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ELECTRICAL PHENOMENA IN THE LIVING CELL[1]

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TO AVERT any suspicion that my subject has only academic interest let me recall two aspects of it. You will remember that when Waller began to study the electrical disturbances accompanying muscular contraction in intact animals, using the simplest sort of apparatus, only academic interest was aroused, but afterwards another physiologist, Einthoven, not content with the capillary electrometer used by Waller, devised the string galvanometer which made possible the electrocardiogram which is of such practical importance today.

My second instance is in recent work on sensation. Adrian finds that pinching a cat's foot sets up electrical disturbances in the sensory nerve; the harder the pinch the more rapidly do they follow each other and it would seem that the sensation depends on such disturbances, the intensity varying with their number. In the psychological laboratory of Princeton it was recently demonstrated that when an amplifier and a telephone were connected to the auditory nerve of a cat, words spoken into the cat's ear were reproduced in the telephone, showing that the electrical disturbances in the auditory nerve may account for the sensation of hearing. Indeed, all our sensations seem to depend on such electrical disturbances.

Phenomena of this sort are not confined to muscle and nerve but are found, for example, in glandular tissue and in plants, and may be very general. They are best studied by using single cells of large size, but as single nerve or muscle fibers (completely separated from other cells) are difficult to obtain, we have resorted to the use of single plant cells which offer such important advantages that I venture to ask your attention to some results obtained with

[1] Lecture delivered April 17, 1930.

them, especially with the multinucleate cells of the fresh water plant *Nitella* which reach a length of six inches or more.

What do we know about these disturbances? In spite of all their differences in various animals and in plants there are two points in which they always agree. In the first place, the excited region is electrically negative to the unexcited so that when an experiment is arranged as in figure 1 the current flows through the

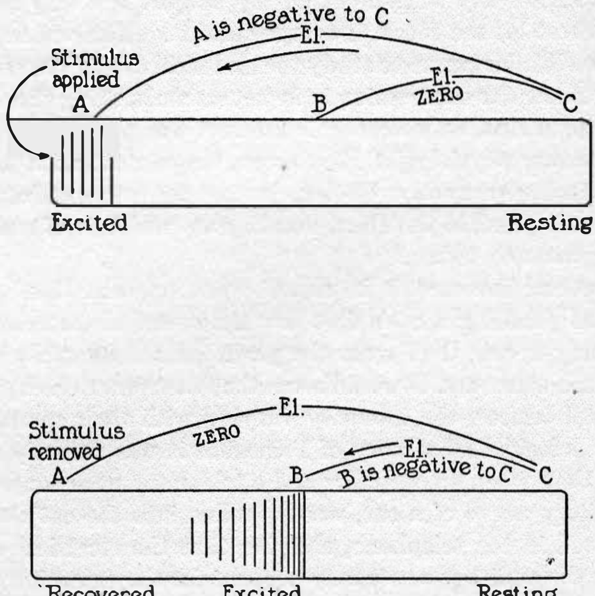

Fig. 1. Diagrams to show that an electrical disturbance starting where the stimulus is applied travels along the cell after the stimulus is removed, leaving behind it a region in the process of recovery: the excited region (*B*) is negative to a resting region.

galvanometer from the resting to the excited region. Hence (regardless of its origin) the term negative variation is appropriate. In the second place starting at the point where the stimulus is applied, the disturbance travels along the cell (always remaining negative to the region which is not yet excited): when it has passed, the protoplasm returns to its resting state and the process may be repeated by applying a new stimulus.

Why is the excited region negative? Because some or all of its potential difference has disappeared. This can be shown in *Nitella* by leading off to a spot which has been killed and in consequence has lost its potential difference (fig. 2): we then see that the excited spot has likewise lost its potential difference since no current flows from it to the killed spot. But current will flow

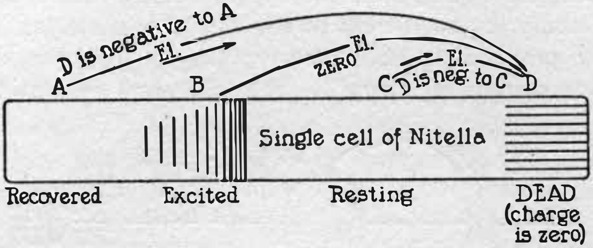

FIG. 2. Diagram to show that the excited region may lose its potential difference as completely as a killed spot.

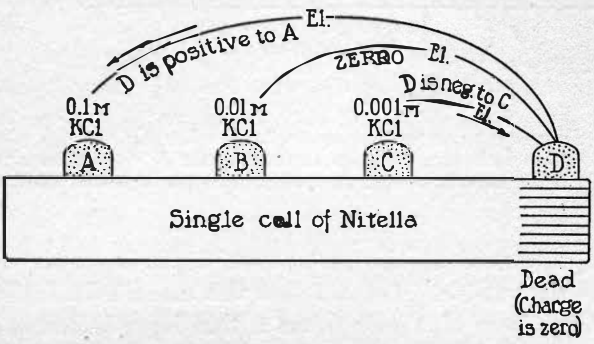

FIG. 3. Diagram to show that the potential difference of the protoplasm depends on the solution applied externally: in this way the "current of injury" may be made positive, negative, or zero.

from the resting to the excited region since the resting region has a positive potential difference.

What produces the potential difference of the protoplasm? It is due to local differences in the concentration of ions, as is beautifully illustrated by applying solutions to a cell of the fresh water plant *Nitella*, as in figure 3 (which shows an experiment carried

out in collaboration with E. S. Harris). We see that the killed spot which has lost its potential difference is negative to a spot in contact with a dilute solution, such as 0.001 M potassium chloride. This is the "negative current of injury" everywhere described in the literature as the invariable situation: but *Nitella* is an exceptionally favorable object which shows that this is not always the case. For when we apply 0.01 M potassium chloride we commonly get no current at all, but 0.1 M potassium chloride instantly produces a lasting current in the opposite direction ("positive current of injury"). It is therefore evident that the

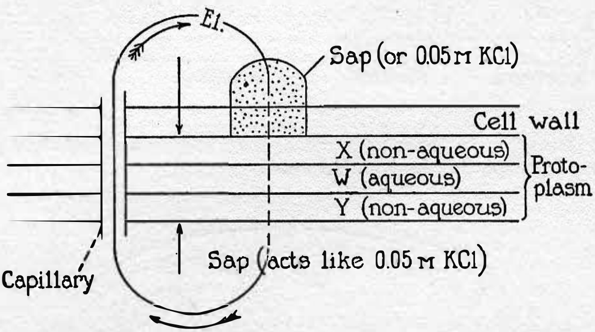

FIG. 4. Diagram to show that protoplasm with sap on both sides gives a current which indicates that its outer surface *X* differs from its inner surface *Y:* it is assumed that *X* and *Y* are nonaqueous and that *W* is aqueous.

potential difference of the protoplasm depends on the solution applied to the outside. Let us follow this clue a little farther.

The protoplasm of *Nitella* forms a thin layer inclosing a clear watery sap (which behaves, when placed on the outside of the protoplasm, like 0.05 M potassium chloride). We picture the protoplasm as composed of layers, as in figure 4, because when sap is placed on the outside a positive current tends to flow outward through a capillary, as shown by the arrow. This could not be the case if the protoplasm were a single homogeneous layer: apparently the simplest assumption is that *W* is an aqueous layer and that *X* and *Y* are nonaqueous (possibly lipoid).

Ions in contact with the nonaqueous layer produce potential

differences which are most easily accounted for by assuming that they are due to diffusion potentials. As diffusion potentials arise only when ions move at different rates, we wish to know the mobilities of the ions in the nonaqueous layers. These have been calculated in the case of the outer layer, *X*; for example, we place 0.01 M potassium chloride at one spot and 0.01 M sodium chloride at another and find a potential difference of 82.9 millivolts, from which we calculate the mobility of the potassium ion in *X* to be forty times as great as that of the sodium ion. With 0.01 M sodium chloride at one point and 0.001 M sodium chloride at another we find a potential difference of 20.9 millivolts, from which we calculate that the mobility of the sodium ion is 2.18 times as great as that of the chloride ion.

