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CONTRIBUTIONS OF PHARMACOLOGY TO PHYSIOLOGY.[1]

LADIES AND GENTLEMEN: Before I enter upon the task for which I ask your kind attention, I desire to express my hearty thanks for the great honor you have extended to me in inviting me to deliver the Herter lectures. The honor I accept, not so much for myself as for the science which I represent.

Experimental pharmacology is a science with essentially theoretical aims—a part of general biology, in which there is nowhere shown a greater interest than in America. I take especial pleasure in asserting that in this land of varied successes the understanding of abstract problems and of purely theoretical work thrives and ever grows, always extending to wider circles, filled with a scientific idealism which invites the most splendid and admirable sacrifices, spiritual and material. Your famous university and, indeed, these lectures themselves owe their origin to such idealistic impulses. And this gives me the courage and the desire to talk to you of the significance and value of pharmacology.

It is, then, not necessary for me to claim your attention for the practical results or for their value to the practising physician; not, however, that I undervalue this important side of pharmacology. But may I not hope at this place to be able to attain my purpose most easily, if I beg your attention to the biological results which we owe to pharmacological investigations?

For the explanation and analysis of physiological function, apart from comparative physiology, stimulation and extirpation of certain organs or parts of organs serve as general methods. Experimental physiology employed to this end mechanical

[1] Being the first of the Herter lectures delivered at the Johns Hopkins Medical School, October 5, 1905.

and physical means almost exclusively. The scalpel and scissors, electrical, thermal and mechanical stimuli have long served its purposes. The manifold means of chemistry have scarcely been utilized. Its appliances and its study belong, indeed, to pharmacology, which is, as an American fellow-worker has tersely said, 'the experimental chemistry of protoplasm.'

The drugs, that is the chemical reagents, penetrate into the interior of the organs and reach parts which are not accessible to the scalpel and the electric current. Indeed, the differential action of poisons—that which has to do with single parts of organs or single especial groups of cells—is the important part of the pharmacological method. But we must concede that it has not attained for the most part the undoubted certainty and clearness of physiological methods, for every drug which we wish to use as an instrument of investigation must first itself be investigated, its mode of action first be recognized and determined. You all know well how difficult and equivocal such investigations are, and it is easily intelligible that, especially in the beginnings of such investigations, while there was no large array of pharmacological facts supporting one another, one scarcely ventured from these to draw far-reaching conclusions.

An interesting example of this sort is the admirable investigation of Felice Fontana on Indian arrow poison, which was carried out more than one hundred years ago. Fontana was forced to the conclusion, through ingenious experiments, which resembled the much later ones of Claude Bernard, that the arrow poison paralyzes neither muscle itself nor the whole nerve, but only the endings of the latter and that, indeed, the latter must possess a structure different from the nerves themselves, of which anatomy and physiology took no cognizance. Fontana, however, did not dare to draw the right conclusion because the proof was indeed a pharmacological and not an anatomical one. Only much later was it learned that properly conducted and correctly interpreted pharmacological experimentation possesses the same power of conviction as any other exact scientific method. And it is precisely the curara poison which has led to positive physiological discoveries. By its help Boehm and Nussbaum, through the discovery of the so-called paradoxical vagus action, discovered the vasopressor nerves and the accelerator fibers in the trunk of the vagus nerve in dogs and cats; and later, with the help of the same poison, Boehm obtained the proof, otherwise inaccessible to physiology, that the nerve endings in the muscles possess the same capacity for fatigue and recovery as the muscle itself. The important problem of the close connection between the irritability and the conductivity of nerves was not soluble except by the aid of the pharmacological method, that is, the methodical utilization of poisons like curara, veratrin and carbon dioxide.

Formerly it was impossible to detect any physiological or morphological difference either in the arrangement or in the general structure of centrifugal and centripetal nerve tracts. But the narcosis experiments of Fraser, Alms, Joteyko and especially the more recent ones by Dixon with cocain, showed that they must be chemically different from one another, inasmuch as they react differently to poisons.

Highly important, also, are the physiological results which Langley obtained with the help of nicotin poisoning in relation to the sympathetic ganglia. He was able to show that by means of nicotin the sympathetic ganglia, and through them all the preganglionic nerves, were paralyzed, while the post-ganglionic nerves escaped. So it is possible to decide by this means

whether a nerve ends in a sympathetic ganglion or passes through it, as is the case, for example, with the trigeminus fibers through the ciliary ganglion.

