TO BOND OR NOT TO BOND: CHEMICAL VERSUS PHYSICAL THEORIES OF DRUG ACTION

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In 1903, Arthur Cushny, Professor of Materia Medica and Therapeutics at the University of Michigan, published an article in the *Journal of the American Medical Association* entitled "The Pharmacologic Action of Drugs: Is It Determined by Chemical Structure or by Physical Characters?"[1] To a chemist today, this question might seem odd. The physical properties of a drug and its chemical structure are, after all, intimately related, and even if one wants to distinguish between closely integrated physical and chemical properties, surely both are involved in drug action. Physical properties such as solubility and chemical reactivity due to the presence of certain molecular structures can and do both influence pharmacological effects.

At the turn of the twentieth century, however, the understanding of the nature of chemical bonding and of cellular structure and function was still in its infancy, and many chemists and pharmacologists sought a simplified answer to Cushny's question. There was thus significant controversy over whether the physical or the chemical properties of a substance could best explain its pharmacological action, and over the value of attempts to relate the physiological activity of a drug to its chemical structure.

The fact that drugs may exert a selective action on specific organs of the body had long been recognized empirically and expressed vaguely in the traditional designation of certain remedies as cordials (acting on the heart), hepatics (acting on the liver), etc.[2] As early as the seventeenth century, the noted chemist Robert Boyle had tried to explain the specific effects of

drugs in terms of the mechanical philosophy by suggesting that since the different parts of the body have different textures, it is not implausible that when the corpuscles of a substance are carried by the body fluids throughout the organism, they may, according to their size, shape and motion, be more fit to be detained by one organ than another.[3]

Attempts were also made in the sixteenth and seventeenth centuries, under the influence of Paracelsus and his followers, to explain drug action in more chemical terms. The iatrochemists, for example, tended to attribute most physiological and pathological phenomena (including pharmacological action) to acid-base interactions.[4] It was not until the nineteenth century, however, when chemistry had become firmly established as a science, that the chemical approach could be given a clearer and more specific expression. Around mid-century, for example, Jonathan Pereira, who was not himself a confirmed adherent of the chemical theory, explained this viewpoint as follows:

> "The action of a medicine on one organ rather than on another is accounted for on the chemical hypothesis, by assuming the existence of unequal affinities of the medicinal agent for different tissues. Thus the action of alcohol on the brain is ascribed to the affinity of this liquid for the cerebral substance."[5]

Other scientists were more specific in attributing the action of drugs to chemical interaction. In the early 1870s, for example, British pharmacologists Thomas Lauder Brunton and Thomas Fraser both voiced the view that it seemed likely that the physiological action of drugs is usually due to a chemical reaction between the drug and some constituent of the cell or tissue. At the turn of the twentieth century, German investigator Sigmund Fränkel argued that the selective action of drugs can only be understood by assuming that certain groups in the drug

molecule enter into a chemical union with the cell substance of a particular tissue. Once fixed in the cell in this manner, the drug can exert its pharmacological action.[6]

The chemical viewpoint was given a boost by a number of studies in the late 19th century on the relationship between pharmacological action and chemical structure. Among the most important of these early structure-activity studies was the work of the afore-mentioned pharmacologist Thomas Fraser and his chemistry colleague at the University of Edinburgh, Alexander Crum Brown. Their first paper on the subject, published in 1869, began with a declaration of faith: "There can be no reasonable doubt that a relation exists between the physiological action of a substance and its chemical constitution, understanding by the latter the mutual relations of the atoms in the substance."[7]

Brown and Fraser were aware of the need to go beyond relating activity to just chemical composition, i.e., to the presence and proportion of certain elements. It was necessary to attempt to relate activity to the chemical structure of the molecule. Unfortunately, the structure of most organic compounds, the substances of greatest pharmacological interest, was not known in 1869. They refused to allow such considerations to deter them, reasoning that one should still be able to discover the nature of the relationship between structure and constitution in at least an approximate manner.