From these values we calculate that the conductance of potassium chloride in *X* should be about twenty-seven times as great as that of sodium chloride: the observations of Dr. Blinks show that for the whole protoplasm it is from twenty-five to fifty times as great.

Calculations on the basis of phase boundary potentials or of Donnan potentials are not satisfactory. Hence we may assume for purposes of convenience that diffusion potentials play the principal rôle.

On this basis the results shown in figure 4 could be accounted for by supposing that the sap has a greater diffusion potential against *X* than against *Y* (experiments *in vitro* indicate that the diffusion potential of an aqueous salt solution may differ considerably with different nonaqueous substances, such as *X* and *Y* are assumed to be). In certain cells greater effects are observed: in the marine alga *Valonia* (as shown by experiments carried out with E. B. Damon) with sap outside, 35 millivolts are observed (as against 15 in *Nitella*), and in the marine alga *Halicystis*, L. R. Blinks has found about 40 millivolts in the opposite direction (i.e. an apparently greater diffusion potential of sap against *Y*).

A lowering of the concentration reduces the diffusion potential, and the effects shown in figure 3 can be quantitatively accounted for on this basis.

We thus arrive at a simple explanation of the potential differ-

ences of the protoplasm, and consequently of the negativity of the disturbance.

How does the disturbance (negative variation) travel along the cell? A loss of potential difference at any point causes a flow of current from neighboring points and this causes them to lose their potential difference in turn. Let us consider an unstimulated *Nitella* cell growing in pond water which we may picture as at *B*, *C*, and *D* in figure 5 where the arrows show the direction in which the positive current tends to flow. On applying 0.05 M

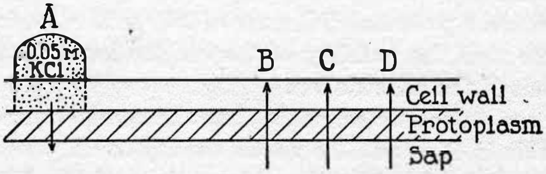

FIG. 5. Diagram of protoplasmic potential differences. The arrows show the direction in which the positive current tends to flow: at *B*, *C*, and *D* the cell wall is imbibed with pond water (positive potential difference); at *A* the application of 0.05 M potassium chloride makes the potential difference negative.

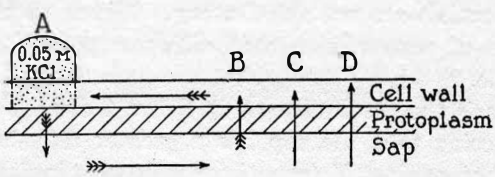

FIG. 6. As in figure 5, but with an actual flow of current between *A* and *B* as shown by the feathered arrows.

potassium chloride at *A* so that the arrow is reversed we suppose that a flow starts between *A* and *B* as shown in figure 6 where the feathered arrows denote the flow of current. The outward flow at *B* causes its potential difference to fall approximately to zero so that a flow starts between *B* and *C*, and then between *C* and *D*, and so on: in this way the negative variation travels along the cell. This accords with the "local circuit theory" developed by various investigators, which is most advantageously tested by the use of such single cells as those of *Nitella*.

How does the outward current (as at *B*, figure 6) remove the

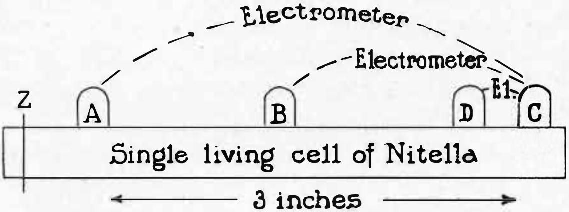

FIG. 7*a*

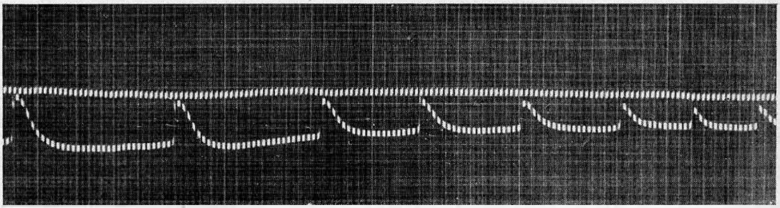

FIG. 7*b*

FIG. 7*b*. Photographic record of an experiment arranged as shown in figure 7*a*: the upper broken line shows the P.D. of *B* against *C*, and of *D* against *C*, and is a little above zero. The lower broken line shows the negative variation at *A*. This is due to a stimulus which is blocked so that it does not reach *B*, *D*, or *C*. The vertical lines represent 5-second intervals. Here the potential difference is lost each time a negative variation occurs but does not recover its full value after the action current has passed; hence the potential difference becomes smaller with time.

charge? The fall of resistance observed by Blinks indicates that this may be due, in part at least, to the fact that the current in passing outward from the sap (abounding in potassium) sweeps potassium ions into the protoplasm (as a rule the inward current has no such effect because the concentration of potassium in the external solution is too low). Since the protoplasmic potential difference depends chiefly on the deficiency of potassium ions in the protoplasm as compared with the surrounding solutions, it tends to disappear when potassium ions move into the protoplasm or into the film just outside it. In addition reversible changes of structure may play a part, for any openings in the nonaqueous layers, or electrical leaks, will reduce the potential difference.

Until these potassium ions leave the protoplasm (aided by the reversal of the current which normally occurs after the negative variation) and any structural changes are repaired, the protoplasm is said to be in a refractory state: when this is over it returns to its resting state. But if enough potassium ions remain in the protoplasm or just outside it they may produce some of the phenomena commonly called "fatigue" (e.g. the next negative variation will be less marked because there is less potential difference of the protoplasm so that its loss produces less change, as shown in figure 7-*b*).

It should be added that the protoplasm can recover during the application of a continuous electrical stimulus: this may indicate that structural changes play a part.

If the movement of potassium ions suffices to explain the facts we need not assume that changes in structure or in permeability occur during the passage of the current action.

It may be asked why the potassium ion is so important. Evidently because it produces large diffusion potentials and high conductance through its high mobility. Its mobility in X appears to be about eighty-five times as great as that of the chloride ion and about forty times as great as that of the sodium ion: the mobility of the cesium ion is about the same as that of sodium; the ions of ammonium, lithium, magnesium, and calcium have a lower mobility than that of sodium. (These mobilities differ from those in water where potassium and chloride ions move at nearly the same

speed, and the cesium ion moves faster than that of the potassium ion. This indicates that the protoplasmic surface is non-aqueous.)

Although the hydrogen ion appears to have a high mobility in the protoplasm, its concentration is so low in the sap, for example, that it does not play an important part so that the diffusion potential of the sap depends chiefly on the potassium ion.

Potassium is important in conductance because, other things being equal, the higher the mobility of the cation the higher the conductance. We therefore expect an increase of conductance when we increase the concentration of potassium ions in the protoplasm, and Dr. Blinks finds this to be so. In the excited region the conductance is greater than in the resting region (even when the external concentration of potassium is low), which seems to be due to the fact that potassium ions are swept into the protoplasm from the sap by the outward current which accompanies excitation.

This picture of the production of electrical disturbances has enabled us to make some interesting predictions, as, for example, that whenever we can reduce the potential difference at any point to zero (or reverse it) and retain this condition for a time we should be able to make a *Nitella* cell produce successive negative variations like a heart muscle. This proves to be the case, as is evident from figure 8-*b*, showing successive negative variations set up by potassium chloride. Similar results are obtained by killing one end with chloroform instead of applying 0.05 M potassium chloride (this experiment and the two following were carried out in collaboration with Dr. Hill).

We could also predict that even when the potential difference is reduced at any point a variation will not start unless neighboring points have sufficient potential difference to make a rather steep electrical gradient and hence set up enough outward flow at such points to reduce their potential differences to zero. By arranging a proper sequence of solutions of potassium chloride along the cell we can produce any electrical gradient we please and we find that when the gradient is gentle no variation passes because not sufficient outward flow occurs; in other words, there is a block.