The study of the action of a wholly different type of poison, namely tetanus toxin, has also furnished a series of important facts relating to the field of neurophysiology. If one injects into an extremity of a warm-blooded animal a sterile toxin derived from tetanus bacilli, there occurs, as is well known, a local tetanus, that is to say, the inoculated limb enters into tonic extension and shows, especially in the later stages of the poisoning, an increased reflex irritability, while all the remaining parts of the body continue to retain their normal position and normal reflex excitability. Now, it was possible to show that this remarkable phenomenon arose through the circumstance that the poison was absorbed by the adjacent motor nerve-ends and carried upward in the axis cylinder to corresponding centers of the spinal cord. The blood and lymph channels are wholly unconcerned in this transportation of the poison, and there consequently remains only the possibility that there is constantly flowing through the axis cylinder of the motor nerves a centripetal protoplasmic stream, reaching as far as the ganglia of the neurones. This was a previously unknown fact which must be of significance for the nutrition of the nerves and also for the trophic disturbances of the central ganglia which develop after section of the peripheral nerves. I have also found that such a centripetal flow of diphtheria toxin occurs in the nerves and the same thing seems to be true of certain metals which, like lead, give rise to chronic neuritic palsies. Perhaps a stream of this kind passes also along the sensory nerves, but in any case its course is arrested by the spinal ganglia, so that the tetanus poison is here held fast and is unable to reach the sensory apparatus of the spinal cord. If, on the other hand, one injects the posterior nerve-roots between the root ganglion and cord, there occurs an irritation of the sensory pain-exciting apparatus in the spinal cord and, indeed, without simultaneous irritation of motor or reflex structures. There thus arises the pure so-called tetanus dolorosus, which is characterized by the periodical recurrence of extremely painful seizures, excited apparently through the summation of minimal and, ordinarily, wholly inactive stimuli. It makes no difference, as regards the development of the phenomenon, whether the spinal ganglion has or has not been removed—a fact which was shown by Fletcher. In this manner has arisen the proof of the existence of wholly special pain-subserving structures in the central mechanism of the spinal cord (the existence of which was long denied by French physiologists)—structures distinct from those subserving tactile and motor functions.

Finally these investigations have brought to light another remarkable fact. In the ordinary poisoning through tetanus toxin the muscles are the seat of two distinctly different kinds of phenomena. In the first place, the involved muscles become shortened without undergoing contraction in the physiological sense. This condition may exist alone. In the resting state they show neither the electrical phenomena nor the heat production nor the muscle tone that characterizes a state of activity. They shorten only slowly and the affected extremity thus becomes stiff and gradually immobilized. If the muscles have not undergone maximal shortening, they are still capable of voluntary or reflex contraction, as in the case of normal muscles. It is only later that we see the well-known strychnine-like reflex tetanus in which the muscles are implicated in rapidly recurring, increasingly accentuated contractions. Since it is

possible to show that both the phenomena are subserved wholly by the spinal cord, it follows that there are present in the spinal cord various structures, quite distinct from the ordinary motor mechanism, which determine the state of inactive tension of the muscles, that is to say, their length while in a state of rest. These tonus-subserving structures are not excited by other poisons, like strychnine, and we have here the fundamental distinction between strychnine poisoning and poisoning by tetanus toxin. Indeed, it was only by means of the latter poison that the existence of these length-regulating tonus centers in the spinal cord was brought to light.

