THE OUTLOOK IN PHYSIOLOGY[1]

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In obedience to the custom of the Academy that the retiring president "shall deliver an address," your speaker invites your attention this evening to the field of animal and human physiology with a view of noting the progress which this science is making in understanding the complex phenomena in living bodies.

Physiology is a growing science. In 1926 over 19,000 original papers were published dealing with specific problems in physiology. The report for 1929, when it is issued, will probably show over 20,000 such reports. If we throw out half of these as inconsequential and intended merely to pad professorial publishing lists, there still remain 10,000 papers dealing with original research in this field.

At the XIIIth International Physiological Congress held in Boston this last summer, over 1,200 members were present. An attendance of almost five hundred distinguished foreign physiologists, coming from thirty-five different nations of the world, shows the interest which this subject holds in the attention of men of science. That these many investigators have not been fruitless in their work is indicated by the fact that in this group of physiologists there were present three persons to whom had been awarded in former years the Nobel prize in science.

The contributions which the science of physiology is making are not at first quite so striking as some of those of physics and chemistry. The discoveries in physiology have not been translated in their applied form into aeroplanes or radios, household comforts or chemical products of outstanding commercial value. In fact, the great contributions of applied physiology are usually not credited to physiology at all, but to practical medicine. The discovery of *insulin* and its preparation in pure form is an epoch-making achievement of modern medicine and is saving the lives of innumerable persons suffering from the disease of diabetes. It is a discovery, like many others of its kind, of world significance. It is, however, seldom credited to its real discoverer, the physiologist Hedon, who in 1892 presented a brief report of some of his experiments at the Physiological Congress at Liege, reporting that he had found that the removal of the pancreas from the animals under his observation had resulted in producing an intense glycosuria, that is—an intense diabetic condition. In 1892 this simple little announcement had no practical implications and the report went almost unnoticed, but the happy discovery had been made that there was a connection between the pancreas and the ability to assimilate sugar in the body, and upon this hint other physiologists took up the investigations that finally gave us this internal chemical with which medicine has been able to conquer in large part at least, another serious human disease.

It is becoming clearer and clearer that most of the problems of disease are physiological and that even in those diseases where bacteriology and serology and clinical observations play their essential roles, the main questions are still those of functional disturbance.

[1]Address of the President at the forty-fifth Annual Meeting of the Academy of Science at Earlham College, Richmond, Indiana, December 6, 1929.

The tremendous help which physiology has given to medicine is reflected in the fact that physiology as a college study has been bodily absorbed by our medical schools. This is as it should be for the medical schools, but the science of physiology ought to be re-established in its pure form also, and be made an independent science in the curriculum of our colleges and universities. It has often been pointed out that some of the most valuable applications of science come from pure science itself and it may be that in this instance also outstanding medical applications of the future may come from laboratories not interested primarily in the strictly medical point of view.

In the second place the laity, that is, the intelligent public, must have a reasonable first-hand acquaintance with the scientific foundations in anatomy and physiology, upon which alone a larger program of personal and public hygiene can be built. Dr. Evermann pointed out to us several years ago that we had practically quit teaching Zoology in our public schools and as a result the ordinary citizen, even outside the State of Tennessee, has often only the remotest idea, if any at all, what is meant by a "species." Is it any wonder, therefore, that he can not understand what biologists mean when they speak of species and their mode of origin.

Similarly a public that has no scientific understanding of the bodily organism can not be expected to differentiate readily between the scientific physician and the medical fakir and advertising quack. Indeed the chances are that such a public will frequently take more kindly to the extravagant and assuring statements of the mountebank than to the cautious procedure of a trained health expert.

If the valuable findings of physiology are intended for our medical practitioners alone, then the medical profession will have to assume a greater responsibility in seeing that the general public is properly and scientifically informed on matters of public and personal health. Otherwise new agencies will arise to take over in a larger part the safe-guarding of our individual and corporate health. It is clear that business is determined to have workmen sound in body, and institutions of all kinds, large and small, are setting up agencies to prevent unnecessary illness in their own memberships. Insurance companies are finding that it pays enormous dividends to keep every policy holder informed of a sound program of preventive measures.

It may be that in the future, society will use its medical knowledge and its medical men to keep itself well, rather than to cure itself when sick. Fortunately increasing numbers of our physicians are meeting this new challenge and are in generous and unselfish ways leaving nothing undone to make continued health more certain and the mere curing of disease less necessary.

But it is not our purpose this evening to deal with the medical aspects of physiology. We shall leave these details entirely out of the picture and address ourselves wholly to those investigations in the field of pure physiology which make clear to us in scientific manner, how these bodies of ours function under normal conditions.