A further prediction was that we should be able to get around

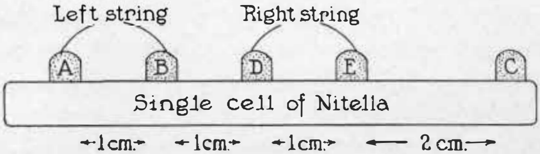

FIG. 8*a*

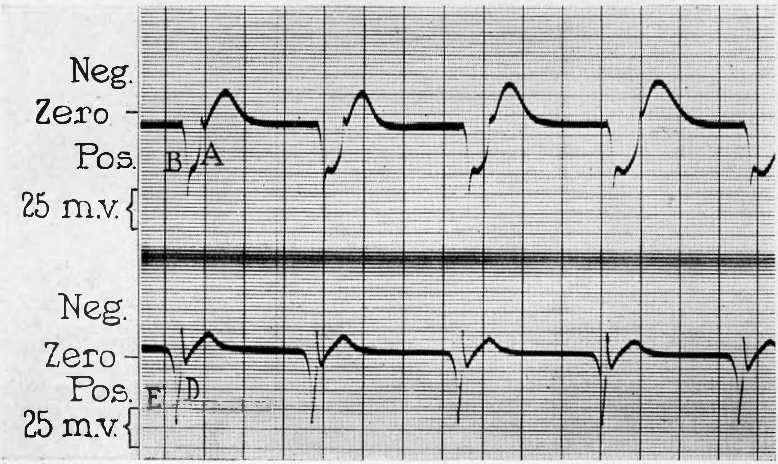

FIG. 8*b*

FIG. 8*b*. Photographic record of an experiment arranged as shown in figure 8*a*. A double string galvanometer is employed, the left string giving the upper and the right string the lower record. On applying 0.05 M potassium chloride at *C* a series of negative variations is set up (the first movement in each is negative but appears positive because the instrument records the potential difference of *A* against *B* and of *D* against *E*). The time marks represent 5-second intervals.

that when a negative variation reaches a given place that spot loses its potential difference entirely, just as a charge of powder in a cartridge explodes completely or not at all: in our discussion hitherto we have assumed this to be true and in general it seems to be so. But in *Nitella* there are apparent exceptions, such as are shown in figure 10-*b*, where we see that sometimes the protoplasm loses all and sometimes only a part of its potential difference. (It should be noted that this figure differs fundamentally from figure 7-*b* where the potential difference is completely lost each time.)

It may be that in such cases the inner layer, *Y*, loses all of its potential difference (because the concentration of potassium ions becomes temporarily equal on both sides, due to the outward current) but that this is not always the case with the outer layer, *X*, so that the positive or negative potential difference of *X* may persist during the passage of the negative variation.

Let us now examine certain interesting possibilities. Stimulated protoplasm loses its potential difference wholly or in part and it therefore becomes negative to resting protoplasm with a positive potential difference: should it not therefore become positive to resting protoplasm which has a negative potential difference? In the case of *Nitella* we can easily give the resting protoplasm a negative potential difference of 30 millivolts or more by applying 0.1 M potassium chloride to the exterior. A reversible loss of potential difference has not yet been obtained under these conditions but an irreversible one is easily produced by cutting. We then obtain a "positive variation" (fig. 11) which travels along the cell like the negative variation but with much greater speed. It can pass a killed region and appears to be due to a mechanical wave traveling in the sap, and hence differs from a negative variation or propagated disturbance in the protoplasm. (These experiments were made in collaboration with E. S. Harris.)

This irreversible "positive variation" seems to be due to the fact that the outer layer of the protoplasm loses its potential difference more rapidly than the inner, probably because it is in contact with a solution containing more potassium.

This assumption of the presence of layers in the protoplasm raises interesting questions. In *Nitella* and *Valonia* such layers

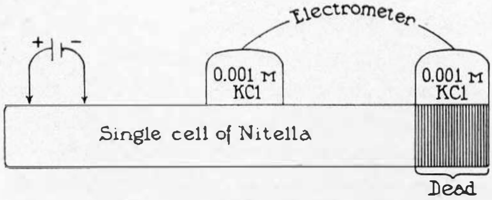

FIG. 10a

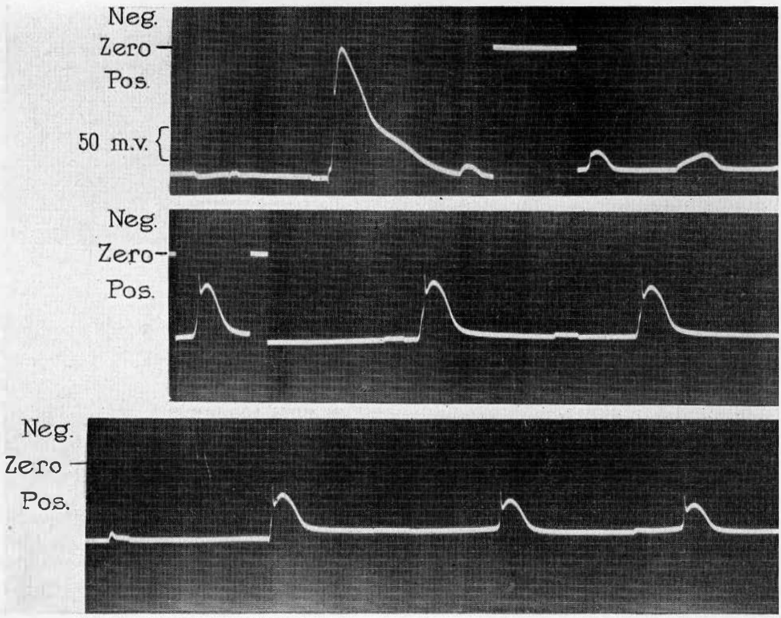

FIG. 10b

FIG. 10b. Photographic record of an experiment arranged as shown in figure 10a: the stimulus was either electrical or chemical. The right end was killed by applying 0.001 M potassium chloride saturated with chloroform. The upper part of the record shows a complete loss of potential difference during the negative variation (*i.e.*, the response goes to zero), followed by three partial losses of potential difference. The middle and lower portions of the record are from another cell of the same lot and show negative variations accompanied by incomplete loss of potential difference (i.e. not going to zero).

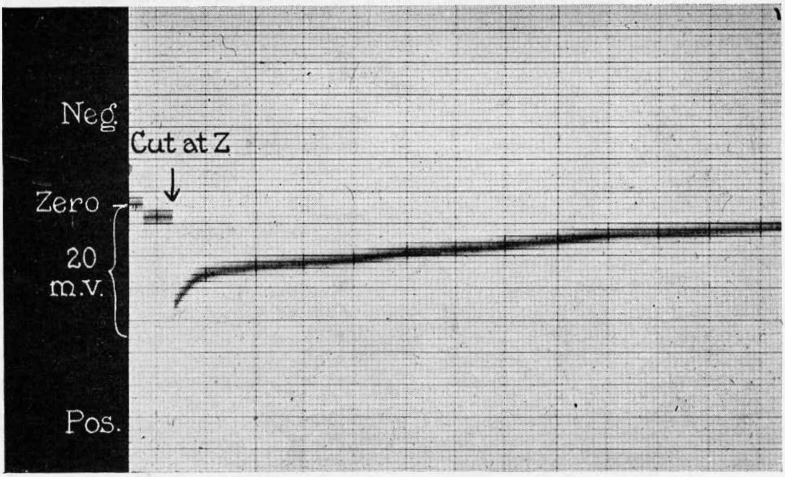

FIG. 11. Photographic record of an experiment arranged as in figure 7*a* but with *B* and *D* omitted; 0.1 M potassium chloride was placed at *A* and *C* and the cell was then cut at *Z*. The vertical lines represent 5-second intervals.

seem to have a real existence and the outer, X, seems to differ from the inner, Y. For example, in *Valonia* we find chlorophyll in the protoplasm and, since this contains magnesium, we may suppose that magnesium penetrates X but it cannot pass through Y for it is not found inside the vacuole except in traces which may be due to abnormal conditions. Also it was found (in experiments carried out with A. G. Jacques) that if we apply manganese to Y by injecting it into the vacuole the cell dies much sooner than when we apply it to X by adding it to the external solution. (The introduction of the capillary for purposes of injection does not account for this result for it is introduced into every cell, including the controls.)

We have found methods of killing X without killing Y by applying toxic solutions to the outside and we are trying to kill Y before killing X by applying toxic solutions to the inside. In this way we hope to study each layer separately.