I have spoken hitherto of the nervous system itself, but it is true that the physiology of structures closely connected with the nervous system, as the glands, heart, blood vessels and muscles, has been materially advanced through the use made of pharmacological agents. You are all aware of the progress in our knowledge of lymph formation and the glandular function, which we owe to studies of Heidenhain; and these again were dependent in a great degree upon the help of pharmacological methods involving the application of specific chemical stimuli. I shall mention the results of some more recent investigations in this same direction, in the belief that they may be less familiar to you. Very recently Wertheimer and Lepage, in Lille, reported a series of pharmacological investigations on secretion by the pancreas, which led them to important results. It has long been known that the pancreas may be stimulated to secretion in a reflex manner and also, as Pawlow showed, through direct irritation of the vagus nerve. We know also, as a result of Starling's work, that the pancreas can be thrown into activity directly through the specific chemical stimulus furnished by the presence of secretion in the circulating blood. Now, Wertheimer and Lepage were able to show that the gland has at least two distinct mechanisms through which it is possible to excite the secretion of pancreatic fluids; first, certain structures intimately connected with the vagus nerve, which may be excited by pilocarpine, physostigmine or muscarine, or completely paralyzed by atropine; and secondly, another set of structures which are not acted upon by these poisons, being neither excited nor paralyzed by them, but which react to certain other definite chemical stimuli like secretin. Possibly the latter apparatus is part of the sympathetic nervous system; at all events the case of the submaxillary gland has been brought forward by Wertheimer and Lepage as analogous, since in this case the terminations of the chorda may be influenced by pilocarpine and atropine, whereas the sympathetic nervous mechanism remains intact. And, finally, just as the salivary secretion differs according as it arises through the stimulation of the chorda or of the sympathetic nervous system, so does the pancreatic secretion resulting from the pilocarpine differ from that which is obtained through the action of secretin. In the latter case the secretion contains entero-kinase, that is to say, is able to digest albumin without the addition of succus entericus.

In this connection it may be mentioned that the use of pilocarpine has led to a physiological understanding of an entirely different kind of secretion, namely, the liberation of a gas. It has long been known that the swimming bladder of fishes contains a gas, the presence of which can hardly be explained by a process of simple diffusion out of the tissues. This fact, which we owe to the observation of Huefner, led Dreser to investigate the process of liberation of oxygen into the swimming bladder of the pike, with a view to determining whether pilocarpine and other

glandular stimulants gave rise to an increased accumulation. And, indeed, he found that when fishes were repeatedly injected with pilocarpine, the content of the swimming bladder in oxygen gas was distinctly greater than in the case of the gas from the normal fishes, which permits the conclusion that the epithelia of the swimming bladder liberate a gas in a manner analogous to the liberation of secretions from true glands, and further that these epithelia are not penetrable in either direction like a diffusing membrane.

Another fact deserves brief notice in this relation. It is the interesting observation of Magnus that when ammonia gas is injected into the veins the alveolar epithelium of the lungs is not penetrable, since no trace of ammonia can be detected in the expired air, whereas after the inhalation of ammonia the gas penetrates readily into the blood through these same epithelial cells. This is merely one striking example of the many known cases in which animal epithelial membranes are penetrable in one direction for certain substances like water, salts or urea, while opposing strong resistance to the passage of these in the opposite direction. The mechanism of this regulatory arrangement has not yet been cleared up and further progress seems hardly possible without the aid of pharmacological methods.

To enter upon the physiology of the heart at this time would carry us too far. Pharmacological facts which have proved of importance in giving us our present knowledge are doubtless sufficiently known to you. We may say, however, that even in regard to the recent controversy over the myogenic and neurogenic theories of the cardiac motions and over the general character of the heart muscle, the systematic study of the cardiac poisons has contributed much that is important and, as Harnack has indicated, may perhaps furnish the final decision.

Permit me now to direct your attention, for a few moments, to some of the physiologico-chemical results of pharmacological investigations. It lies in the nature of things that the results should be numerous in a field that has to do solely with the chemical inter-relations between the pharmacological agent and the living organism. I shall not tire you with an enumeration of facts already well known. I shall refer only to a few of the more significant biological reactions which we owe to pharmacological investigation. The study of poisoning by acids led to the discovery of ammonia-production in the organism, and this in turn to the Schroeder experiments, which positively demonstrated the production of urea in the liver. Pharmacological methods have also contributed materially to the elucidation of numerous other important problems in metabolism. One of the most actively discussed problems has been the question whether sugar can arise from proteid, and this question has been definitely answered, as it seems to me, by the experiments of Rolly. This observer conducted experiments on animals which had been rendered glycogen-free by means of fasting and strychnine spasms. He then brought about an increased destruction of proteids by means of fever, induced through the action of bacteria and toxines and was able to demonstrate that there occurred a new production of glycogen under these circumstances in the liver and in the muscles. As the fat-reserve of the animals had already sunk to a minimum during the period of fasting, it is clear that the source of the newly formed glycogen is to be sought in the increased destruction of proteids in the organism. The same sequence of events was demonstrated by Rolly in fasting rabbits at the time of the

great destruction of proteids that immediately precedes death.