The outlook here seems so promising and so hopeful that it is somewhat difficult not to be over-optimistic. Investigations are bringing to light so many new facts of the remarkable manner in which the equilibrium of life is maintained that one may claim entirely too much as already fully established. It may be fitting, therefore, to preface this brief account of physiological achievement with a touch of humility and acknowledge at the very outset that we are facing in this field of inquiry such difficult problems that the physiologist is forced to admit

his inability to explain as yet some of the most elemental phenomena of living things.

With all the work that has been done on the physiology of "muscle and nerve" we have no clearer causal picture of the contraction of a muscle than we have of the fall of an apple to the ground. The physiologist may write volumes about contractile tissues, but he is not yet able to explain to you in the simple terms of physics and chemistry, how he crooks his finger. Much is known about the circulation of the blood but we can not yet account satisfactorily for the rhythmic beat of the heart. The directing causes that unfold the single egg-cell into the complex adult we can not explain. We can do no more than watch the unfolding mystery step by step. When it comes to such an organ or system of organs as the brain, and we try to answer how it registers sensations, retains them in memory, coördinates and transforms them into motor impulses, we are perhaps almost as far from final explanations now, as we ever were.

But not all the fields of investigation in physiology have been so refractory as those just mentioned. Of many of the living processes in the body we now have a very clear scientific understanding. At the very head of these stands probably the chapter on *respiration*. The intake of air into the lungs, its transportation through the blood stream by means of the red corpuscles in the form of oxyhaemoglobin, the release of the oxygen in the tissues, are all things that fall in completely with our known laws in physics and chemistry.

The process of oxidation in the living cells, while not quite so clear, perhaps, is now known to be governed in large part by special oxidizing ferments which make oxidation possible at low temperatures and specific for the various chemical substances in the tissue. To some extent all this can be duplicated in the laboratory.

Similarly the end products of respiration, the carbon-dioxide, the water, and other substances, are fairly well known and seem to conform in the strictest ways to known laws. We can measure the "basal metabolism" of the body with almost the same accuracy that we can measure the efficiency of an engine. The automatic stimulation of the center of respiration by the excess of carbon-dioxide in the blood is the simplest and clearest instance of the action of a hormone.

Not far behind this chapter on respiration is the chapter on the *circulation of the blood*. Since the days of William Harvey this has been a favorite field of investigation because it lends itself so readily to quantitative determination. The dynamics of the blood flow is understood with almost mathematical precision. When one considers that here we have enclosed vessels which if laid end to end, arteries, capillaries, and veins, would be literally several thousand miles in length, and note that this blood stream is kept in constant motion and makes on an average two complete circulations within the brief space of a minute, we have a system that might well excite the wonder and envy of a hydraulic engineer.

More striking though than the mere anatomical complexity of the sytem is the plasticity and adaptability of the same. Under nervous and chemical control some of the vessels may become larger or smaller, and pressures fall and rise. The central pump, the heart, can be accelerated or inhibited, to suit the necessities of the body. Internal secretions such as adrenin can powerfully affect the system. The physiologist has probaby not yet discovered all the manifold ways in which this circulatory system can be influenced, or the delicate arrangement through chemical or nervous forces by means of which the blood flow is regulated. We have but to recall the brilliant work of Professor Krogh of

Copenhagen on the capillaries to see what unworked fields still exist in such a familiar subject as the circulation of the blood.

Physiology has a third chapter in which very satisfactory progress is being made. This is the general field of *Digestion and Nutrition* and our new knowledge of the physiological *value of foods*. Our greatly increased knowledge of foods and nutrition is due to the fact that physiology has called to its aid the biochemist. Biochemistry has indeed risen to the position of an independent science, and its field has become so extended that even here no single chemist can wholly encompass it. We have gone many a mile in understanding organic compounds since the day just a hundred years ago when Wöhler first synthesized urea.

In the study of foods the greatest advances have been made in the study of the proteins. These have been taken apart step by step until we now know in fairly exact terms twenty or more of their end-products, the amino-acids and their derivities, out of which proteins are built up in varying proportions, and out of which the body, after proper digestion, rebuilds its tissues. It is probable that new end-blocks or amino-acids will be discovered and chemically determined, for there is still a protein remnant that up to this time has not responded to the chemists' analysis.

We now know that the food value of a protein depends in the main on these end-blocks which it contains. The body is unable to make these "protein neuclei" for itself and they must be furnished in foods. We also know that many of these protein neuclei or end-blocks can not be replaced by other amino-acids. As proteins differ widely in the number and amount of these end-blocks which they contain, so the problem of nutrition has become one of selecting those proteins that furnish the combinations of end-blocks best suited for the growing body.