What one needed to do, Brown and Fraser argued, was to produce a known change in structure which would be the same in a number of different compounds, and then observe the effect on physiological activity. From an examination of the literature, they concluded that physiological activity was often associated with an unsaturated valence, i.e., with the presence of an atom which could undergo further addition. Chemical addition often seemed to remove or

diminish physiological activity. For example, carbon monoxide is highly toxic, but addition of another oxygen to produce carbon dioxide results in a much less toxic substance.

Brown and Fraser decided to work with alkaloids because so many important drugs (e.g., morphine and quinine) fell into this class and because there was some evidence that the addition of methyl iodide to these compounds (i.e., methylation) destroyed or diminished their physiological action. This fact lent support to their theory about the relationship of addition and saturation to activity.

In their first experiments on the subject, they studied the pharmacological activity of six alkaloids, as well as their methylated derivatives. They found that upon methylation the ability of these alkaloids (e.g., strychnine) to produce convulsions disappeared. The narcotic properties of morphine and codeine were also diminished. At the same time, the methylated compounds exhibited a very different toxic effect, although generally only at doses much greater than those required by the alkaloids to produce their usual toxic effects. The methylated derivatives all exhibited a paralyzing, curare-like effect. A relatively small change in structure had thus produced a dramatic change, both quantitative and qualitative, in the pharmacological properties of the alkaloids.[8]

Brown and Fraser expanded their studies to other substances, and soon found that in general the compounds now known as quaternary ammonium salts (which included the methylated alkaloids) were associated with a paralyzing action.[9] The two Scottish scientists had been quite fortunate in their choice of compounds to study, because such clear-cut relationships between structure and activity are not that common. In fact, some three decades later, in 1901, British biochemist F. Gowland Hopkins declared that the results obtained by Brown and Fraser

were still “the most satisfactory instance to hand, of obvious relation between chemical constitution and physiological action.”[10]

Nevertheless, Hopkins was convinced that such a relationship existed, and that the difficulties involved in investigating the question did not render the study unprofitable. Hopkins went on to list other examples which, while not as definitive and elegant as those brought to light by Brown and Fraser, supported this view. For example, he cited various studies that had demonstrated relationships between certain structural features of molecules and specified pharmacological actions (such as the characteristic intoxicant and narcotic properties of primary alcohols).[11]

These early results had led some physicians and scientists to be overly optimistic about the immediate prospects of structural studies on drugs for therapeutics. For example, Thomas Lauder Brunton suggested in the 1870s that the time might not be far off when scientists would be able to synthesize substances that would act on the body in any desired way.[12] A decade later, he retained his faith in the advances that would be produced by structure-activity investigations, stating that “the prospects of therapeutics appear to me very bright.” He thought it highly probable that before long physicians would have different series of remedies, arranged in order of comparative strength, that would modify various body functions, such as the circulation of the blood, the action of the heart, and the biliary secretion of the liver.[13]

The noted biologist Thomas Huxley was also impressed by the advances made in chemical pharmacology during his lifetime, and in 1881 he wrote:

> “...there surely can be no ground for doubting that, sooner or later, the pharmacologist will supply the physician with the means of affecting, in any desired sense, the functions

of any physiological element of the body. It will, in short, become possible to introduce into the economy a molecular mechanism which, like a very cunningly contrived torpedo, shall find its way to some particular group of living elements, and cause an explosion among them, leaving the rest untouched."[14]

By the turn of the twentieth century, as reflected in the statement by Hopkins previously quoted, this overly optimistic outlook had been tempered by the recognition that the task was more difficult and progress would be slower than originally anticipated. Nevertheless, there was still substantial interest in the field and a number of studies were able to demonstrate a relationship between a particular physiological action and the presence of some functional group within the molecule. To cite several examples, structure-activity studies were carried out on tropeines at the Wellcome Chemical Research Laboratories in London, on organic halogen compounds at St. Andrew's University in Scotland, and on amino alcohols at the Pasteur Institute in Paris.[15]