What is the nature of the outer and inner layers, X and Y? In many respects they behave like lipoids as, for example, in their high electrical resistance which, according to Dr. Blinks, amounts to 250,000 ohms per square centimeter for *Nitella* in contact with 0.01 M sodium chloride. Such high resistances have not hitherto been reported because single cells of large size have not been employed; for example, a value of less than 1 ohm per square centimeter has been reported for red blood corpuscles of beef, but this low figure is doubtless due to leaks between the cells and to injury.

Most of this resistance is due to a back electromotive force developed during the passage of the current, but in the absence of a nonaqueous phase this would not be possible and such a phase is most probably lipoid in nature.

The fact that the mobilities of potassium and chlorine ions are so different in the surface layer of the protoplasm shows that this layer is composed of a nonaqueous substance and again the most natural assumption is that it is lipoid.

In respect to permeability these layers also act like lipoids, as is strikingly shown in the experiments on dyes carried out by Miss Irwin, who is able to predict the penetration of dyes into *Nitella* by means of an artificial model consisting of a lipoid layer bathed

on both sides by aqueous solutions; this applies even to cases which are not in harmony with Overton's theory and has led to the substitution of the multiple partition coefficient theory in place of that of Overton.

If these layers are lipoid how do salts penetrate? We have seen that the mobility of the potassium is in some cases higher than that of sodium. In these cases the penetration of potassium is greater than that of sodium, but this does not exclude the possibility that most of the potassium may penetrate by forming undissociated molecules at the outer surface and so pass through the lipoid layer, dissociating on the other side just as hydrochloric acid passes through air from one aqueous solution to another or as silver perchlorate passes from an aqueous solution into benzene. To a certain extent ion pairs may penetrate or ions may exchange across the protoplasm, but the high electrical resistance of the protoplasm for most ions indicates that this cannot happen to any great extent. If the outer layer of the protoplasm is lipoid it would probably contain a much higher concentration of molecules than of ions so that (unless the mobility of ions were much greater than that of molecules) penetration would be chiefly in molecular form.

In some respects the protoplasmic layers act like certain collodion membranes, *e.g.* in the behavior of their electrical potential differences and in admitting undissociated molecules more freely than ions. In still other respects they act like metallic surfaces, e.g., when subjected to direct and alternating electrical currents. Here are problems which are highly interesting.

More fascinating still is the fact that these surfaces play such an important part in life phenomena. We may recall in this connection Loeb's definition of organisms as "colloidal machines" and his dictum that the colloidal properties of matter are manifest only in the presence of semipermeable surfaces without which life phenomena would be impossible. One of the most remarkable feats of protoplasm is the construction of thin, nonaqueous, surface layers in contact with aqueous solutions on either side. They are found not only at the external surface of its cells but also at those of nuclei, plastids, vacuoles, and other inclusions. By determining

what passes in and out they not only control metabolism but they localize its processes and make possible the differentiation which accompanies development. And indeed the distinction between living and dead protoplasm is closely connected with such surfaces, for any break in the surface, unless instantly repaired, quickly causes death accompanied by loss of protoplasmic potential difference and of electrical resistance.

In consequence of this we are able to follow the process of death step by step by measuring alterations in protoplasmic potential and in electrical resistance and, since our methods permit us to observe very minute changes lasting only a fraction of a second, we can detect the very onset of injury as well as the course of recovery; hence we have a method of determining whether a cell is in normal condition. It may be of interest to add that the general laws governing these phenomena in tissues, which were presented to the Harvey Society when I last had the honor of addressing it, have been confirmed and extended by Dr. Blinks, using single cells of *Nitella* and of *Valonia*.

Since the surface is an extraordinarily delicate indicator of the condition of the cell and minute changes in it can be detected by electrical methods, they are of fundamental importance in the study of vital phenomena. It is said that life processes must always elude us because they are so complex. But mere complexity should no longer baffle the analytical resources of modern science when all the variables are measured. The real difficulty is that in the process of measurement we may alter variables or create new ones without being aware of it. To study life phenomena satisfactorily such changes should be detected at the very start and avoided throughout our investigations. Electrical methods offer a way of doing this.

Only a few aspects of these methods have been touched upon but it is evident that a rich field awaits exploration.

PROGRESS OF MEDICINE DURING THE PAST TWENTY-FIVE YEARS AS EXEMPLIFIED BY THE HARVEY SOCIETY LECTURES[1]

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THE constitution of this society states its object to be the diffusion of knowledge of the medical sciences, or, more specifically, "the diffusion of scientific knowledge in selected chapters in anatomy, physiology, pathology, bacteriology, pharmacology and physiological and pathological chemistry." This statement implies that these sciences form the foundation on which the superstructure of medicine is built. That medicine itself is omitted from this catalogue of sciences suggests that medicine is something different, that as an independent branch of human knowledge it does not exist, or, if so, that its content and the methods for its pursuit are not of a character to justify its inclusion in this family of sciences. Time would not permit me, even if it were profitable, to discuss the justification for this attitude, but I may point out the great and important change that has taken place in the past twenty-five years toward this point of view. The independent position which this discipline now occupies in certain universities, its elevation to a rank equivalent to that of the other sciences mentioned and its disinterested pursuit by men whose chief object is its advancement indicate one of the most striking changes which has occurred in medicine, and to-day, if the constitution of this society were to be written, its object would probably be stated to be the diffusion of scientific knowledge in medicine and related sciences.

For this reason, as a humble disciple in this new science, yet one of the oldest, I feel gratified in being asked to discuss briefly the changes that have taken place in it during the past quarter century.

[1] Lecture delivered May 15, 1930.

Possibly the simplest way to approach this task would be to analyze carefully the entire series of lectures, pick out the new facts, or apparent new facts, presented by each one of the speakers, carefully catalogue and index and group them, possibly give them a statistical treatment, and then present to you my results, and conclude with an apotheosis of modern science, particularly of those sciences in which we are interested, not forgetting to point out the great and beneficent practical results that have been attained. I have preferred, however, to consider this subject in a somewhat different manner, and if I sometimes seem to strike a critical note I trust you will remember that I have endeavored to consider my subject in a purely objective and disinterested manner, as befits this society.

The historian of an epoch is usually granted a retrospection of a sufficiently distant past that he can discriminate between the momentous events of the period and the less significant details which are apt to be magnified in the eyes of contemporaries. For one who has lived in the midst of events to attempt, at the end of so short a period as twenty-five years, critically to survey that period is a hazardous undertaking. Moreover, no period in history can be satisfactorily isolated from that which precedes and follows.

That changes in concepts are constantly occurring, new facts being brought to light, in medicine, as elsewhere, is obvious to all. What we are considering, however, is not change but progress. With the exception of a few philosophers, people of to-day believe in progress. It is almost axiomatic. But man did not always accept that assumption. The Greeks kept looking to the past as the halcyon days and longed for their return. It was only at the end of the eighteenth century, when the multiplication of discoveries in natural science enormously amplified knowledge of the environment, that the idea of progress was clearly formulated and became generally accepted, and that man became so hopeful of the future.

To-day we have to ask ourselves not whether medicine has progressed but at what rate progress has occurred. The scientist would have great difficulty in finding a formula by which to solve this problem. The only method that suggests itself is that of

comparison. Let us, therefore, take a sample period from times past, and for a few minutes consider an imaginary course of Harvey Society Lectures given a hundred years ago, from 1805 to 1830. Who might have been our lecturers and of what progress could they have told us?

This era is not considered by historians an outstanding one as regards medical progress, but we are prepared for some advances, since in other realms of human interest men's minds showed no signs of sterility. Keats and Shelley were making their great additions to English poetry; Beethoven during this period composed all but two of his symphonies, and Goethe wrote "Faust," besides making contributions to comparative anatomy and metamorphosis of plants of no mean importance. Rapid changes were also taking place in men's habits of life. The steam locomotive was being developed, gas was becoming a common illuminant in the houses and streets, thus making transportation more rapid and lengthening men's hours of activity.

