a more systematic showing of the importance of chemistry to the wise use of natural resources; and its purposes have gained a far wider and more appreciative understanding by our people as a whole.

Again we find evidence in the recent issuance of a special chemistry edition by a prominent trade journal, *The Manufacturers Record.* The purpose of that unusual issue was not merely to emphasize the advantages of a great section of the country for the upbuilding of chemical industries, but of far greater importance it sought to vitalize the thought of the people of that section as to the fundamental character of chemistry among the factors of industrial development.

Furthermore, it must be noticeable to all that slowly but surely an educational campaign is getting under way in the daily press and in periodical literature which will eventually result in the arousal of our people to a full comprehension of the value of chemistry as a national asset.

These are simply signs of the times. We can not, however, feel that the national thought has as yet grasped in its entirety the all pervading influence of chemistry so long as Cornell University, with its strong chemistry staff, must delay the replacement of its burned laboratory through lack of funds; so long as Johns Hopkins University, the cradle of American chemical research, must undergo such struggle for the means to erect a new laboratory on the beautiful new site of that institution; so long as members of congress view chemists and chemical manufacturers as fit subjects for hard bargaining; so long as railway presidents feel that chemistry has no part in the development of the natural resources of the sections traversed by their lines; and so long as waste in any form is allowed to continue unheeded.

Further expansion of the relations of chemistry to the national thought involves—

First. Continued educational effort through the press. Plans for such are being evolved, and these plans are meeting the quickened sympathy of the leaders of the press. Each of us must cooperate in this work. As a class we are not qualified to write in popular style, and in the past we have not troubled ourselves very much about such matters; but we can furnish facts and sound opinion to those who have the work and responsibility of popular presentation, and we should stand ready, each in his own community, to share in such cooperative effort.

Second. An awakening of the financial interests of the country to the fact that the ways of chemistry are not mysterious but applied common sense which constitutes a sure guide.

Third. Continued worthiness of our own efforts. This is our direct responsibility. Thoroughness of training, untiring zeal in work, aggressive conservatism in counsel, courage in new undertakings, independence in thought, generous cooperation, constant search for truth—these must surely lead us to that vantage ground where we can best serve this our country.

Chas. H. Herty

ON THE ANALYSIS OF LIVING MATTER THROUGH ITS REACTIONS TO POISONS[1]

I am told that the chair of Section I has not been held by a pharmacologist for many years, and I wish to express the pleasure I feel in the honor that has been done me personally, and even more in the recognition vouchsafed to one of the youngest handmaidens of medicine. Pharmacology

[1] Address before the Physiological Section of the British Association for the Advancement of Science, Newcastle-on-Tyne, 1916.

has too often shared the fate of the bat in the fable: when we appeal for support to the clinicians we are told that we represent an experimental science, while when we attempt to ally ourselves with the physiologists we are sometimes given the cold shoulder as smacking too much of the clinic. As a matter of fact, we should have a footing in each camp, or, rather, in each division of the allied forces. And the more recent successes in the application of pharmacology to diseased conditions are now beginning to gain it a rather grudging recognition from clinicians, while the alliance with the biological sciences is being knit ever more closely. The effect of chemical agents in the living tissues has assumed a new and sinister aspect since the enemy has resorted to the wholesale use of poisons against our troops, but I must leave this for the discussion to-morrow.

I wish to-day to discuss an aspect of pharmacological investigation which has not been adequately recognized even by the pharmacologists themselves and which it is difficult to express in few words. In recent years great advances have been made in the chemical examination of the complex substances which make up the living organism, and still greater harvests are promised from these analytic methods in the future. But our progress so far shows that while general principles may be reached in this way, the chemistry of the living organ, like the rainbow's end, ever seems as distant as before. And, indeed, it is apparent that the chemistry of each cell, while possessing general resemblances, must differ in detail as long as the cell is alive. No chemistry dealing in grams, nor even microchemistry dealing in milligrams, will help us here. We must devise a technique dealing with millionths to advance towards the living organism. Here I like to think that our work in pharmacology may perhaps contribute its mite; perhaps the action of our drugs and poisons may be regarded as a sort of qualitative chemistry of living matter. For chemical investigation has very often started from the observation of some qualitative reaction, and not infrequently a good many properties of a new substance have been determined long before it has been possible to isolate it completely and to complete its analysis. For example, the substance known now as tryptophane was known to occur in certain substances and not in others long before Hopkins succeeded in presenting it in pure form. And in the same way it may be possible to determine the presence or absence of substances in living tissues, and even some of their properties, through their reaction to chemical reagents, that is, through the study of the pharmacology of these tissues. A simple example may render the point clearer: It is possible that if the toxicity of the saponins to different cells were accurately known, the relative importance of the lecithins in the life of these cells might be estimated, and this might give a hint to the chemist in approaching their analysis. I do not claim that pharmacological investigation can at present do much more than the qualitative testing of the tyro in the chemical laboratory, but even a small advance in the chemistry of living matter is worthy of more attention than this has received hitherto.