The chemical viewpoint found its clearest expression in the receptor theory of drug action, developed independently by John Newport Langley in England and Paul Ehrlich in Germany around the turn of the twentieth century.[16] Langley, a physiologist, had come to his theory largely as a result of the study of the antagonistic action of drugs. As early as 1878, in attempting to explain the antagonism between atropine and pilocarpine in their action on the submaxillary gland, he postulated that "there is a substance or substances in the nerve endings or gland cells with which both atropine and pilocarpine are capable of forming compounds." The combination depended upon the relative mass of the two drugs and their chemical affinity for the cell substance involved.[17]

Although this statement contains the germ of the receptor theory, it was not until the first decade of the twentieth century that Langley elaborated on these views. Once again it was a case of antagonism between drugs that prompted him to suggest the idea of a receptive substance in the cells with which the drugs combined. Langley noted that curare antagonizes the ability of nicotine to cause contraction of the muscle. A sufficient dose of curare could completely annul the contraction produced by a small dose of nicotine; further injection of nicotine once again resulted in contraction. Langley concluded that the two drugs must act on the same protoplasmic substance or substances in the muscle cells, and presumably this process involved a combination of the alkaloid with what Langley termed the "receptive substance" of the protoplasm. The two drugs competed with one another for this substance, thus explaining their antagonistic action.[18] As result of further studies, Langley concluded that many drugs and poisons act by combining with specific constituents of the cell. He generalized:

> "I conclude that in all cells two constituents at least must be distinguished, (1) substances concerned with carrying out the chief functions of the cells, such as contraction, secretion, the formation of special metabolic products and (2) receptive substances especially liable to change and capable of setting the chief substances in motion. Further, that nicotine, curare, atropine, pilocarpine, strychnine, and most other alkaloids, as well as the effective material of internal secretions produce their effects by combining with the receptive substance..."[19]

By this time, Paul Ehrlich, the founder of modern chemotherapy, had developed his own receptor theory to explain immunological phenomena such as the neutralization of microbial toxins by antitoxins produced in the body. In the late nineteenth century, Ehrlich adopted the

then common view that protoplasm can be envisioned as a giant molecule consisting of a nucleus of special structure which is responsible for the specific functions of a particular cell (e.g., a liver cell or a kidney cell), with attached chemical side chains. These side chains are more involved in the vital processes common to all cells, such as oxidation and nutrition.

In the 1890s, he applied this concept to immunology. In his view, one of the "receptive side chains" of the cell possesses an atom group with a specific combining property for a particular toxin, such as tetanus toxin. This side chain is normally involved in some ordinary physiological process, such as nutrition, and it is merely coincidental that it has the ability to combine chemically with the toxin. Combination with the toxin, however, renders the side chain incapable of performing its normal physiological function. The cell then produces more of the side chains to make up for the deficiency, but it overcompensates so that excess side chains are produced, break away from the cell and are released into the bloodstream. These excess side chains in the bloodstream are what we call antitoxins or antibodies. They neutralize the toxin in the blood when combining with it, thus preventing it from anchoring to the cell and exerting its poisonous effect.[20]

Langley recognized that his theory of receptive substances was similar to Ehrlich's side chain theory of immunity. He even speculated that his receptive substances need not be distinct compounds, but could be side chains on the protoplasmic molecule.[21] Interestingly enough, for reasons that will be discussed later in the paper, Ehrlich himself did not immediately extend his receptor theory from immunological agents such as antitoxins to simpler chemical drugs. When he did finally do so, Langley's work was one of the motivating factors.

Meanwhile, however, not all drug researchers were convinced that most drugs exerted

their action by forming chemical bonds with constituents of the cell, or that the investigation of structure-activity relationships, largely driven by the field of structural organic chemistry, would lead to great advances in therapeutics. The rise of physical chemistry as a distinct discipline at the end of the nineteenth century provided an alternative model for pharmacologists and others engaged in the study of drug action. These scientists devoted their attention to the influence of physicochemical properties, such as solubility and surface tension, on the physiological activity of drugs and poisons. Although it was recognized by many that one could not always distinguish clearly between physical and chemical factors in drug action, there was a tendency to emphasize either one or the other approach, leading to the chemical and the physical camps.[22]