In our hypothetical course we should not have had many lecturers dealing with infectious diseases, but we should have had Edward Jenner. The subject of his lecture would, of course, have been vaccination, but he could also have told us something about the reactions (now called allergic) which he had observed in vaccinated persons who had previously had small-pox. Daniel Drake would have been invited to speak on epidemiology, although his classic book on "Diseases of the Interior Valley of North America" was not published until somewhat later. Possibly he would rather have spoken on medical education, since his papers on this subject have been called "the most important contributions ever made to this subject in this country." We should also have asked Elisha North to come down from New London and talk about cerebrospinal meningitis, as his book giving the first description of this serious disease was published in 1811. There were other American physicians and scientists (most of the scientists of those days were physicians) who might have been invited, but then, as now, we should have endeavored to obtain as much foreign talent as possible. Auenbrugger was getting too old to make the long journey, but after the publication of Corvisart's book in 1818 we should

certainly have invited him to come over and discuss the new method of percussion. An invitation would also have been sent to Piorry to address us on mediate percussion and to show his pleximeter. Laënnec would, of course, have given us a lecture, and not only demonstrated his stethoscope, but told us about a half dozen chest diseases we had never heard of. Louis would have been one of our best lecturers, for he could have presented abstracts from his masterly book on phthisis or from that on typhoid fever. But, more important, he could have told us much about the new so-called numerical method for studying disease. His method, however, was not very complicated, the essential features of it consisted in making careful observations and keeping records. He would not have presented very complicated mathematical formulas. Moreover, it would have been interesting to have had a full-time teacher of medicine. He was one of the first. There would have been a very distinguished group of clinicians among the lecturers; Bretonneau would have lectured on diphtheria; John Cheyne would have talked to us about a peculiar type of respiration; Robert Adams, about heart block, although he did not give it that name; Thomas Hodgkins, about a new disease of the glands, and of course Sir Dominic Corrigan, who would have given a lecture on the pulse. One of the best lecturers would have been Richard Bright, who in 1827 published his description of nephritis. Several years earlier we might have had a lecture by William Charles Wells, a native of Charleston, who, in 1811, pointed out the relationship between dropsy and albuminous urine and thus prepared the way for Bright. We should thus have presented to our New York audience the two men who have made the most important observations concerning nephritis from that day to this. A German clinician whom we should have attempted to obtain as lecturer was Schönlein, for he would have addressed us concerning the importance of examinations of the blood and urine, especially chemical examinations, as he was an ardent advocate of this kind of clinical study.

But besides physicians we should then, as now, have invited anatomists and physiologists, chemists and physicists. Among the anatomists, we should have invited Lamarck and Cuvier, and

also the German comparative anatomist Johann Friederich Meckel, who, as you know, was also a pathologist.

Unfortunately, John Hunter had died ten years before our course began, and Claude Bernard was not born until 1813, but we should have had Magendie, who would probably have spoken of his experiments concerning digestion. He might also have described his observations regarding sensitization to egg white. Johannes Müller was a little young, but he might have come over at the very end of the course and lectured on "Law of Specific Nerve-energies." We should earlier have had a lecture by Sir Charles Bell on the differentiation of sensory and motor nerves, but Müller would have elaborated and developed this theme. Our own William Beaumont would certainly have been invited to speak on the physiology of gastric digestion, and I imagine he would have been so pleased by the invitation that he would have brought Alexis St. Martin with him for demonstration.

There would have been some chemists, too, of first-rate standing. At the very end of our course we should have invited Liebig, even though he were still quite young. He discovered hippuric acid in 1829, and the year before his associate, Wöhler, had succeeded in synthesizing urea, so we should have made a great effort to get one or both of them. Humphry Davy, or Sir Humphry if he had not come before 1812, would have been one of our most popular lecturers. He would have brought his apparatus and performed experiments before us as he did at the Royal Institution. He would probably have demonstrated the anesthetic effects of nitrous oxide on some member of the audience.

We might have had one or two physicists also, although at that time their work did not seem to have any direct relation to medicine. However, Thomas Young was a doctor and he might have lectured on the differences between the physical and physiological properties of light, or even on the circulation. At the dinner before the lecture he might have told us something about his deciphering the Rosetta stone.

It is true that some of the men I have mentioned might have been overlooked when sending out the invitations to lecture before the Harvey Society. Certain of them were ignored by their asso-

ciates; others were openly opposed. Some who were most loudly acclaimed in their day are now ranked much lower.

I have described this hypothetical course of Harvey Society Lectures in the years 1805 to 1830 in order to recall to your minds the state of medicine one hundred years ago, and to indicate the kind of men who were making contributions to medicine during these years. It is evident that the chief advances being made were in somewhat different directions than those in which the advances during our own era have occurred. There was great activity in clinical description and in the differentiation of diseases. The center of medical advance was undoubtedly in France, where new methods of clinical investigation, which even to-day are of first importance, were being devised. Physiological discoveries of great significance in pathology, especially as concerns diseases of the nervous system and of the digestive tract, were being made. Finally, advances were being made in chemistry and physics which were of material aid in increasing knowledge about disease. It is evident, however, that comparatively little of this advance originated in America. In our hypothetical course of lectures most of the talent would have had to be imported.

As has always been the case in science, the discoveries of the period are associated with the names of individuals, and as time has passed these men have received an ever-increasing glorification. Nevertheless, they must have had great intellectual vigor and possessed high powers of imagination. This is evident not only from the methods they employed in solving their problems but from the actual height of the steps which were mounted. Starting with little knowledge, they scaled great heights with comparative suddenness.

During the seventy-five years which elapsed between our hypothetical course of lectures and the opening of our present course in 1905 important advances were made. During this period occurred the development of experimental physiology, and later the extraordinary growth in pathological anatomy, especially that which resulted from the formulation of the cell theory. Then came the important discoveries regarding infection and immunity, which increased knowledge concerning disease as had never

occurred before. The advance in medicine in the last third of the nineteenth century will undoubtedly always be considered to be related to infectious diseases.

In the middle of the century physiology had turned its back on vitalism and maintained the possibility of a physicochemical explanation of all life phenomena, going even so far as to maintain that in the "ultimate analysis biology is only a branch of physics and chemistry."

The great increase in knowledge of the structure of the proteins which took place around the turn of the century led to high hopes that an understanding of these substances would go far in revealing even the nature of life itself. Advances in chemistry were not confined to structural chemistry, however, but a new science developed which had for its parents both physics and chemistry, and had for its content the dynamics of chemical reactions. Shortly before the opening of our era the possibility of direct measurements of energy exchange in man was made possible by the construction of chambers in which men, even sick men, could be studied with the greatest attention to detail.

At the beginning of the era we are considering, therefore, rapid progress in the knowledge of infectious disease was occurring. Progress in organic chemistry was at a high level, and probably this field seemed to offer the greatest hopes for fundamental advances in biology and medicine. There was developing a tendency to lay emphasis upon the importance of studying biology from the dynamic standpoint, "regarding an animal as something that happens."

Germany was at the height of her activity and a greatly increased momentum was observable in this country in the study of the underlying features and phenomena of disease.

Thus was the stage set for the course of lectures designed to promulgate the new knowledge concerning disease as fast as it should be disclosed. It was a happy and fortunate inspiration which in 1905 led Dr. Lusk, Dr. Meltzer and a group of their associates to found this society, at a period when interest in scientific medicine was beginning to glow more bright, not only in New York but throughout this country.

The Harvey Society Lectures do not deal with any single phase of human biological phenomena. They represent a sort of symposium in which workers from various fields of science report their results. In choosing the lecturers, however, the attempt is made to bring together men who have some interest in the problems of human disease, though it is realized that at times this interest may be very remote. In discussing the advances in medicine which the lectures disclose, therefore, one must carefully delimit the field and not include all the results presented. For example, it might be very advantageous for physiologists to have a course of lectures in which physicists, chemists, psychologists, geneticists, anatomists, bacteriologists, even mechanical engineers were asked to speak. They might all contribute new knowledge which would be very important for physiologists to know about, and new facts which might have a very close bearing on physiological problems. Yet one could not assume that all the discoveries in these various fields represented new contributions to physiology. In the past there has been a tendency to assume that all contributions to physiological knowledge or that all advances in biological chemistry represent advances in medicine. Indeed, it has even sometimes been intimated by the votaries of these and certain related sciences that the advances in these sciences form the only contributions to medicine that are of real importance. In my opinion, both physiology and medicine have suffered from this concept.

