Special Report

Reflections on the First Gordon Research Conference on Molecular Pharmacology

A new series of Gordon Research Conferences, on the subject of "Molecular Pharmacology," was initiated in the summer of 1969. The first conference was held during the week of June 16–22, 1969, at Tilton School in Tilton, New Hampshire. The purpose of these conferences is to consider in a coherent manner that group of major unsolved questions of contemporary biology which may be summarized under the heading: "How do small molecules do great things?"

Answers to this question can be said to constitute the substance of modern pharmacology. The term pharmacology succinctly describes interest and concern with question of this type and was therefore adopted, even though the organizing committee recognized that the majority of contributors to this field may have no direct affiliation with the academic discipline of pharmacology. Pharmacology is thus defined here neither in terms of a particular methodology, nor in terms of existing academic tradition, but simply as a body of knowledge required to reconstruct the sequence of events which intervene between exposure of a biological system to a chemical agent, and its ultimate physiological consequences. It is a science in the same sense as genetics is a science—defined by the object of study, rather than by a particular technical skill.

A concerted attack on the group of problems implied in the above question requires the methology, expertise, and ingenuity of several conventional disciplines. In the existing framework the problems are therefore approached in many diverse manners, and the investigators working on different aspects have relatively little opportunity for formal discourse and exchange of ideas. Quite often they remain insufficiently aware of complementary approaches and find themselves unable to carry their work beyond the limits of their own technical competence into a realm that might produce definitive answers to the integrated question. Interdisciplinary thinking and work are essential to solve these kinds of problems, and interdisciplinary meetings are needed to provide a starting point.

The crucial importance of the question itself to several fields of endeavor—such as mechanisms of genetic regulation, regulation of enzyme function and antibody response, triggering of membrane transport, of muscular contraction or nerve transmission, molecular mechanisms of drug action and drug design—is sufficiently self-evident to require little justification. The point which does need emphasis is that in all of these areas the problems are (from the vantage point of physical science) in essence similar, and therefore should be tackled on a common ground. In all cases, the primary event is a combination of a small molecule with a macromolecular receptor. The ensuing chain of events, whose outcome is observable as one physiological response or another, may be considered in terms of answers to five additional questions which further elucidate this problem:

(1) What is the chemical identity of the structure with which the small molecule interacts (the receptor)?
(2) What is the structure of the complex between the small molecule and the receptor, i.e., which parts of each are directly involved in the binding?

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(3) What is the process triggered by the formation of this complex?
(4) How can the binding and the triggered process be accounted for by known physical forces?
(5) What is the mechanism for transmitting the changes triggered in the receptor to other structural components of the cell through which they become observable as a physiological response?

The first question related to primary receptors is in essence a problem in chemical isolation and identification. It has been answered with some degree of success in only a few instances. Three major examples were discussed at the conference: the isolation and characterization of the *lac* repressor by W. Gilbert; the isolation of the estrogen binding protein by E. V. Jensen; and the partial purification of the Na^+-K^+-dependent ATPase by L. Hokin.

The second question concerning the characterization of the complex is a structural problem and can only be answered by modern physical methods, such as X-ray crystallography and high resolution nuclear magnetic resonance. Prototype answers to this question were discussed for antibodies by H. Eisen, E. Haber, F. F. Richards, and Carolyn Converse; for the enzyme lysozyme by D. C. Phillips and A. C. T. North; for ribonuclease by F. M. Richards, Donella H. Meadows, and G. C. K. Roberts; for staphylococcal nuclease by C. B. Anfinsen, J. L. Markley, E. E. Hazen, Jr., and F. A. Cotton; for papain by Arieh Berger and Jan Drenth; for carbonic anhydrase by K. K. Kannan; and for nucleic acids by W. Fuller, M. Waring, E. Reich, D. Crothers and S. I. Chan.

Our knowledge on the third question pertaining to the processes triggered by these types of complexes is indeed very limited. In certain cases, such as enzyme inhibition, the answer is simple inactivation by physical hindrance. However, in other important areas, such as enzyme regulation, derepression of a gene, or initiation of a nerve impulse, it is likely that the mechanism consists of far-reaching structural changes in the receptor. The techniques for studying this question—magnetic resonance and some other branches of spectroscopy—are available. Examples of a detailed definition of multiple conformational changes were provided by the NMR studies of J. Markley on staphylococcal nuclease. Their general significance in pharmacology was discussed by J. P. Changeux.

It is not surprising that a serious theoretical effort to answer the fourth question on the definition of the physical forces involved in these interactions is just beginning, particularly since the structures of the complexes to which the calculations have to be applied have only recently been determined. No results were presented at this meeting, but the relevant theory was reviewed by S. I. Chan for quantum mechanics and by G. Nemethy for thermodynamics.

The concepts and methods needed to answer the fifth question in molecular detail (translation of the interaction into physiological response) are to a large extent the same as those required to deal with the first four. At this stage of our knowledge this question can only be dealt with in gross morphological and biochemical terms. F. Reithel, G. A. Robison, E. G. Krebs, and T. Mansour discussed different aspects of possible transmission and control mechanisms, and A. S. V. Burgen gave a final summary of the problems and experimental approaches offering promise for further progress.

At present there exists no system for which all of these questions have been fully and adequately answered, so that we cannot claim to understand in detail the molecular mechanism of action of any single small molecule. However, the prototype answers which have been obtained for each question, albeit on different systems, do provide a framework onto which such understanding can be built. Some receptors have been isolated; X-ray structures of several proteins are available; some insight into the geometry of enzyme-inhibitor binding has been gained; some appreciation of the relative role of hydrogen bonding and van der Waals interactions in determining specifi-

city has emerged; conformational changes have been described. The time is rapidly approaching to exert a concerted effort involving the necessary variety of techniques on a single system, so that the sequence of events involved in the biological action of a small molecule may be elucidated from beginning to end. The first Gordon Conference on Molecular Pharmacology provided a forum for defining and focusing upon these crucial biological problems.

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