In other words, proteins have a relative value. Thus it is possible to overeat with poor proteins and yet starve the tissues, or live on a lessened diet of proper proteins and be amply fed. The scientific dietitian of today, therefore, does not speak altogether in terms of pounds and calories, but of such a selection of foods as will furnish to the body those necessary elemental constituents, organic and mineral, without which normal growth is impossible. Of course the energy intake in foods such as fats and sugars must correspond to the outlay of work which the body is to do, but with our newer knowledge of nutrition the emphasis has changed from a quantitative study to a qualitative study of foods.

This becomes especially clear when we regard the significance of the so-called *vitamins*. What these vitamins are chemically we do not know. Thus far they have not been isolated in anything like pure form, but we know that they are easily oxidized and destroyed especially at high temperatures. We know, however, that when any one or more of these so-called vitamins are absent, serious nutritive disturbances appear in the body. In their extreme forms the symptoms are easily recognized as scurvy, or beri-beri, or polyneuritis, or sterility, but medical authorities have stated repeatedly that such nutritive disturbances in their milder forms are perhaps much more common than we suspect and that there are many more persons among us afflicted than we imagine. The great abundance of all varieties of food in this country has perhaps spared us in the main. Physiological starvation is, however, not by any means always an effect of poverty. No one can make a careful study of our present knowledge of foods and nutrition without realizing that with our national prosperity and the artificial development of our culinary art, many of us eat "in glory" instead of "in wisdom."

The present interest and importance attached to the study of the vitamins is indicated by the fact that one of the Nobel prizes awarded this year went

jointly to Professor Frederick Gowland Hopkins of Cambridge, England, and Professor Christian Eijkman of the University of Utrecht, for "pioneer work in proving the existence, usefulness, and necessity of vitamins in nutrition."

The study of the chemical changes involved in the process of digestion and nutrition has brought to the front at this time another chapter in physiology, namely, the *nature of biological ferments.* Nearly all of the chemical changes in the body are effected by specific enzymes, that is, enzymes or ferments that act, each upon a specific chemical substance only, and under the conditions obtaining in the body, split or change them chemically into other specific products, and do this with a rapidity which is surprising when one considers how slow in their action most highly complex organic substances are.

Thus we have the salivary ferments, the pepsin, the pancreatic ferments, the intestinal "erepsin" recently shown to be composed of two separate ferments, and others concerned in the digestion of foods. But these enzymes are not limited to the digestive tract. In practically every tissue and organ there are such ferments, accomplishing the specific chemical steps required in the process of nutrition, and so throughout all the living cells there are oxidations, reductions, splittings, deaminizations, and innumerable other chemical changes, effected with a swiftness and a definiteness, and under such immediate control that it may well make the ordinary chemist humble, when he considers the relatively crude chemical processes which go on en-masse in his test tube or retort.

We may liken these ferments to keys which fit special locks only, but which when properly fitted, readily unlock the combination. We are beginning to learn what the delicate molecular configurations are which make this interlocking of ferments and matrix possible. It is not altogether wrong, therefore, to say that in the tissues in which a thousand different chemical substances, completely mingled, come and go, there are carried on literally hundreds of different chemical processes side by side, yet each one largely independent of the others and specific in its results.

Much work has recently been done on the nature of ferments. Dr. Northrop of the Rockefeller Institute has just announced that an enzyme has now for the first time been crystallized. Dr. Northrop accomplished the crystallization of pepsin. It is significant that the Nobel prize in chemistry for this year, went jointly to Dr. Arthur Harden of London University and Professor Hans von Euler-Chelpin of Upsala University, Sweden, for their joint research on "enzyme action in the fermentation of sugar." That researches on ferments and vitamins should have received two of this year's prize awards indicates the interest which these fields hold.

I can not dismiss the matter of ferments without calling to your attention the recent announcement of Simon Flexner of the Rockefeller Institute that the filtrable viruses which transmit certain diseases may belong to a special class of substances of a peculiar chemical nature closely related to or perhaps identical with ferments. If this is so, then ferments approach very near to living matter, for these filtrable viruses that cause disease not only act as poisons but they grow and increase in amount, reproducing themselves. One case of small-pox may engulf an entire community. If these filtrable viruses that will pass through the very finest of Berkefeld filters are ferments, then we are not only obliged to change our concept of the nature of infection, but we shall certainly have to draw in closer lines the boundaries that are to separate living from dead matter.