As has been pointed out, "the various branches of science are not limited by the training and antecedent interests of the persons who cultivate them, but are defined by their subject-matter." Medicine has for its subject-matter disease in its various aspects, and disease involves modification of function, but it also involves modification of structure, whether this be conceived of only in its more superficial aspects, morphology, or its more intricate nature, chemical or physical. But not all modifications of function or structure constitute disease, at least in a practical sense. Although any disturbance of function is probably accompanied by alterations throughout the entire organism, medicine is really concerned with particular, usually gross, alterations in certain specific func-

tions which constitute the symptoms of disease. Medicine has for its field phenomena which occur in nature, not hypothetical possibilities. The student of disease is interested not only in describing and understanding these disturbances, but in determining the factors, intrinsic or extrinsic, on which they depend. And, just as in the other sciences, even physics, its disciples are interested in obtaining accurate knowledge in order that predictions may be made, and even that the natural course of events may be modified.

The student of disease is interested in all physiological problems for the light that may be thrown on disease processes. The student of physiology is interested in certain problems of disease for the light that may be shed on physiological problems. But he is not interested in all problems of disease, except as matters of general interest. He is not primarily interested in etiology or causation, so far as they relate to external agents, or to environment; he is not keenly interested in the voluntary modification of disease processes, or therapy; he is not deeply interested in the psychological aspects of disease. He is not necessarily interested in disease at all. The interests of the student of physiology and those of the student of medicine overlap, but they are not identical, nor are the contents of these two sciences identical. Virchow was wise enough to see that "each department of medicine must have its own field and must be investigated by itself." As he said, "Pathology can not be constructed by physiologists, therapeutics not by pathological anatomists, medicine not by rationalists," nor, may be added, by chemists, physicists or mathematicians.

If our attention is confined to the results presented before the Harvey Society it will be necessary to omit from consideration certain special fields relating to medicine which have barely been touched upon in these lectures. This is especially true as regards psychiatry and the pathology of the nervous system. Such important developments as conditioned reflexes, the study of behavior, the newer modes of thought concerning psychoanalysis and psychotherapy have been considered very briefly if at all. So too in these lectures comparatively little attention has been given to the great advances which have been made in surgery, not only as regards the

technique of operating and maintaining asepsis, but also as concerns the improvement in methods of diagnosis and treatment of so-called surgical conditions, advances which are based on recent discoveries in physiology.

We shall also have to omit from consideration certain great movements, such as the organization of private and governmental agencies, and of the medical profession, whereby applications of new knowledge concerning disease can be made rapidly and to a previously unbelievable extent. This has certainly been an outstanding feature of the present quarter century.

Medical education has undergone an extraordinary extension, and a very striking modification in method, especially as concerns organization and teaching, has occurred in the medical clinics during this period. Whatever the effect these changes may have had on the education of students, and thus on practice, they have resulted in a tremendous increase in the opportunities for the investigation of disease. These opportunities consist not only in better material equipment in the way of laboratories, but also in protection of the followers of the science of medicine from the burdens of private practice.

These are all matters which have been very lightly touched upon in the Harvey Society Lectures, but they can not be neglected when thinking of the history of medicine during these twenty-five years, as it will be written by our followers.

To point out certain specific outstanding contributions to medicine is not difficult. Knowledge concerning several important diseases has been enormously increased.

One of these diseases is syphilis. At the time the course of lectures began the nature of the inciting infectious agent was unknown and diagnosis depended entirely on superficial clinical features. The relationship of tabes and general paralysis to this infection, though strongly suspected, was uncertain. Its treatment was fundamentally that of a hundred years before. During the period, the inciting agent has been isolated, even cultivated, and in most instances may be demonstrated in the lesions; a reliable, accurate, purely objective, quantitative method of diagnosis has been devised: the specific nature of tabes, general paralysis

and of many other manifestations of the infection, such as aortitis, has been established, and finally a greatly improved method of treatment has been devised. Moreover, the disease has been produced experimentally in animals, and very much knowledge concerning the mode of infection and the reactivity of the host, as exhibited by hypersensitiveness and immunity, has been obtained. Hardly in the whole history of medicine has such a striking increase in knowledge concerning any important disease occurred within so short a period as twenty-five years.

Also a great increase in knowledge has occurred concerning certain forms of heart disease. Shortly before the beginning of our course of lectures anatomical studies had demonstrated the presence in the heart of special fibers having the particular function of conducting the impulses giving rise to contraction. Through the intensive study of arrhythmia in patients, at first by very simple instruments, even by direct observation and palpation of the arterial and venous pulse, and later with the aid of a galvanometer especially suited to the study of these problems, it has been possible accurately to localize the specific lesions upon which the various types of arrhythmia depend. Knowledge has also been gained concerning the effects of certain drugs in modifying rhythm, and as a result it has been possible to employ these drugs with greatly increased accuracy and efficiency.

At the beginning of the era knowledge concerning diabetes was fragmentary. Much was guessed but little was known. During the past twenty-five years many facts concerning the metabolism of sugar in health and in disease have been disclosed, the underlying factors in the production of coma have been determined, the disease has been accurately reproduced in animals, the demonstration has been made that a substance secreted by the pancreas greatly influences sugar metabolism and that the disease is associated with the lack of this substance and, finally, a practical method of supplying this substance, when lacking, has been devised, so that the symptoms of the disease may be made to disappear.

The more recent contributions to knowledge concerning pernicious anemia are also significant. This most serious malady has remained one of the mysteries of medicine ever since its

description by Addison in 1849. Now, by a series of experimental studies, not only has a practical therapeutic measure been found, but it seems not unlikely that much progress has been made toward understanding its essential nature. The culminating discovery that in this disease the production of new red blood cells may be stimulated by the intravenous injection of a few drops of a solution of a substance normally present in liver, and to a less extent in other tissues, signalizes a notable triumph for the experimental method.

The discovery that in rickets the phosphorus as well as the calcium metabolism is disturbed, the demonstration of the therapeutic value of sunlight in this disease and especially the demonstration of the remarkable fact that anti-rachitic properties may be conferred upon particular fatty substances by exposing them to ultra-violet light rays of definite wave-lengths, and that the specific reaction which is thus induced consists in a polymerization of ergosterol, seem to me to be of extraordinary theoretical interest as well as of practical value.

These are a few of the diseases concerning which striking and significant new knowledge has been obtained. They have been specifically mentioned because in these instances, as a result of new knowledge, improved methods of treatments have been developed. In many other instances, however, although no practical results have so far been obtained, much has been learned about particular pathological phenomena.

In all these cases various sciences have contributed to the advances, although it is impossible to evaluate the relative importance of the rôle which each of them has played. While in most instances the discoveries did not depend upon the most recent advances in physics and chemistry, it is certain that they could not have been made in the absence of the organized systematized knowledge which comprises natural science. Nor could they have been made without the growth in anatomical and physiological knowledge which has occurred during the past three hundred years. The facts of importance to medicine, however, did not emerge spontaneously from the accumulated knowledge of the past. In most instances the discoveries were made because some one was

interested in the problems of the particular disease, and because some one thought of a new way of solving these problems, using of course for this purpose any of the accumulated knowledge, or any technique of any science, that was suitable for his purpose. This is not only the prerogative and custom of the followers of the science of medicine but it is the method employed in every other science, including that of physics.

In certain of the instances which I have mentioned, the discoveries were not the outcome of entirely new modes of thought or procedure. The emergence of these discoveries can be traced to specific preceding discoveries which supplied the example or pattern to be followed. For example, in several instances the discoveries have to do with so-called internal secretions of the ductless glands, or with a deficiency of these secretions. In the middle of the last century clinicians observed that, in individuals who exhibited special groups of symptoms, pathological lesions were present in certain glands. This was a discovery of great significance which physiology owes to medicine. It was found that in certain instances removal of these glands from animals was followed by symptoms similar to those seen in patients in whom the same glands were affected. Gradually evidence accumulated which indicated that in some cases the function of the diseased glands could be replaced, at least in part, by feeding the fresh glands of normal animals, by grafting, or better, by injecting extracts of these glands. The conception, however, that these glands secrete chemical substances, or "messengers," by means of which "correlation of the functions of the organism are brought about through the blood, side by side with that which is the function of the nervous system" is a physiological principle well established only in the present era, and one which is probably of great significance both to physiology and to medicine, and may possibly prove to be the most important contribution made to medicine in the present era. The fact that at least two of these "messengers," or hormones, have been isolated, and their chemical constitution established by American workers, exemplifies in a striking manner the interdependence and helpfulness of the various sciences, and also indicates the important position which American investigators have come to occupy.