All forms of living matter to which they have free access are affected by certain poisons, and some of these have obvious chemical properties which suggest the method of their action; thus the effects of alkalies and acids and of protein precipitants hardly need discussion. Others such as quinine and prussic acid, which also affect most living tissues, have a more subtle action. Here it is believed that the common factor in living matter which is changed by these poisons is the ferments, and quinine and prussic acid may therefore be regarded as qualitative tests for the presence of some ferments, notably those of oxidation, and, in fact, have been used to determine whether a change is fermentative in character or not. Formaldehyde was stated by Loew to be poisonous to living matter through its great affinity for the NH_2 group in the proteins, a suggestion which has perhaps not received enough attention of late years, during which the importance of this group in proteins has been demonstrated. The toxicity of other general poisons, such as cocaine, is more obscure. But what has been gained already in this direction encourages further investigation of the action of the so-called general protoplasm poisons and further efforts to associate it with the special constituents of the cell.

In other poisons the action on the central nervous system is the dominating feature, and among these the most interesting group is that of the simple bodies used as anesthetics and hypnotics, such as ether, chloroform and chloral. The important use of this group in practical medicine has perhaps obscured the fact that they act on other tissues besides the central nervous system, though we are reminded of it at too frequent intervals by accidents from anesthesia. But while they possess this general action, that on the nervous tissues is elicited more readily. Not only the nerve-cell, but also the nerve-fiber react to these poisons, as has been shown by Waller and others. And even the terminations are more susceptible than the tissues in which they are embedded, according to the observations of Gros. The selective action on the nervous tissues of this group of substances has been ascribed by Overton and Meyer to the richness in lipoid substances in the neurons, which leads to the accumulation of these poisons in them, while cells containing a lower proportion of lipoid are less affected. In other words, Overton and Meyer regard these drugs as a means of measuring the proportion of lipoids in the living cell. This very interesting view has been the subject of much discussion in recent years, and, in spite of the support given it by several ingenious series of experiments by Meyer and his associates, no longer receives general acceptance. Too many exceptions to the rule have to be explained before the action of these bodies can be attributed wholly to their coefficients of partition between lipoids and water. At the same time the evidence is sufficient to justify the statement that the property of leaving water for lipoid is an important factor in the action of the bodies, although other unknown properties are also involved in it. And whatever the mechanism of the characteristic action, these substances in certain concentrations may be regarded as tests for the presence of nervous structures and have been employed for this purpose.

Other bodies acting on the nervous system have a much narrower sphere. Morphine and strychnine, for example, appear to be limited to the region of the nerve-cells, but there is still doubt whether they affect the cell-body alone or the synapses between certain of its processes. They have not been shown to act on peripheral nervous structures in vertebrates, nor on any but specific regions of the central nervous system. Nor has it been established that they affect invertebrates. The substance with which they react is obviously limited by very narrow boundaries around the nerve-cell.

More interest has been displayed in recent years in the alkaloids which act on the extreme terminations of various groups of nerves. These are among the most specific reagents for certain forms of living matter which we possess. Thus, if an organ reacts to adrenaline, we can infer that it contains the substance characteristic of the terminations of sympathetic fibers, with almost as great certainty as we infer the presence of a phenol group from the reaction with iron. And this sympathetic substance can be further analyzed into two parts by means of ergotoxine, which reacts with the substance of the motor sympathetic ends, while leaving that of the inhibitory terminations unaffected. Similarly the endings of the parasympathetic nerves are picked out with some exceptions by the groups represented by atropine and pilocarpine, and here again there must be some definite substance which can be detected by these reagents.

Further, some light has been thrown on, at any rate, one aspect of these nerve-end substances by the observation that they all react to only one optical isomer in each case. Thus the dextro-rotatory forms are ineffective in both atropine and adrenaline, and this suggests strongly that the reacting body in the nerve-ends affected by these is itself optically active, though whether it bears the same sign as the alkaloid is unknown. This very definite differentiation between two optical isomers is not characteristic of all forms of living matter. For example, the heart muscle seems to react equally to both lævo- and dextrocamphor. The central nervous system contains substances which react somewhat differently to the isomers of camphor and also of atropine, but the contrast is not drawn so sharply as that in the peripheral nerve-ends.

Another test alkaloid is curarine, the active principle of curare, which in certain concentrations selects the terminations of the motor nerves in striated muscle as definitely as any chemical test applied to determine the presence or absence of a metal.