That the problem of diabetes mellitus, though still unsolved, has received light from many sides through pharmacological investigations, I need hardly state. I will merely remind you that the discovery of phlorhizin diabetes showed us a hitherto unknown capacity of the kidney to secrete sugar, that the work of Lusk and his associates led to the establishment of a definite ratio between nitrogen and dextrose excretion in diabetes, and that Blum and Herter found an adrenalin glycosuria which may perhaps throw some light on the puzzling nervous forms of diabetes.

Again, through poisoning by phosphorus and arsenic the relation of lactic and the amido-acids to the intermediary metabolism was first shown, while as regards the more intimate metabolic processes and their relation to ferment action, the toxicological experiments of Jacobi and of Wakeman have brought us important light. Through poisoning by chloral, by camphor and nitrotoluol, the discovery of glycuronic acid was made, the normal occurrence of which in the organism was only later established. Indeed, the various chemical reactions of the organism, of which we have examples in the formation of hippuric acid in the kidneys, in sulphocyanide, in methylation, in oxidation and reduction, were all of them first discovered through the action of chemical or pharmacological agents. Furthermore, as regards the location and intensity of these processes, the investigations of Ehrlich and of Herter have given us definite information. I would like to refer here to an interesting observation from Herter's studies which demonstrates with special clearness to the eye the oxygen requirements of the muscles and shows with what energy the muscles appropriate oxygen not only from oxyhemoglobin, but also from other reducible substances. Herter found that if animals receive intravenous infusions of methylene blue the pectoral muscles were soon colored deep blue, but that if during the experiment the access of oxygen was hindered by giving the animals air mixed with carbon monoxid, the blue muscles in a few seconds recovered their natural red color; they had almost momentarily reduced the methylene blue to the colorless leucobase. It is also known that through the action of hydrocyanic acid the capacity of the organs to take up oxygen from the blood is much reduced or destroyed. This process also it was possible to render easily visible by the method of methylene blue infusion. As we have seen, the pharmacological method has revealed to us a series of functional characters of the organism; but its biological significance appears to extend even further. It seems possible with such methods, if only gradually, to reach a more intimate knowledge of the chemical constitution of protoplasm, and finally, perhaps, to arrive at an insight into the chemical interpretation of its functions. If, under the influence of a pharmacological agent, we observe an immediate essential alteration in the function of a cell, we have to assume that a chemical change has occurred in its vital center—in what Ehrlich has called the 'Leistungskern,' that is, the chemical center of vital activity. On the other hand, if we have before us a gradually developing alteration, this may have been called forth in a secondary manner, through chemical changes in the reserve material or in the supporting elements of the cells, perhaps in the groups of atoms which we conceive as side-chains. Given a knowledge of the constitution and the chemical mode of action of agents operating as acute intoxicants, we should also be able to reach conclusions as to the chemistry of their point of attack, that is to say, regarding that substratum of the living sub-

stance which corresponds to the chemical constitution and action of the poison. With a similar idea in mind Oscar Loew, twenty years ago, considered himself justified in assuming the presence of an aldehyde group in the living protoplasm, basing this view on a series of merely qualitative toxic reactions like those obtainable by hydroxylamine, diamid and other substances.