While many of these ferments or enzymes have been known for a long time, there has come to light within recent years another group of chemical substances

in the body which, instead of producing immediate chemical changes, exert their influence directly upon distant organs or tissures, stimulating them to functional activity. These substances are familiar to you under the name of *hormones*, or *internal secretions*. The study of these hormones has indeed opened up one of the most fascinating chapters of physiology. It has revealed the fact that in addition to the nervous system there are ways of coördinating the different organs of the body through chemical means. While our reactions to the outside world are almost wholly under the control of the nervous system, the internal or visceral reactions are to a very large extent governed by these hormones. These are specific chemical substances liberated by one organ or tissue, thown into the lymph or blood stream and carried over the entire body. Upon most organs and tissues they are without any apparent effect, but reaching the organ for which they are specifically intended they have a profound effect upon the same.

The insulin of the islands in the pancreas makes the assimilation of sugar possible in the tissues; the carbon-dioxide produced in the acting tissues throws the center of respiration into action. Hormones generated during the period of gestation stimulate the mammary glands to functional activity so that when the little mammal is born its food supply is at hand. Hormones from the sex glands call out in the most striking manner secondary sexual characteristics. The adrenin from the adrenal glands is a powerful stimulant for the circulatory system. The pituitary gland at the base of the brain is believed to affect the matter of stature and bodily proportions. The thyroid and para-thyroid glands are known to play an important role in maintaining normal metabolism. A new hormone called eutonon, recently discovered in the liver, seems to exert an effect in maintaining the proper tonus of the heart. This list could be considerably extended if time permitted.

Some of these hormones such as adrenin and insulin have been prepared in almost pure form. It suggests the possibility of a new day in therapeutic medicine when we can have at our disposal in the treatment of disease the natural hormones in a pure state which may be concerned in that disease. It reveals that the complicated blood stream is not only an open highway for the transportation of all necessary foods and the elimination of all necessary waste products, but is also, as it were, the postal road over which organs and tissues scattered throughout the body may communicate in their own chemical language directly with one another, thus securing concerted action for common ends.

That chapter of physiology dealing with the reproductive system of the body and the manner in which the germ cells carry forward the "torch of life" from generation to generation has received so much attention and from so many different sources that it has become the important and independent *science of genetics*. The discoveries in this field have of course been striking and valuable. They are too many to be enumerated here. While we are still very far from being able to make and unmake species, to determine sex, or to add or subtract genetic characters at will, enough has been learned of the laws of heredity to warrant the hope that when these have been carefully and scientifically applied the quality of stock in the plant or animal or human being may be profoundly influenced for good.

It seems strange and worthy of note that the most important system of the body is the very one about which we know the least. This is the *nervous system* and *the brain*. Investigations have been largely limited to anatomical and histological studies. Recently, however, physiologists have addressed themselves anew to the objective and scientific study of the real physiology of the nervous

system and the brain. We are perhaps familiar with the extended work of Pavlov and his school from his recent book on "Conditioned Reflexes."

The brain seems infinitely complex anatomically, and its physiology is as yet almost wholly beyond our ken. But as light has come to most other problems by careful investigation, we have every reason to hope, though it may be at a distant time, that light will break, enabling us to understand this structure, perhaps the most complex organism in the universe.

The improper functioning of the liver, stomach and kidneys may be individually quite serious, but the improper functioning of the brain has not only individual results, it has tremendous social consequences. We need to know more about normal brain functioning so that we may find out what relation the impaired functioning of the brain bears to crime or delinquency, and if such a relation is found to exist, how normal functioning can be restored. This has been done with almost all the other organs of the body. Why should we deny this possibility to the most important organ of them all?

We still think in medieval terms about the brain and nervous system. In exactly the same way they thought about the heart and liver several centuries ago. Now we view these latter organs with clear and scientific eyes and our control over them has been extended marvelously. He would indeed be weak in his scientific faith who would not at least hope that the scientific approach to the nervous system might lead to substantial successes and that with real objective knowledge of its functionings, our social control of it would be correspondingly extended.

Yale University has just announced the establishment of a new clinic for the study of *mental hygiene*, made possible under the generous help of the Rockefeller Foundation and other agencies. A distinguished scholar and scientist has been appointed as director of it and the aim is to place our knowledge of mental hygiene upon neurological, neuro-pathological, and physiological foundations.

It has been the purpose of this paper not so much to give to you the detailed results of the recent researches in physiology, as to indicate to you where on the frontiers of this science the battle seems most active in pushing back the limits of our knowledge. Even to state the findings of a few outstanding contributions would over-tax the limits of this occasion. It has been our purpose rather to show in which directions the far-flung battle line of inquiry has been extending, and to note a few of the strategic positions that have been taken and are now being consolidated.