The tyro in the chemical laboratory is not often fortunate enough to be able to determine his analysis with a single test. He finds, for example, that the addition of ammonium sulphide precipitates a considerable group of metals, which have then to be distinguished by a series of secondary reactions. The pharmacologist, as an explorer in the analysis of living matter, also finds that a single poison may affect a number of structures which appear to have no anatomical or physiological character in common. But as the chemist recognizes that the group of metals which react in the same way to his reagent have other points of resemblance, so perhaps we are justified in considering that the effects of our poison on apparently different organs indicate the presence of some substance or of related substances in them. A great number of instances of this kind could be given, and in many of these the similarity in reaction extends over a number of poisons, which strengthens the view that the different organs involved have some common reacting substance.

One of the most interesting of these is the common reaction of the ends of the motor nerves in striated muscle and of the peripheral ganglia of the autonomic system. It has long been known that curare and its allies act in small quantities on the terminations of the motor nerves in ordinary muscle, while larger amounts paralyze conduction through the autonomic ganglia. More recently it has been developed by the researches of Langley that nicotine and its allies, acting in small quantities on the ganglia, extend their activities to the motor ends in large doses. Some drugs occupy intermediate positions between nicotine and curare, so that it becomes difficult to assign them to either group. These observations appear to leave no question that there is some substance or aggregate common to the nerve-ends in striated muscle and to the autonomic ganglia. As to the exact anatomical position of this substance, there is still some difference of opinion. Formerly it was localized in the terminations of the nervous fibers in the muscle and ganglia, but Langley has shown that in the latter the point of action lies in the ganglion-cell itself, and his researches on the antagonism of nicotine and curare in muscle appear to show that the reacting substance lies more peripherally than was supposed, perhaps midway between the anatomical termination of the nerve and the actual contractile substance. Another analogy in reaction has been shown to exist between the ganglia and the terminations of the post-ganglionic fibers of the parasympathetic, for Marshall and Dale have pointed out that a series of substances, such as tetramethyl-ammonium, affect each of these in varying degrees of intensity. The specific character of the reaction is shown by the fact that while it is possessed by the tetramethyl-ammonium salts, the tetraethyl-ammonium homologues are entirely devoid of it.

Another close relationship is shown by the reaction of the glucosides of the digitalis series on the heart and vessels. These all act on the muscle of the heart, and in higher concentration on that of the vessel-walls. There must therefore be a common base in these which is affected by the drugs. And the existence of this is perfectly intelligible in view of the fact that the heart is developed from the vessels. A more obscure relationship is shown by the reaction of this group to the inhibitory cardiac center in the medulla, which is thrown into abnormal activity by their presence in the blood, as has been shown alike by clinical and experimental observations. A similar relation is shown by the common reaction of the heart-muscle and the vagus center to aconitine and some other related alkaloids. On the other hand, the saponin series, which shows a closer relationship to the digitalis bodies in the heart-muscle, is devoid of its characteristic action on the medulla. The reacting substance in the heart is thus capable of responding to digitalis, saponin and aconitine, while that in the vagus center can associate only the first and last and is not affected by the saponins; the common reactions indicate that the two are related, while the distinctive effect of saponin shows that they are not identical. A similar relationship may be drawn from the action of morphine and the other opium alkaloids on pain sensation, on respiration, and on the movements of the alimentary tract. Exact determinations of the relative power of these alkaloids in these regions are not at our disposal as yet, but sufficient is known to suggest that while morphine affects a common substance in the medullary center and the intestinal wall, the other members of the series act more strongly in one or other position.

It was long ago pointed out that caffeine affects both kidney and muscle-cell, and Schmiedeberg has attempted to correlate the intensity of action of the purine bodies at these points and to measure the probable diuretic action by the actually observed effect on the contraction of muscle. Other reactions of the kidney suggest a relationship to the wall of the bowel. For example, many of the heavy metals and some other irritant bodies act strongly on the kidney and bowel, and again, according to one view of renal function, many of the simple salts of the alkalies affect the kidney in exactly the same way as the bowel-wall. This last may, however, be due to the physical properties of the salts, and the likeness in reaction to those of kidney and bowel, which is striking enough, may arise from a likeness in function of the epithelium rather than from any specific relationship to the salts which is not common to other forms of living matter.

Many other examples might be cited in which organs which are apparently not related, either morphologically or in function, react to poisons in quantities which are indifferent to the tissues in general. And this reaction in common can only be interpreted to mean that there is some substance or group of related substances common to these organs. The reaction may differ in character; thus a drug which excites one organ to greater activity may depress another, but the fact that it has any effect whatever on these organs in preference to the tissues in general indicates some special bond between them, some quality which is not shared by the unaffected parts of the body. I have, therefore, not differentiated between excitation and depression in discussing this relation. One is tempted to utilize the nomenclature introduced by Ehrlich here and to state that the common reaction is due to the presence of haptophore groups while the nature of the reaction (excitation or depression) depends on the character of the toxophore groups. But while these terms may be convenient when applied to poisons whose chemical composition is altogether unknown, they merely lead to confusion when the question concerns substances of ascertained structure. Thus, as Dale has pointed out, it is impossible to suppose that such substances as tetramethyl-ammonium and tetraethyl-ammonium owe the difference in reactions to specific haptophore groups in the one which are absent in the other. It seems more probable that in this instance and in others the difference in the effect of these bodies in the tissues arises from differences in the behavior of the molecule as a whole than in differences in the affinities of its special parts; that is, that the action of these poisons is due to their physical properties rather than to their chemical structure, although this, of course, is the final determining cause.