The key issue in the dispute was whether or not drugs formed chemical bonds with cell constituents, the receptive substances or side chains proposed by Langley and Ehrlich. Supporters of the physical view contended that in most cases drugs acted not by combining chemically with cell constituents, but by altering the surface tension, electrolytic balance, osmotic pressure, or other physicochemical properties of the cell. They tended to criticize the structure-activity approach to pharmacology. This challenge was clearly stated by the Scottish-born pharmacologist Arthur Cushny in the 1903 article cited at the beginning of this paper. Cushny analyzed the meaning and value of structural formulas, "...which adorn so many pharmacological treatises but which I fear fail to enlighten as many readers as they repel." The formula, he stated, indicates such things as the origin of the molecule and what compounds it is likely to react with, but it gives no information about the physical properties of the substance. Yet in Cushny's view, these properties (such as volatility and solubility) played a crucial role in determining the action of drugs. One could not therefore expect to predict the physiological

effects of a drug accurately from a knowledge of its chemical structure.[23]

Critics of the structural chemistry approach pointed out that sometimes compounds of very different structure exhibited similar pharmacological activity. A favorite example was the group of drugs known as general anesthetics, substances that produce narcosis. This pharmacological group includes compounds of widely different structures, such as ether, chloroform, pentane and urethane. This situation was difficult to explain in terms of structure-activity relationships or on the basis of the receptor theory. One could not associate any particular group of atoms in these molecules with the anesthetic activity, and it was not clear how these compounds of rather varied chemical constitution could all combine with the receptive substance responsible for narcosis. This latter point was further emphasized by the fact that the general anesthetics were relatively inert chemically. Moreover, it was shown that the depressant activity of these narcotic agents was directly proportional to their partition coefficients between lipids and water. In other words, lipid solubility, a physical property only indirectly related to chemical structure, played a key role in the action of these compounds.[24]

There were other examples of compounds of widely different structure that exhibited similar pharmacological action, or the reverse, i.e., chemically similar compounds which differed markedly in their pharmacological action. Of these substances, pharmacologist-biochemist Carl Alsberg said: "...we may be sure that their action depends upon their physical rather than their chemical properties."[25]

The most extreme example of compounds with very similar structures that had widely different pharmacological action involved optical isomers, whose structures are mirror images. Today these compounds are used to support the receptor theory and the importance of chemical

structure for pharmacological action, because it is believed that they demonstrate that the shape of a drug molecule must be such that it fits a structure complementary to it on the surface of the receptor. One scientist in the 1960s, for example, wrote:

> "To explain some of the types of structural specificity just referred to is difficult unless we infer that there are 'drug receptors' which bear much the same relationship to certain drugs as do locks to the corresponding keys. Some of the best evidence for the existence of drug receptors has been obtained by comparing the effects of stereoisomers...Since optical isomers have identical properties except insofar as their molecules are mirror images, we are led to suppose that the shape of the drug molecule is important in these cases because part of the drug must fit a structure complementary to it."[26]

Yet the scientist who first provided convincing proof that optical isomers can have very different properties did not explain this phenomenon in terms of the receptor theory. That scientist was the afore-mentioned Arthur Cushny. In 1903, he argued that this difference in action between optical isomers illustrated the relative independence of pharmacological action and chemical structure, "...for nothing can be more nearly related chemically than the two hyoscyamines, yet some of the most characteristic features in the action of one are almost entirely wanted in the other." Since optical isomers have identical physical properties, however, Cushny had to admit that some chemical combination in the cell was probably involved in this phenomenon. But he did not envision this reaction as involving one isomer structurally fitting a receptor surface better than another. Instead, he postulated that the two optical isomers combined with some chemical in the cell to produce compounds that were no longer mirror images, but were now diastereoisomers. These diastereoisomers would have different physical

properties, and Cushny attributed their different pharmacological activities to this fact.[27]

Biochemist-pharmacologist Carl Voegtlin of the Public Health Service's Hygienic Laboratory, the forerunner of the National Institutes of Health, agreed with Cushny that the chemical structure of a drug was important only insofar as it determined the physical properties of a drug. These physical properties in turn determined the retention, distribution, etc. of a drug in the organism, and hence its physiological effects.[28]

