept as low as possible. The association very much needs a substantial endowment for the holding of the annual meetings, which are surely almost a national necessity now and which can not be expected to be self-supporting. I should like here to make a personal suggestion that the National Academy might perhaps be interested to aid in finding means by which the effectiveness of these annual conventions may not be curtailed through too great economy.

Through the democratic nature of its organization and through the publication of its official journal the American Association cultivates the feeling among all of us scientific workers that we all belong together, no matter how wide may be the apparent separation of the scientific details with which we deal individually. We are now a happy family of nearly 15,000 members. In this part of our endeavor to bring science home to the scientists the National Research Council is also actively engaged.

The very fundamental project of improving the education of those who are soon to be the future scientists and appreciators of science is of course primarily the concern of the Education Section of the association. With that section are affiliated several societies, including the National Education Association. Other sections deal with the same project. A special committee of the American Association as a whole, on the place of science in education, is making a special study of present trends in this very important branch of scientific work, for the science of the future will depend on the education of the present. The National Research Council has also taken a prominent part in this line of work.

The general education of the public at large, in scientific matters, and the cultivation of public appreciation of what professional workers in science are trying to accomplish are being carried on especially by Science Service, for the guidance of which the National Academy, the National Research Council and the American Association are jointly responsible. An important feature of recent annual meetings of the association is a well organized news service, which aids the representatives of the press and other non-technical writers to secure information about the papers presented at the meeting and to make personal contacts with the scientists.

I have tried to bring before you some of the main ways in which an important present trend of the best scientific thought is being jointly supported by the National Academy and the American Association. The two organizations cooperate in many other ways and we hope that new ways may be developed from time to time. The select nature of the academy and its consequent reliability and prestige make it logically the upper house in the parliament of American science workers, as Cattell has remarked, while the democracy of the association and the fact that most young scientists, as well as those of riper experience, are enrolled as members and are actively interested in its work, make it logically the lower house.

BURTON E. LIVINGSTON

THE ACTIVITY OF NERVE[1]

UNTIL the nineteenth century practically all hypotheses as to the nature of conduction assigned to the nerve fiber a passive rôle. Energy or substance entered at one end and was carried to the other, where it produced its effect. In the middle of the eighteen hundreds the production of an electric change by nerve during activity was discovered; and later were found, first, the existence of a refractory phase for a few thousandths of a second after an impulse had passed during which a nerve could not transmit a second impulse, and, second, the independence of the intensity of the effect produced from the intensity of stimulus applied. These facts indicated the active participation of the nerve fiber in carrying the impulse. In the early years of this century it was further found that a nerve slowly lost its conductivity under conditions of asphyxia and recovered with oxygen, suggesting an oxidative basis for this activity. Attempts to follow the respiration of nerve were partly successful, but careful experiments failed to demonstrate the production of heat (which must accompany oxidations) during nervous activity, so the interpretation of chemical findings was rendered very uncertain.

The series of researches to be described,[2] carried out in the laboratories of Professors Hill and Meyerhof,

[1] Summary of a lecture delivered at the Biochemical Laboratory, Cambridge University, August 2, 1927.

[2] See R. W. Gerard, *Am. Jour. Physiol.*, LXXXII, 381, 1927, for further details and literature.

began with a redetermination of the heat production of nerve. Isolated frog sciatics were arranged for stimulation at the upper end, the lower halves resting on a thermopile so wound as to bring several hundred insulated constantan-silver junctions against the nerve. Although the thermopile sensitivity under these conditions was about 2,000 microvolts per calorie liberated, tetanization of the nerves for ten seconds at 280 shocks per second gave only about one tenth of a microvolt. Through the thermopile and galvanometer resistances currents of about 10^{-10} amp. would result, which are much too small for even high sensitivity galvanometers. A successful means of amplification was found; the thermopile current passed through a sensitive moving coil galvanometer, the mirror of which reflected a strong vertical beam of light. At rest this fell half way across the slit of a radiation thermopile, setting up a constant potential and current through a second sensitive moving magnet galvanometer connected with it. Movements of the first instrument of a small fraction of a millimeter allowed more or less of the reflected light and heat to reach the thermopile and, by varying the potential this produced, gave large deflections of the second galvanometer. The sensitivity of the whole system was 2×10^{-12} amp. = 1 mm. deflection at 1 meter, and tetanizing the nerves gave deflections of about 200 mms. For purposes of calibration a known amount of heat could be produced in the nerves by passing an alternating current, too weak to stimulate, through their length.