Another example of chemical coordination through the blood was given by the discovery that the respiration is regulated by the carbon dioxide tension of the arterial blood, or more properly, by H^+ ion concentration of the arterial blood, acting on the respiratory center. The physiologic importance of the maintenance of the neutrality of the blood which was thus emphasized has led to very extensive and accurate investigations of the mechanisms involved in maintaining the "constancy of the internal environment," a happy phrase coined long ago by Claude Bernard. This work is undoubtedly of much importance, especially for physiology but also for medicine. But I should again like to emphasize that not all disturbances in equilibrium constitute disease. It is only when these disturbances exceed the limits of the factors of safety, as described by Dr. Meltzer, that disease may be said to occur.

Another field of physiology in which great activity has taken place during the present era is that of total metabolism or energy exchange in the body, and this is reflected in the considerable number of lectures dealing with this topic. It is to the great credit of American workers that much knowledge has been gained concerning metabolism under pathological conditions.

Also in the field of nutrition, the discovery has been made that not all proteins are capable of supporting life, but that proteins containing certain specific amino acids are essential. The great advance in the field of nutrition, however, was made by the demonstration that animals can not live and thrive on a diet composed solely of pure protein, fat and carbohydrates combined with inorganic salts and water. Certain other "accessory food factors" were shown to be necessary. When these are lacking, disease supervenes, and this fact has been of value in explaining certain diseases, now called deficiency diseases, such as beriberi, rickets and probably pellagra. Certain analogies have been pointed out between the vitamins and the hormones, indeed the former have been called exogenous hormones. The chemistry of the vitamins and the nature of their action, however, still remain to be studied thoroughly.

Another advance in physiology which is of great significance for medicine consists in the demonstration of the rôle which so-

called oxygen carriers play in oxidations within the body, and the demonstration of reactive, ferment-like substances which stimulate oxidation.

In the study of infectious agents and the reactions of the body to parasitic invasion, progress has also been made in many directions. Many of the results obtained, however, have undoubtedly consisted in the application and extension of discoveries which were made during the latter decades of the last century. The important relation of the so-called filterable viruses to human diseases has been demonstrated, and the evidence suggests that this importance is even much greater than is now obvious. The conception of "haptens" and the investigation of the chemical structure of the bacteria, especially in relation to their antigenic properties, the introduction of specific local therapy are all directions of activity which afford promise of wide application. Whether, however, advances in the field of infectious diseases have taken place at the same rate as in the preceding era seems doubtful.

Time will not permit me to speak of the specific contributions of organic chemistry to medicine during this era. Much attention has been given to the constitution of the chemical substances isolated from the tissues and secretions; many more than 200,000 organic substances (mostly synthetic) have now been analyzed and investigated, and much study has also been given to the intermediate stages through which organic compounds pass in their transformation within the animal body. A particular development in this field, namely chemotherapy, has possibly not entirely fulfilled the expectations that were aroused by its great success in supplying a remedy in the treatment of syphilis. Nevertheless, the introduction of this essentially new mode of thought and procedure is of great significance, and it occurred in our era.

Not only have the new developments in physics, especially in in the field of light and of electricity, received wide application in the study of biological phenomena, but a new branch of physics, biophysics, has developed. The use of X-rays in diagnosis has been greatly extended. More recently the study of the physiological effects of X-rays and of light of various wave-lengths is being made.

It is obvious that I have been able merely to mention a few of the topics discussed in the Harvey Society lectures. The professional activities of the 220 lecturers indicate to some extent the fields covered. It is rather surprising to find that the largest group of lecturers consisted of clinicians, of whom there were fifty-two; the next largest group was composed of physiologists; the other groups, arranged in order according to size, consisted of biochemists, bacteriologists and parasitologists, pathologists, biologists and geneticists, anatomists and pharmacologists. The list of lecturers has included many of the most distinguished students of medicine; about one-fourth of them were from foreign countries.

As one goes over the twenty-four volumes containing the Harvey Society Lectures (the omission of one volume represents one of the losses of war) he can not help experiencing a sense of mystery, almost of awe. Here, beside the wealth which is very evident, there also undoubtedly lie hidden masses of gold, which in many cases are unsuspected, even by the donors. In future years some one will discover and make use of them and reveal riches to us of which we can not dream. On the other hand, these volumes probably conceal deep tragedies. Instead of leaving to their scientific descendants what they believe to be fabulous treasures, some investigators have probably left only ashes to be scattered and lost.

That the number of workers in the science of medicine has tremendously increased during this period and that there is no lack of activity are shown by the wide expansion of the medical literature. In his presidential address before the Thirteenth International Physiological Congress, Professor Krogh stated that in the first year of the century titles were given in the *Zentralblatt für Physiologie* of 3,800 papers; in 1926 there were 18,000. Moreover, that, while in 1901 there were only one hundred papers, or 2½ per cent. of the total, published in America or by American authors, in 1926 there were 3,500 papers, or nearly 20 per cent., from this source. What has occurred in physiology has taken place also in medicine. Professor Krogh also had the temerity to state that in his opinion "too many experiments and observations are being made and published and too little thought bestowed upon them."

During the past twenty-five years there has been a gradual change in the kind of investigation employed in the study of disease and in the methods used. It is only a comparatively few years since Rokitansky expressed the conviction "that pathologic anatomy must be the foundation not only of medical knowledge but also of medical treatment, yes, that it contains everything that there is in medicine of positive knowledge and of foundations for such knowledge." It is evident, however, that during the present century interest in the so-called descriptive sciences, such as anatomy, morphological pathology and possibly organic chemistry, has waned. Indeed, most of the anatomists who have lectured before the Harvey Society have not discussed structure at all. With the anatomists and pathologists experimentation is replacing observation. At the beginning of the century high hopes were entertained for the results that were to follow the chemical analysis of the cells of the body. One of the lecturers has stated that "the action of the cell depends essentially on the nature and quantity of the various substances of which it is made." The same complaint, however, that had been raised against pathological anatomy, namely, that it is concerned only with dead material, began to be raised against organic chemistry. Even the chemists themselves suggest this. One of the most distinguished said in a Harvey Society Lecture, "these descriptive studies [meaning structural chemistry] we may regard as a sort of chemical anatomy of the human body." The biochemists are also becoming experimentalists, employing the methods of chemistry only more or less incidently.

Careful observation and description are no longer fashionable. Even the word "description" causes a certain shrinking, or a shrugging of the shoulders, depending upon who utters it. At the very beginning of the century there occurred a marked tendency to return to the methods of experimental physiology, the kind of activity developed by Magendie and Claude Bernard. But reflections are now being cast even on this kind of investigation. It has been maintained that the entrance of bacteriology on the stage, in the last quarter of the nineteenth century, for a time displaced physiological experimentation. One writer said a few years ago,

"With Pasteur and his successors the will was more important than the reflective intellect, and this interlude [the bacteriological] had the effect of narrowing the outlook and rendering medicine less rational." And again, "In default of the physicochemical foundations, during a period when bacteriology was the dominant influence in medical science, and next to it, perhaps, the highly specialized science of organic chemistry, when the prevailing activity was somewhat unintellectual, physiology continued along the old paths."

To my mind this attitude toward bacteriology seems narrow and unjustifiable. However this may be, there is little doubt that during the present century the influences which we have previously noted, especially the attempts to obtain a physicochemical explanation of life itself, and the promulgation of the idea that "physiology is but a special case of the physics of the colloids and the chemistry of the proteids" have led to a very distinct and striking shift in the thought and methods of physiology which is also affecting medicine. To designate this new physiology the term "general physiology" has been employed, or it has been called abstract as contrasted with applied. The field of general physiology, however, does not seem to be very accurately defined, and sometimes the term is used to limit the field to the study of phenomena which are common to all living matter, and again is used to indicate the methods employed in investigation. It may be said, however, that the main problem of general physiology is to describe the properties of living matter in purely physicochemical terms.