Other supporters of the physical theory of drug action included the British physiologist William Bayliss, the German pharmacologist Walther Straub, and the German physical chemist Isidor Traube.[29] Even Paul Ehrlich, whose receptor theory of immunology was discussed earlier in this paper, was hesitant at first to extend this theory to drugs. Ehrlich did not think it likely that drugs acted by forming a firm combination with the cell, as bacterial toxins did. He pointed out that the action of many drugs is of a transitory nature, and that they can often easily be extracted from tissues by solvents, thus they could not be firmly bound to the protoplasm of the cell. Instead, he thought that drugs were fixed in cells by forming solid solutions involving the lipoid portion of the cell or by combining with certain "non-living" constituents of the cell (and not the protoplasm itself) to form "feeble salt-like formations" (similar to the insoluble, salt-line compounds called "lakes" formed by dyes). Langley's work and Ehrlich's own studies on drug resistance finally convinced Ehrlich that drugs did indeed combine chemically with protoplasm. He then extended his side-chain or receptor theory to cover drugs as well as immunological agents[30]

This controversy over a chemical versus a physical (or physicochemical) approach drug action was part of a wider disagreement in the early twentieth century over the relative value of

these two viewpoints. As other historians such as Joseph Fruton, Robert Kohler, and Pauline Mazumdar have shown, a similar debate was taking place in immunology and biochemistry in efforts to explain the actions of antibodies, enzymes, and other biological molecules[31]

The controversy did not result in a resolution in favor of one or the other side, but instead came to lose its meaning and relevance. In a sense, both sides were right, since both the physicochemical properties of molecules and their ability to form chemical combinations play a role in drug action. The borderline between "physical and chemical" has also become blurred as our understanding of molecular interactions has progressed. In a period where relatively little was known about the biochemistry of the cell, and when an understanding of the nature of chemical bonding was just beginning to emerge, it is not difficult to see why a distinction developed between physical and chemical factors which may seem to us to be rigid and artificial. To scientists at the beginning of the twentieth century, a chemical bond implied a firm union, either what we would call a covalent or ionic bond, and the concepts of hydrogen bonds and Van der Waals forces had not yet been developed.

This debate helped to sharpen the focus of questions relating to the mechanism of drug action. Proponents of both views were forced to reexamine their thinking and clarify their views as they responded to critics. Reasonable parties on both sides of the controversy eventually had to admit that both physical and chemical properties were involved in drug action, and that it was not always easy to distinguish between them. It was also generally recognized that pharmacological activity was at least ultimately related to molecular structure, for few would deny that structure determined physical as well as chemical properties.

In 1920, the British physiologist-pharmacologist Henry Dale argued that "we must

recognize the improbability that the whole of the widely different types of activity of chemical substances will ever be brought under one principal of interpretation." Whether physical or chemical properties are more important may vary with the substance. Dale also recognized cases where a particular chemical structure not tied specifically to a physical property governs the reaction with the cell, and yet the reaction cannot be regarded as involving a firm chemical combination. Rather, it must involve "some looser type of additive molecular combination." Here, he added, we are "in the borderland between chemical and physical union, the exploration of which holds out such promise for the illumination of biological conceptions."[32]

The exploration of this "borderland" did indeed lead to significant advances in biomedical science. In the paper cited above, Dale was concerned that the attempts by scientists to force all kinds of pharmacological action under one scheme of explanation retarded progress towards a rational conception of drug action. On the other hand, as I have argued, the debate over these questions helped to pave the way for a broader view of drug action, which essentially absorbed both positions and made the controversy no longer meaningful. Today both physical chemistry and structural organic chemistry are utilized in the effort to explain the mechanism of drug action.

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John Parascandola received his Ph.D. in History of Science at the University of Wisconsin-Madison under Aaron J. Ihde in 1968. After a postdoctoral year at Harvard University, he joined the Wisconsin faculty to teach history of pharmacy and history of science in 1969. In 1983, he became Chief of the History of Medicine Division of the National Library of Medicine. He assumed his present position as Public Health Service Historian in 1992.

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