It was soon found that the deflection during tetanization at 280 shocks per second at 15° C. corresponded to a liberation of 7.6×10^{-6} cal. per grm. per sec. The deflection, however, fell very slowly, requiring ten minutes after stimulation was stopped to return to zero, whereas a current heat deflection was over in less than a minute. It was obvious, therefore, that nerves continued to produce heat for about ten minutes after they had been active, and comparing the areas of the curves for nerve heat and current heat showed that the total heat produced per gm. and sec. stimulation was 6.9×10^{-5} cal. The resting heat production had to be determined indirectly from the change in base line when a nerve was asphyxiated, and was found to be 2×10^{-5} cal. per gm. and sec., to which the above values are an addition.

Analysis of the galvanometer curves obtained by stimulation yielded information as to the amount of heat produced second by second and showed that nerve, like muscle, produces its heat in two distinct phases. For each impulse there is an outburst of heat lasting a few thousandths of a second which is followed by a feeble but prolonged heat liberation. Although the rate of heat liberation in the initial phase is 5,000 times as great as at the start of the delayed, only 11 per cent. of the heat is produced during the first phase, the remainder appearing in the delayed one, most at first and slowly fading out.

The values given so far were determined by tetanization at 280 shocks a second. To obtain the absolute heat production for a single impulse, stimulation was carried out at different frequencies and the heat production of the nerve measured. The heat per second does not rise as fast as the frequency, so that the heat per impulse falls as successive impulses follow one another more and more closely. The fall is already apparent when impulses are as much as .030 sec. apart, so that the effect of one impulse lasts longer than this time. Presumably when an impulse traverses a nerve some energy-giving reaction takes place, and the reactive substance is then rapidly reformed. If all that is present at any time is discharged by an impulse, the return of heat-producing power gives a measure of the course of reformation. Also since reformation is very probably itself accompanied by wastage of energy and heat formation, the initial phase of heat may well be made up of two subsidiary phases, one accompanying conduction itself and the second accompanying the immediate restitution of the system. Aside from these considerations, the frequency experiments showed that at 280 per second each impulse gives only one fourth as much heat as an isolated one, so that the initial heat per impulse per gm. of nerve is 10^{-7} cal., and the total heat almost exactly one millionth of a calorie. For a single impulse traversing 1 cm. length of a single fiber the values are one millionth of these.

Further insight into the underlying chemical processes was gained by studying the effect of oxygen-lack on heat production and later by direct chemical studies. In the well explored case of muscle, it has been found that the initial phase of heat production accompanying contraction is independent of oxygen and is associated with the formation of lactic acid from glycogen, whereas the delayed phase occurs only when oxygen is available and is associated with oxidation of about one fourth of the lactic acid and reconversion of the remainder into glycogen. In absence of oxygen, a muscle is able to continue activity for a long time, securing its energy from the formation of lactic acid which then simply accumulates. The picture of nerve activity is essentially different; for in absence of oxygen both initial and delayed heats fall gradually to practical extinction in about three hours (at which time the nerve is asphyxiated and also loses its power of conduction) but the ratio remains the same throughout. The fall in heat is probably due largely to a gradual failure of one fiber after another, though the heat in each fiber is also probably less,

due to conduction of subnormal impulses. These results are better interpreted with the aid of data on respiration.

Isolated sciatics were placed in small glass chambers with electrodes fused through the walls and fitting by ground glass joints to one or both limbs of a manometer. With alkali present in the chamber to absorb CO_2 any volume decrease represented oxygen consumed; and with opposite nerves in chambers on the right and left limbs of a manometer the resting oxygen consumption balanced out and the effects of stimulation of one side were obtained directly, with an error of only a few per cent. With no alkali present, the CO_2 produced could also be estimated. Experiments carried out under the same conditions as those on heat production showed the resting oxygen consumption to be 16 cmm. per gm. and hour, and the increase on stimulation (when tetanized with 280 shocks a second for twenty-two seconds every four minutes) 61 cm. per gm. and hour stimulation. The oxygen needed to produce the previously measured heats, if these were entirely due to oxidation of ordinary foodstuffs, is 14 cmm. for the resting and an extra 48 cmm. for the active states; so that there is little question that all the energy of the resting as well as the active metabolism is obtained by oxidations. Further, the extra oxygen consumption does not appear or cease sharply with the start and stop of stimulation, but shows a lag of about a quarter of an hour before reaching its maximum at start or its zero at stop, indicating that much, if not all, the oxygen consumption is delayed in time, corresponding to the delayed heat.