Of course it goes without saying that many problems other than those here indicated are being attacked. One of the newest, and it would seem one of the hardest of these problems is the scientific attempt now to go beyond tissues and organs and even cells as ultimate units, into the complex anatomical, histological, and chemical structures within the cell itself. It is certain that physiologically the cell is not the unit, but that within the cell we have contained smaller living units of such number and variety as may surprise us when we shall know more about them. We have followed the grosser changes of the chromosomes, but the chromosome itself is in all probability a very complex structure consisting of genes or bionts that in their minuteness may not differ widely from the concepts which the physicists and chemists have of molecules and atoms. In a living cell the microscope shows us a picture of threads, lines, dots, granules, and droplets of infinite shape and appeareance. It will be the duty of the cytologist of tomorrow to tell us what physiological significance this picture has. Probably

behind this microscopic picture there is an ultra-microscopic one that we shall never be able to sketch through a camera-lucida but which will have to be wrought out by painstaking experimental research a little like the physicist thinks he has wrought out the shapes of the atoms.

As in other fields so in physiology there is the apparent paradox that the more science learns about the subject the more numerous and the more involved the questions become. This fact has shown itself in a distinct trend in physiological thought at present, reflecting on the part of many leading physiologists a growing belief that a purely mechanistic theory can not account for all the phenomena of life. The laws of physics and chemistry as we now know them, seem to these investigators not quite wide enough in their reach to embrace all the phenomena in living tissues. They hold that the theories so ably advanced a few years ago and still maintained by many, that purely mechanistic reactions are sufficient to explain all biological phenomena, are no longer satisfactory and are losing ground.

I have but to recall to your mind the recent utterances of the noted physiologist Haldane of Oxford University in his new book "The Sciences and Philosophy" to indicate a growing conviction that in living physiological processes there are adjustments which transcend our present laws of the laboratory. Now these persons do not refer primarily to that supreme human question whether behind the outward functions of body and brain there exists an abiding personality of mind and spirit, for this is a question which every person will have to settle for himself on grounds other than physiological. On this point the science of physiology has not a single fact either to affirm or deny. But no matter how this supreme question may be answered by any one, the same physiological question remains—How then does the physical organism function? These physiologists have in mind biological processes of life, growth, and death as seen in living organisms throughout the plant and animal worlds.

Biology is facing the danger that such pronouncements by men of science will cause the popular thought to run into the vagaries of a discarded vitalism or an impossible supernaturalism. Surely the scientist can admit nothing less than a self-consistent universe in which finally all the fragmentary bits of knowledge will fit into one great single pattern of truth.

But it may be that we must modify and enlarge our present conceptions of physical and chemical laws. These last few years have certainly compelled us in other fields of science to question and modify accepted views that seemed to us to be the ultimate axioms upon which all future investigations would have to rest. What the physicist and chemist have been obliged to do the biologist may be forced to do also.

It may be that chemical elements lifted into higher and higher combinations of greater and greater complexity may finally reach a configuration in which new properties appear, new possibilities arise, and new laws operate. Would anyone not informed suspect that when hydrogen and oxygen unite they form such a substance as water. The two entering substances are light and are gases and subject to the laws of gases. The new substance is a liquid and the laws of gases give place to the laws of hydrostatics. That we have thus far been unable artificially to build up such living configurations is beside the point. That new living tissue can be built up only by laying it over the existing patterns of already living tissues is not unnatural. Such directing influences are familiar to the physical chemist and it suggests the idea that the physical chemist ought to be called to the aid of the biologist. Indeed this has been happening. I note

here the titles of some new books snatched at random from my library shelf: "The Colloids in Biology and Medicine," "Contributions Toward a Colloid Chemistry of Life," "Colloid Chemistry and Biology," "Physical Chemistry in Internal Medicine," "Physical Chemistry of Proteins," "The Colloid Chemistry of Egg-Albumins."

But no matter what the final and ultimate facts may be this much is certain: that at this time there is no other method of attack open to us except the scientific method of critical observation and experimentation.

I beg to close with the happy reflection that the outlook in physiology, as in other sciences, is full of promise, because the fight to push back the frontiers of knowledge in this field is going on in laboratories, in hospitals, in quiet and unnoticed places of research, in the unshaken confidence that this method which has so enriched our knowledge in the past will not altogether fail us with the multiplied problems still ahead.

If as a student of physiology I do not altogether mis-read the signs of the times, the years just ahead of us will bring us epochal discoveries in the field of biology, just as the years behind us have brought us epochal discoveries in the field of the physical sciences.