MOLECULAR PHARMACOLOGY, 7, 567–568

"Small Molecules and Great Things"

The Second Gordon Research Conference on Molecular Pharmacology

The second of a biennial series of Gordon Research Conferences on Molecular Pharmacology was held during the week of July 5–9, 1971 at Proctor Academy, Andover, New Hampshire. This conference, organized by A. S. V. Burgen, brought together investigators with diverse backgrounds and expertise in a concerted attack on the basic problem of how small molecules produce profound effects in living organisms. The basic questions of molecular pharmacology were succinctly stated by O. Jardetzky in his report of the initial Gordon Conference on Molecular Pharmacology held two years ago [see *Mol. Pharmacol. 5*, 546 (1969)]: What is the molecular conformation of a drug; what is the structure and identity of its receptor; what conformational changes occur in the drug and/or receptor resulting from their interaction; what are the binding forces involved in such interactions; and finally, how does such an interaction lead to the sequence of biophysical, biochemical and physiological events of increasing complexity, resulting ultimately in the overt response of the intact organism? No existing discipline, or small group of investigators could answer all these questions even for a single drug. Indeed, the conference was notable for the agglomeration of chemists, biophysicists, biochemists, physiologists, and theoretical mathematicians working on such diverse problems as X-ray crystallography of acetylcholine congeners, and a mathematical analysis of drug effects on the cellular slime mold.

The diversity of approaches to a single problem, such as the conformation of a drug, was indicated by the first session in which the conformation of acetylcholine was studied by X-ray crystallography (P. Pauling), NMR spectroscopy (J. Feeney), theoretical calculations using extended Huckel theory (L. B. Kier), and chemical synthesis of analogues (W. Beers). Nuclear magnetic resonance spectroscopy was used to study the conformation of angiotensin (P. Fromageot), gramicidin S (W. A. Gibbons), and vasopressin and oxytocin (G. C. K. Roberts). An elegant use of X-ray crystallography allowed H. M. Sobell to elucidate the mechanism of actinomycin D interaction with DNA.

The search for specific drug receptors is the central theme of molecular pharmacology. The acetylcholine receptor was the focus of one session in which A. Karlin, J. P. Changeux, and L. T. Potter reviewed the current status of their studies on chemical characterization and isolation of this important and prototypic receptor. H. P. Rang provided a definition of the receptor in the functioning tissue. The search for specific drug receptors and some of the problems involved were the subject of a series of reports by F. R. Dastoli on taste-receptive proteins, by L. Aronow on glucocorticoid binding protein in mouse fibroblast cells in continuous culture, and by A. Goldstein on narcotic binding proteins in mouse brain.

Detailed information on the binding of drugs to receptors and potential and actual conformational changes produced by such interactions was the subject of another session. Background information was provided by the report of J. C. Metcalfe on an analysis of molecular constraints of lipids in model membranes. A. Rich discussed interactions of barbiturates with nucleic acids, and R. Matthews reported on the interaction of *lac*-repressor protein with inducer as studied by NMR techniques. O. Jardetzky described studies on the pH-dependent unfolding of staphylococcal nuclease as studied by NMR spectroscopy. These studies continue to provide the groundwork of concepts and techniques required to understand drug-induced conformational changes in receptors.

Tracing the sequence of events from the drug–receptor interaction to an eventual under-

standing of the physiological response requires detailed knowledge of the multitude of biochemical and metabolic properties of cells. Two sessions dealt with control of cell processes. D. Nebert discussed the regulation of mixed function oxygenases as studied in cell cultures, and R. Schimke discussed steroid hormone regulation of specific protein synthesis in chick oviduct. The regulation of putrescine synthesis was discussed by S. Snyder. Control of protein (enzyme) degradation was the subject of presentations by A. Grossman (tyrosine transaminase), J. Bertino (folate reductase), and A. Goldberg (proteins in *E. coli*). The role of cyclic AMP was the subject of a number of reports, including its role in muscle contraction (S. E. Mayer, G. I. Drummond), neuronal control (B. Breckenridge and F. Bloom), and the organization of slime molds (A. Robertson).

It is obvious that a satisfactory definition of action of any drug in terms of the questions posed by molecular pharmacology is not at hand. This Gordon Conference was perhaps most notable for the concerted approach to the mechanism of action of acetylcholine by X-ray crystallographers, biophysicists, biochemists, mathematical theoreticians, and physiologists, each providing necessary expertise and information. This case is also instructive of the difficulties of the task posed for molecular pharmacologists, since there is so little information available about the fundamental properties of receptors, including membrane lipid and protein interactions, and the properties of sodium and potassium flux through membranes. This Conference differed from the initial Gordon Conference in its inclusion of more sessions dealing with biochemical and physiological consequences of drug–receptor interactions. This is perhaps a recognition of the fact that in many cases the definition of a receptor requires demonstration of its consequent effect on biophysical and biochemical properties of the cell.

The "great things" alluded to in the title of this report refers to the potential advance of understanding of biological phenomena that can come from the interdisciplinary approach to molecular pharmacology represented by the second Gordon Conference on Molecular Pharmacology. At the rapid rate at which technology for the isolation of receptors and the study of drug–receptor interactions has developed in the last two years, we can look forward to an even more stimulating conference in the summer of 1973.

ROBERT T. SCHIMKE, *Vice-Chairman, Gordon Conference on Molecular Pharmacology, 1971*