The R. Q. during rest is 0.77 (between 0.75 and 0.80), corresponding to the burning of a mixture of fats, proteins and carbohydrates. The R. Q. of the extra metabolism of activity is 0.97 (between .95 and 1.0), corresponding to the burning of carbohydrates, though the R. Q. of protein would also be 0.95 if the nitrogen ended in the form of ammonia rather than urea. As a matter of fact, about 0.45 mgm. per cent. of extra ammonia is formed during an hour of continued activity which, if all freed by protein oxidation, would mean enough protein oxidized to account for the oxygen consumed. It is improbable that the ammonia comes from this source, for at rest 0.2 to 0.3 mgms. per cent. of ammonia per hour is also formed, and equally whether the nerve is in oxygen or nitrogen, but pending further evidence it is not safe to conclude that carbohydrate is the sole fuel used by nerve for its activity.

Another significant fact appears when stimulation is continued without interruption rather than for short periods with rests between. The extra oxygen consumed then is only 18 cmm. per gm. and hour of stimulation, though this value may be maintained for several hours. The heat production per stimulus is also decreased when stimulation is repeated at short intervals. It appears, therefore, that the amount of energy a nerve can liberate per unit time of activity depends upon what fraction of the total time is spent in activity and what in rest. For short periods of activity it is able to discharge more energy than for longer ones. This can hardly be a "fatigue," in the sense of progressive failure due to activity, since the characteristic level of energy liberation is reached within a few minutes after any particular type of stimulation is begun and then remains constant for hours. It is suggested, therefore, that this coming to some equilibrium value be called "equilibration."

The evidence so far presented shows that during activity (as well as rest) a nerve obtains all its energy ultimately from oxidations. Little, or none, of the oxidations accompanies the nerve impulse itself, but rather they follow in the next 10–15 minutes; so at least two processes, probably three, occur in sequence. These can not be segregated or separated in time by oxygen lack, but after the impulse has been conducted the whole series of changes must run to completion in the usual manner. By analogy with muscle the thought occurs that the first stage is the formation of lactic acid and the last is its oxidation. (The ratio of initial to delayed heat is 1:9 instead of 1:1.5 as in muscle, which would correspond to the production of lactic acid followed by its total oxidation rather than partial restitution to glycogen.) If this were so, and the second stage must follow the first, no lactic acid should accumulate as a result of activity even in the absence of oxygen.

Sciatic nerves resting in nitrogen produce lactic acid, as do most other tissues. The production starts slowly and reaches a maximum rate of about 7 mgm. per cent. per hour in two to three hours after a nerve is put in nitrogen, then gradually falls to zero. If glucose (but not levulose or galactose) is added to the solution containing the nerves lactic acid formation continues at the maximum rate for days or until all the added glucose has been used up. Without added glucose about 100 mgm. per cent. lactic acid is formed in all, in 30 hours at 15° C., in seven to eight hours at 28° C., and there is in fresh nerve just about this quantity of carbohydrate. These facts leave little doubt that nerve will form lactic acid when kept in nitrogen as long as any precursor is available, and that the main precursor is glucose. These figures are similar to those for muscle, as is also the resting oxygen consumption, and indicate no great dissimilarity between the resting processes in the two tissues.

On stimulation in nitrogen, however, the story with nerve is entirely different, for, as anticipated from

the previous evidence, there is no increased accumulation of lactic acid. If more is formed it is also oxidized and, indeed, there is no direct evidence that lactic acid appears even as an intermediary step in the breakdown of sugar accompanying nerve conduction.