An example of another pharmacological method which may, perhaps, prove of utility is the investigation of the narcotics. The quantitative comparison of the action of aliphatic narcotics (alcohol, ether, chloroform, etc.) leads to what I believe to be the unavoidable conclusion that certain fat-like substances like lecithin must be conceived as constituting integral parts of the 'Leistungskern.' It happens that one can compare with considerable exactitude in a quantitative way, the efficacy of this numerous group of bodies. This comparison has brought out the fact that the degree of activity is approximately proportional to the individual chemico-physical affinities of all these substances, that is their solution-tensions for fat-like bodies compared with their solution-tensions for watery media. From this almost rigid parallelism it follows with a high degree of probability that in the union of ether, chloroform, etc., to a fat-like substance—a lipoid—we have the origin of the narcosis of the cell; in other words, the lipoid belongs to the essential functionally active constituents of the cell. It has been urged against this conclusion that the cell lipoids occasion merely a stronger or a weaker accumulation of the narcotic which then acts on the true albuminoid life-center of the cell in proportion to the degree of this accumulation. There are, in reality, only two possibilities. First, one may assume that the narcotic operates only through its presence in lifeless lipoids whence it acts from a distance, perhaps through a sort of induction, upon the living cell-center itself, without entering into reciprocal chemical action with its center. Such a view could be neither refuted nor established. But in order to explain the above-mentioned parallelism, it would be necessary, on this supposition, to invoke the aid of the very improbable hypothesis that all the different narcotic substances, compared on an equimolecular basis, exert an equally strong induction. And this hypothesis wholly fails to allow for the different influence of special groups of atoms, as, for example, the ethyl group, the methyl group, etc. Hence it is clear that such an action at a distance must remain problematical, and furnishes us no actual explanation. On the other hand, we may make the much more likely assumption that the narcotic substance enters into a reciprocal, reversible, chemico-physical action with some constituent of the 'Leistungskern' or 'life-center,' the strength of which reaction is dependent on the intensity of this reciprocal action. Then again, the law of mass action here comes into play, that is the law of distribution. We may even leave the lipoid for the moment out of account. In this case it would have to be regarded simply as an intermediary solvent and would remain without influence upon the equilibrium established by the narcotic between the blood and lymph plasma on the one hand and the 'Leistungskern' or 'life-center' on the other. Experiment, however, showed that the affinity of the living cell substance for a narcotic, measured by the observed intensity of action, runs parallel to the experimentally observed fat affinity of the narcotic, or, in other words, that the unknown constituent of the living cell or 'Leistungskern' must itself possess certain properties of a fatty substance, or, in short, must itself be a fat-like or lipoid body. And thus we come back to the very conclusion of which I have already spoken. I have expressed

myself in somewhat greater detail than is perhaps warranted by the importance of the question. I have, however, thought such a critical discussion of the problem of some interest, as it seems of fundamental significance for the evaluation of a pharmacological analysis of this kind.

I have already said that perhaps the highest result of pharmacological investigation may prove to be the winning of an insight into the chemical nature of life processes themselves; indeed, the first important ground in this direction has already been won. You are all familiar with the important investigations of Jacques Loeb, to whom we owe a knowledge of the essential significance of the individual metallic ions, for the general life processes. But what is still more important, Loeb has succeeded in inducing very special biological reactions as the effect of chemical action. He has shown that heliotropism can be excited by definite chemical reagents such as carbon dioxide and other substances, instead of through the action of light, which is a contribution to the understanding of the mechanism of this singular reflex function. Finally, he has shown that through certain definite chemical procedures, like the action of hypertonic salt solutions, combined with ethyl acetate, the unfructified eggs of sea-urchins may be stimulated to parthenogenetic normal development, an observation which may prove of great significance for the understanding of the process of fertilization.

And with the mention of this admirable investigation, permit me to close my address of to-day.

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THE GEOGRAPHICAL DISTRIBUTION OF THE STUDENT BODY AT A NUMBER OF AMERICAN UNIVERSITIES

THE accompanying table explains the geographical distribution of the student body of six of the leading universities of the east and of three western institutions for the academic year 1904–1905, summer session students being omitted in every instance. In the case of Harvard University the students of Radcliffe College (undergraduate women) are not included. Efforts were made to include three other prominent western universities, but it was impossible to secure the necessary figures in shape for comparison. Examining the figures by divisions, we note in the first place that the student clientele of the University of Michigan is by no means confined to the central states, for almost four hundred students at this institution hail from the North Atlantic division. The student bodies of the other western universities included in the table, Illinois and Indiana, are to all intents and purposes local in character, although the former draws some students from the south and west. Harvard has the greatest hold on the New England states, leading in all of them except Connecticut, in which state Yale naturally occupies first place. Columbia has more students from the entire North Atlantic division than any of the other institutions, leading in its own state, and strange to say, drawing more students from the state of New Jersey than Princeton does. The University of Pennsylvania, as we should expect, has the largest following in its own state, Princeton ranking second and Cornell third.

The most striking fact to be noted in the South Atlantic division is the hold that Cornell has on this section of the country. The University of Pennsylvania, chiefly by reason of its proximity to several states in this division—notably Delaware and Maryland—draws the next largest number of students, with Columbia third and Harvard fourth, all of the universities mentioned having over one hundred students from this division. Cornell leads in the District of Columbia, with Harvard a close second.