INTRODUCTION

THE purpose of this volume is to display the methods and tools of cell pharmocology. The study of drug mechanisms begins (traditionally and reasonably) at the level of the whole organism, then proceeds. (hopefully), by successive steps to an understanding of mechanisms at organ level, cellular level, intracellular level and ultimately molecular level.

Cell pharmacology, like cell physiology, encounters problems and raises questions which differ from those familiar in the study of drugs in the whole animal. We become interested in possible selective actions on certain cells of a complex organ such as kidney or brain, and in explanations for such selectivity. We become interested in sites of action on particular structures within those sensitive cells — sites perhaps in cell mebranes, or mitochondria or nuclei — or sites in structures not yet characterized. All this requires different tools from those of whole animal pharmacology.

As is true of pharmacology in general, cell pharmacology needs and receives support from investigators in other fields. Histochemists, cytologists, cell physiologists, electrophysiologists have all struggled with the kinds of problems that concern us here. We are fortunate in having papers from representatives of all these allied disciplines. We anticipate that, as in the past, pharmacologists will, by way of return, make important contributions to all of these allied fields.

Upon examination of the presentations as a whole, two general attributes stand out. The first is ingenuity. The problems that face the pharmacologist, when he asks how a drug may affect an individual cell, bring out all his experimental cleverness. The second attribute is variety. The approaches to the difficult questions are exceedingly varied. This is a comparatively young field. If there is so much variety already in tools and methods, we may anticipate even greater variety in the future. There are many roads to Mecca.

The book opens with five papers illustrating the usefulness of light microscopy for cell pharmacology. Koelle begins with a general discussion of the several varieties of histochemistry as they each might be applied to pharmacological problems, and then goes on to describe some of the solid achievements of his group in the study of the cholinesterases with histochemical methods. Barnhart and Anderson give an example of the use of a histochemical tool of great promise for pharmacology.

They prepared a fluorescent antibody against prothrombin, which they used first to demonstrate which liver cells contain prothrombin, and then to visualize the decrease in prothrombin in those cells after dicumarol treatment. Ullberg gives a very provocative discussion and a review of the applications of radioautography particularly for drug distribution studies. He points out that with techniques he and his associates have developed it is possible to obtain an overall picture of drug distribution in the entire body, after which the more intimate details of distribution within tissues or cells may be determined when necessary. The next paper, by Maren, carries the implication that tagged carbonic anhydrase inhibitors might be used (for example, by radioautography) to determine the localization of carbonic anhydrase within cells.

The papers by De Robertis and by Whittaker make it clear that electronmicroscopy is a tool of necessity for the cell pharmacologist. They also illustrate the power of the combined use of several tools. De Robertis started with the electronmicroscope and then proceeded to isolate and characterize what he had seen, using centrifuge and chemical analysis. Whittaker started with centrifuge and analytical tools and then used the electron microscope to identify what he had isolated and analysed. It is gratifying that the two workers end up very near one another. De Robertis gives many illustrations of the way the electronmicroscope can be of service to the pharmacologist.

One way to begin the study of drug effects at the subcellular level is to separate, as completely as possible, macro quantities of the various kinds of intracellular organelles. The most successful separations at present are based on the differential centrifugation of broken cells using procedures that derive from the pioneer work of Claude and of Hogeboom and Schneider. The papers presented here on this subject fall into two groups. The paper of Von Euler and Lishajko and that of Burach *et al.* are concerned with the isolation of organelles containing pharmacologically active material (norepinephrine and epinephrine). The same is true in part of the papers of De Robertis and Whittaker who seek to isolate organelles containing acetylcholine, serotinin etc. Giarman shows how the treatment of the intact animal with a variety of drugs can markedly change the proportions of free and particulate-bound serotinin. On the other hand another group of papers is concerned with *in vitro* affects of drugs or toxic materials on the organelles themselves. De Duve explores the effects of a wide variety of fat-soluble compounds on liver lysosomes. He raises the question whether a number of toxic agents may not exert their action through damage to lysosomes with release of lytic enzymes and consequent cytological damage. The next three papers are concerned with several aspects of interactions between drugs and mitochondria.

The paper of Giacobini and the four which follow his are concerned with possibilities for direct microchemical analysis as a means for avoiding the difficulties that arise in studying pharmacological effects in a complicated organ. Giacobini has refined the Cartesian diver, as an analytical tool, to the point where he can analyse a single nucleolus for cholinesterase. (There isn't any.) Among the solid achievements of his work may be mentioned the finding that carbonic anhydrase in the central nervous system is probably limited to the glia. Cook and Pickering not only describe the isolation of individual glomeruli from the kidney, but tell how to cut each one in half so that the vascular and distal poles may be analysed separately (for renin). Ullrich's paper can be profitably studied for the variety of ingenious means he has devised for measuring renal function in single tubules. For example he has found ways to make quantitative measurements of the rates of water and solute uptake from a short segment of a single tubule.

The next group of papers are electrophysiological in nature. Curtis describes the methodology for making observations of the electrical behavior of an individual neuron after application of drugs in the immediate vicinity of that neuron. He also discusses the difficulties and promise of studies made in this way. It is possible with multichannel electrodes to apply 3 or 4 different chemical agents simultaneously at the same site. Shapovalov has a comparable paper dealing with the myoneural junction, and presents some very interesting results obtained when he applied a variety of drugs in and around the junction. He describes electrodes with as many as six different channels and tip diameters of less than 1 μ.

The last three papers describe experiments with a test object that would seem to deserve a great deal of attention from cell pharmacologists. This is the cell grown *in vitro*. Aranow and Gabourel, for example, present a study of growth inhibitors employed against lymphoma cells in tissue culture. The paper illustrates how it is possible to quantitate results much more exactly than *in vivo*, and how the time course for the development of resistance can be precisely determined. Best of all the mechanism of inhibition can be examined by chemical studies of the inhibited cells themselves sampled at various times after application of the drug.

Two important areas of cell pharmacology have been deliberately omitted because each constitutes a separate field in its own right. The first concerns the effects of drugs on cell membrane function. (Another volume in this series is devoted to this subject.) The second has to do with the study of drug receptors.

The papers in this volume have all been taken from the program of the First International Pharmacological Meeting held in Stockholm, 22–25 August, 1961.

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