The picture now arrived at is, of course, very sketchy, but two questions require attention before even the broad outlines are complete. First, if the processes of conduction ultimately depend on oxidations, why can a nerve continue activity for several hours in nitrogen? Second, since most if not all the oxidations and energy changes occur after the impulse has been conducted, how do they enter into the system and why are they so essential? The answer to the first seems fairly definite. Nerve contains substances which are in an oxidized state when oxygen is present but can be reduced in its absence and so permit oxidations in the tissue—*i.e.*, an oxygen, or better oxidizing, reserve. Glutathione, cytochrome and similar respiratory intermediates might play such a rôle and, with some assumptions, it may be calculated that glutathione in nerve might alone permit oxidations for an hour's activity. Experimentally it is found that when a nerve is exposed to oxygen after two hours in nitrogen it takes up during the first hour in oxygen considerably more of this gas than later on; in fact, the extra oxygen taken up is about two thirds as much as it would normally have used during the time in nitrogen. Still more direct evidence is found in the fact that, kept over night in nitrogen, a nerve actually *produces* 10–15 per cent. as much CO_2 as it would in the same time in oxygen, and presumably most of this appears in the first few hours. Finally, nerve as other tissues does not produce lactic acid during rest as long as oxidations are in progress and, as stated, the lactic acid production does not get under way for about two hours after a nerve is put in nitrogen. All these facts suggest that, due to a reserve, oxidations may continue several hours after external oxygen is excluded—and during this time a nerve continues in fact to be able to conduct.

The second point has not yet been answered, but some evidence is available. The simplest assumption for the first reaction, accompanying conduction, is that some substance, presumably carbohydrate, is changed to another, $C \xrightarrow{O_2?} X$; and in the second delayed stage $X + O_2 \rightarrow CO_2$. This can not, however, be correct, for after a few hours in nitrogen there is still plenty of C left and accumulation of X is apparently unable to inhibit the first reaction, at least if X is diffusable, for a nerve kept in gas fails no sooner than one in fluid. This would mean that cutting out the second reaction could have no influence on the future carrying out of the first. Such an influence would be present, however, if an accessory substance A, necessary for the first reaction, were changed to an inactive state A^1 in the first stage and returned to its original form by the second. (The change might conceivably be a physical rather than a chemical one.)

$$C + A \xrightarrow{O_2?} X + A^1 \quad \ldots\ldots 1$$

$$X + A^1 \rightarrow CO_2 + A \quad \ldots\ldots 2$$

This scheme is still too simple, as it ignores the changes immediately following the conduction of an impulse, while a nerve passes from the absolutely refractory period to normal conductivity and energy liberating capacity. This intermediate change implies a third reaction, and very probably it is this one that fails as a result of the absence of the delayed changes. The skeleton of the complete system[3] would then be:

$$C + A \xrightarrow{O_2?} X + A^1 \quad \ldots\ldots 1$$

$$A^1 + E \xrightarrow{O_2?} A \quad \ldots\ldots 2$$

$$X + O_2 \rightarrow CO_2 + E \quad \ldots\ldots 3$$

in which the extra factor E is needed to restore A^1 to A and is produced only during the final reaction.

With a limited quantity of the A, A^1 system and a variable excess of E, this hypothesis accounts for the facts given above, as well as many others. During conduction all A present changes to A^1; if less than the normal amount be present the impulses are of subnormal intensity and produce less heat, if less than a critical value conduction is entirely suspended. During the refractory period, reaction 2 restores A, the absolutely refractory period lasts until the critical amount of A is restored, the relatively refractory one until restoration is complete. Reaction 3 is relatively extremely slow, lasting 10 minutes, so that with activity the amount of E falls until an equilibrium is reached between its formation and use. For repeated activity of a few seconds with minutes of rest between, the resting concentration of E will be practically maintained and reaction 2 and so 1 proceed as after rest. But as the activity is prolonged and rests shortened the restoration of E will lag further and further behind, reaction 2 will be progressively slowed and subnormal or less frequent impulses will result. This corresponds to the process of equilibration shown by heat production and oxygen consumption (and

[3] This may also be expressed, to indicate better the nature of reactions 2 and 3 as a means of "winding up" the mechanism for reaction 1, as follows:

$$CA \rightarrow A^1 + X \quad \ldots\ldots 1$$

$$C + A^1 + E \rightarrow CA \quad \ldots\ldots 2$$

$$X + O_2 \rightarrow CO_2 + E \quad \ldots\ldots 3$$

action current as well). It has been found by Field and Brücke, which accords with this hypothesis, that the refractory period steadily increases with continued stimulation for at least 10 minutes and recovers during rest. After equilibrium is established, in several minutes, no further change takes place as long as the same stimulation is continued, until in many hours fatigue, possibly due to exhaustion of C, sets in.