All these problems of methodology, however, do not concern students of disease except indirectly. Medicine is indeed a part of biology, but it is only a part. Through the study of disease broad biological generalizations may emerge, as they have in the past. But the immediate problems of the student of disease are not the problems of the biological philosophers or even of the physiologists. The student of disease is trying to describe and to understand the interrelationships of certain special phenomena with which he comes in contact. Even Galileo was content to ask how, not why. In recent years there has seemed at times to be

some uncertainty in the minds of those professing the investigation of disease as to exactly what they are studying, possibly a reflection of the confusion in the ranks of the physiologists. It seems to me, as it has seemed to many others, that at least one essential in investigation is that there should be a question asked. If the question relates to disease, then the person who tries to answer it becomes a student of disease, whether he be clinician, physiologist or anatomist. On the other hand, and this is important as regards future advance in medicine, a man is not necessarily a student of disease because he is a doctor of medicine or because he works in a laboratory of medicine, even though he may contribute ever so greatly to science, as, for instance, did Gilbert or Young or Mayer, or be as important in philosophy as was John Locke. Questions concerning disease will most frequently arise in the minds of those coming in contact with disease, though they may arise in the mind of any intelligent person. It seems, however, that the person who most carefully observes and describes the phenomena of disease will ask the "best" questions. The method employed to answer the question or to solve the problem will then have to depend upon a decision as to which method is most appropriate. Whether or not the observer can attempt the solution will finally depend upon whether or not he possesses a sufficient mastery of the appropriate technique to justify his undertaking the task.

In attempting to answer biological questions it seems to be generally conceded that the method which has been found most rewarding is that of hypothesis and test, or as it is called, experimentation. Now in performing an experiment, accurate and careful observation and description are just as important as they are in formulating the question. One wonders, therefore, whether there is not an inherent danger underlying the present tendency to scorn and belittle observation, and whether the possibilities of clinical medicine, and anatomy and morphological pathology, and organic chemistry were all exhausted in the nineteenth century. The experience of the past twenty-five years seems to indicate that this kind of investigation still brings its rewards.

In description, various kinds of yardsticks may be employed. For describing some phenomena extremely accurate quantitative

measurements, even formal mathematical treatment of the results, in order to reveal hidden quantitative relationships, are appropriate. For describing other phenomena such measurements are not only unnecessary but quite unsuitable. In recent years there has been a tendency to assume that great accuracy in measurement and the use of higher mathematics in the study of the problems of physiology and disease at once endow the investigation with a sacerdotal dignity. This is also true of the use of the methods of chemistry, physics and physical chemistry. One of the great advances made in the present century consists in the fact that now many students of medicine are trained in these sciences and have more or less mastery of their techniques. But discrimination is necessary in their employment when attempting to describe disease processes. The student of disease should be certain that he is trying to learn about disease and not merely exercising his technical skill. One needs only to recall some of the absurdities and futilities of the iatro-mathematical and iatro-physical and iatro-chemical schools of the seventeenth century to realize the dangers inherent in this attitude of mind. Sanctorius is said to have spent forty years of his life in weighing himself three or four times a day.

Furthermore, there has grown up a certain sanctity about the word experimentation which seems to me to be unjustifiable. Experiments are of two kinds: first, the true experiment carried out to test a hypothesis; and second, the more or less random procedure undertaken to see what may happen. These latter experiments, made without hypothesis, can have only one purpose, and that is, to afford opportunity for observation. As Claude Bernard pointed out, such experiments are at times valuable since, in making the observations, hypotheses are suggested, and these can then be verified or disproved by true experimentation. But the student of medicine has little need for such groping for material. He is daily surrounded by phenomena which are stimulating beyond measure if he but have eyes to see.

It has been assumed that during the present era medicine has become more rational. The introduction of rationalization into medicine is of extreme importance, just as is its employment in all scientific activities. John Hunter's advice, "Don't think, try,"

is all very well in the meaning intended, but the injunction must not be taken too literally. Think first, then try, may be a better maxim. And on what one thinks about will depend what he will do. But the question arises whether the present trend in medical investigation really fosters thinking. Modern medical education has supplied an army of trained technicians. Are they all asking questions concerning disease and attempting to solve them, or are many of them only interested in desultory and fragmentary employment of the techniques they have acquired, having faith in the Baconian concept, that if a sufficient number of observations and experiments are made, the connections will appear and general truths automatically evolve? Such an attitude of mind seems to belong in the seventeenth century, not the twentieth.

What I have said does not mean that the student of disease must always be attempting a direct approach to the solution of his problem. Usually it is necessary to start far away from this goal and often to take a circuitous path, but he should always have the goal in mind, otherwise he really belongs in some other field of scientific endeavor. It has recently been said that "for the first time mathematics, physics, chemistry and physical chemistry, as aids to physiology, have passed into the hospital." I can not but feel that the phrase "as aids to physiology" was introduced by the writer inadvertently. But it is possibly true and may be of some significance.

One wonders whether if the student of disease did but observe, and then describe in language appropriate to the phenomena observed, following Daniel Drake's advice "to write much and publish little," and then if he would think, and think until it hurts, and make experiments only when he has evolved a hypothesis that interests and satisfies him, performing a sufficient number of experiments and employing a technique appropriate for the particular purpose, but publishing only when he had satisfied himself that a conclusion had been reached, even if negative, not only might the bewildering number of publications be reduced, but the increase in knowledge be materially accelerated. For as Professor Whitehead says, "The growth of a science is not in bulk but in ideas." Perhaps this is heretical doctrine, and no one realizes its

dangers better than I. During the past twenty-five years it has been important, at least in this country, that young men be stimulated to investigate. And nothing so urges a beginner to further effort as to witness the birth of his labors. Moreover, there is nothing so much feared at present as inactivity. But is it not time for this naïve attitude to be dropped?

May there not be a lesson for us in the history of physics during the present era? A recent history of science states that "at the end of the last century, it seemed that all that remained for the physicist to do was to make measurements to an increasing order of accuracy." It goes on to describe how physics then suddenly took on new life. New concepts were born. The atom was resolved into more minute corpuscles and these in turn into electrical units. The old concept of mass was overthrown and a new one took its place. Radioactivity was interpreted in terms of atomic disintegration. The quantum theory of radiation superseded the wave theory, or at least was added to it. Space and time became no longer absolute. A particle became a mere series of events in space-time. Physicists have become less certain than they were at the beginning of the century.

Biology and physiology and medicine too have come to have some misgivings, but so far these doubts have not been very coherent or articulate. The speculations of men like Whitehead, who emphasize the relation of the organism to the environment, the development of the theory of emergent evolution, which Jennings calls "the Declaration of Independence for the biologist," the concept of biology as an independent science by Haldane and his followers, have all exerted an influence in stimulating the study of the organism as a whole and not merely as in agglomeration of parts. Nevertheless, while in the study of disease it is not necessary finally to accept any theory of the ultimate nature of life, it is difficult to conceive of any successful method of procedure which in all its steps does not assume a physicochemical basis for living things. This does not mean, however, that it is necessary to make graven images of chemistry and physics. At any rate, the question may be raised whether in the study of disease it is always necessary to resolve the organism into electrons, or whether ad-

vances can not be made also by studying the organism itself. Certainly the history of the past twenty-five years, as of all preceding periods within the era of modern science, seems to answer this question in the affirmative.

Looking backward one wonders whether it would have been possible for any one to foretell the directions in which the greatest progress would be made in medicine during the quarter century just passed. Probably the greatest promise seemed to lie in fields other than those which have apparently yielded the most important results. It would therefore be hazardous to attempt to predict the future. But of one thing we may be sure, the foundations on which the future is to be built have been rendered more solid, more substantial; the builders who are to undertake the new tasks are enormously increased in number; they are better equipped; they have a wider knowledge of the fundamental sciences; they have acquired greater technical skill in experimentation; they have at their disposal greatly increased facilities. This insures a continuation of progress. There is some evidence too that the workers are trained to think more logically and rationally than their predecessors.

But after all, probably what is needed most in medicine is not method but men, and not merely photographers but artists. Whether the coming era will be a golden age depends on whether in medicine "there shall be minds acting upon thoughts so as to color them with their own light, and composing from these thoughts, as from elements, other thoughts, each containing within itself the principle of its own integrity." For these geniuses we are dependent upon the gods.