In the same way the common reaction of tissues, which I have so far ascribed to their possessing some substance in common, may arise from community of physical relationship, and I wish to avoid the implication borne by the word "substance," which I have used in the widest sense, such as is justified perhaps only by its historical employment in theological or philosophical controversy. The reaction of living tissue to chemical agents may arise from a specific arrangement in its molecule, but may equally be attributed to the arrangement of the molecules themselves. And the curious relationships in the reactions of different tissues may indicate, not any common chemical factor, but a common arrangement of the aggregate molecules. We are far from being able to decide with even a show of probability which of these alternatives is the correct one, and my object today has been to draw attention to these relationships rather than to attempt their elucidation. Hitherto the speculative pharmacologist has been much engaged in comparing the chemical relationship of the drugs which he applies to living tissues; much useful knowledge has been incidentally acquired, and the law has been formulated that pharmacological action depends directly on, and can be deduced from chemical structure. This view, first elaborated in this country, has in recent years shared the fate of other English products in being advertised from the housetops and practically claimed as the discovery of more vociferous investigators. On examining the evidence, old and new, one can not help feeling that attention has been too much directed to those instances which conform to the creed, while the far more numerous cases have been ignored in which this so-called rule fails. The difficulties are very great; for example, what chemical considerations can be adduced to explain why the central nervous tissues react differently to bromide and chloride, while to the other tissues these are almost equally indifferent; or how can the known chemical differences between potassium and sodium be brought into relation with the fact that they differ in their effects in almost every form of living tissue?

Less attention has been paid to the other factor in the reaction, the properties of the living tissue which lead one cell to react to a poison, while another fails to do so. I have pointed out some curious relations between different organs, but much needs to be done before any general view can be obtained. Further detailed examination of the exact point at which poisons act, and much greater knowledge of the physical characters of the drugs themselves and of the relation of colloid substances to these characters, are needed. We must attempt to classify living tissues in groups not determined by their morphological or even functional characters, but by their ability to react to chemical agents. Advance is slow, but it is continuous, and if no general attack on the problem is possible as yet, our pickets are at any rate beginning to give us information as to the position of the different groups to be attacked. And when a sufficient number of these qualitative reactions have been ascertained for any form of living matter, it may be possible for some Darwin to build a bridge from the structural chemistry of the protein molecule to the reactions of the living cell. We can only shape the bricks and mix the mortar for him. And my purpose to-day has been to indicate how the study of the effects of drugs on the living tissue may also contribute its mite towards the great end.

A. R. Cushney

FIELD MEETINGS OF THE ASSOCIATION OF AMERICAN STATE GEOLOGISTS

The state geologists of Connecticut, Florida, Illinois, New Jersey, New York, North Carolina, Ohio, Oklahoma, West Virginia and Wisconsin, the director and chief geologist of the Federal Survey, together with the staff of the New York Geological Survey and a few invited guests were in attendance on some or all of the field meetings of the Association of American State Geologists on September 4 to 9. The meetings were held in New York state by invitation of the director of the New York Geological Survey, Dr. John M. Clarke.

September 4–5. The field meetings began September 5 after a preliminary meeting on the previous evening in the office of the director in the State Museum at Albany. The first excursion was by autobus to the Indian Ladder of the Helderberg escarpment, where the classic Helderberg section is well developed. The more refined subdivisions were pointed out by Dr. J. M. Clarke, Dr. R. Ruedemann and Dr. E. O. Ulrich, and the reasons for the subdivisions and for some recent changes in nomenclature were discussed. Contacts between the Indian Ladder beds (Hudson River) and Brayman shales, and between the Brayman shales and Manlius limestone were studied and the cause of the brecciated character of the beds was considered.

The karst topography developed where the Onondaga limestone reaches the surface was seen as the party motored to Thompson's Lake. This lake is believed to rest in a solution basin from which the water drains through underground passages.

At Altamont the party was most agreeably entertained at tea by Mrs. John Boyd Thacher, donor to the state of New York of the Helderberg escarpment, of which the Indian Ladder is the most picturesque portion and which is known as the John Boyd Thacher Park. In the evening the party assembled in the office of the director of the New York Survey for a conference.

September 6. Wednesday morning the party went by train to Saratoga Springs, where it