Absence of oxygen interferes with reaction 3. In nitrogen the oxidizing reserve permits it to continue for some time, but more and more slowly as the reserve is used up, and finally it ceases entirely. The amount of E will correspondingly slowly fall and, exactly as above, reaction 2 and then 1 be interfered with and weaker and less frequent impulses be conducted; the system eventually tending, however, not to equilibrium but to completion with failure of conduction. The fall in heat, prolongation of refractory period reported by Fröhlich and by Kato, spreading out of action current, etc., that accompany the course of asphyxia all find their explanation on this basis.

Other phenomena of nervous activity are in conformity with this scheme, but it is not wise to press it further till more definite knowledge of the actual changes postulated is available. At present there is evidence that other changes than the direct energy yielding ones are indeed present, but what rôle they play, if any, remains to be determined. The formation of ammonia has been mentioned and there are also changes in phosphates (unpublished observations). In fresh nerve there is about 60 mgm. per cent. of "soluble" phosphate (expressed as P_2O_5), of which less than half is free inorganic and the remainder partly in an acid labile combination (phosphagen?) partly in an acid stabile one (lactacidogen?). Long standing in oxygen has little effect on the distribution, but standing in nitrogen sends all or nearly all of the phosphate into the inorganic form.

It remains to correlate this material with some actual mechanism of conduction. The current view that activity of one portion of a nerve fiber is the stimulus to the adjacent portion and so along the entire fiber has much to support it, especially in the form developed by Lillie. Recent evidence indicates that conduction itself may be analyzed into two phases occurring repeatedly in succession. The first is an explosive type of chemical change in a portion of the membrane surrounding the nerve fiber, and it leads, probably by local potentials, to ion movements within the fiber, which constitute the second phase. Local concentration of ions against an adjacent portion of membrane initiates here the explosive change, and so on. Probably the ion movements are associated with only a small fraction of the energy changes, and all the material presented above concerns itself mainly with the behavior of the membrane during and after conduction. Reaction 1 would thus be the one directly entering into conduction, the explosive change determining by its intensity the amount of potential developed, the distance ahead that adequate ion movements take place, and so the intensity and speed of the nervous impulse. Most factors affecting conduction act primarily through the membrane reactions, but some, as for example diameter of the nerve fiber, may act through the ion changes. It seems not impossible to account for the phenomena associated with the activity of nerve along the lines here sketched; and, recalling that the metabolism of central nervous tissue is several hundred times as intense as that of peripheral nerve, there appear to be available many new data to help account for such reflex phenomena as summation and fatigue.

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HAWAII'S TRIBUTE TO DR. NEWCOMBE

DR. FREDERICK CHARLES NEWCOMBE, professor emeritus of botany and retired head of the department of botany at the University of Michigan, died in Honolulu, T. H., October 1, 1927, aged sixty-nine years.

On account of failing health, Dr. and Mrs. Newcombe had made their home in Honolulu since October, 1923, soon after Dr. Newcombe's retirement from the university. Mrs. Newcombe died July 10, 1927.

Although never of robust physique, Dr. Newcombe was an indefatigable worker. Even after coming to Hawaii, he continued his researches on the sensitive reactions of plants at the Hawaiian Sugar Planters' Association with which he was associated.

The rare opportunity was afforded Dr. Newcombe, after retirement from a long, active career of teacher, research worker, executive of his department, editor and counselor to many, to carry his endeavors into a new and different environment. Here he not only continued research in his chosen field, but became a leader in the scientific thought and life of the territory. Few indeed, even if they had not been burdened as he was by failing health and the strain of the long, fatal illness of a loved one, could have grasped such an opportunity. It is a tribute to the man's undying loyalty to the work he loved, to his keen mind, tactful optimistic personality, indomitable will power and sound judgment, which never permitted him to do anything hastily, that he was able, in spite of anxiety, physical and mental suffering, to gather together and unify into two working organizations the many diverse scientific interests of the