

Chemobiodynamics and Drug Design

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CHEMOBIODYNAMICS AND DRUG DESIGN

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PREFACE

This book has been written for all students, teachers, and investigators who have found delight in the serious contemplation of the intellectual puzzles, promises, powers, and profits which are the evidence of man's control of his internal and external life environment through those agencies known as drugs. This gamut of interest necessarily includes pharmaceutical chemists, pharmacologists, pharmacists, and physicians, whose daily tasks bear upon the design, formulation, or use of drugs. Even more, it includes those who have contributed to the foundation knowledge of the nature of life's most intimate processes in the sciences of biochemistry, physiology, experimental pathology, cytochemistry, psychology, and biophysics, and in so doing have frequently found drugs to be expedient tools in their research.

Part I is entitled Chemobiodynamics. This is a coined name and is, therefore, of no consequence except in so far as it represents the author's attempt to contain within a single heading as full an account of the implications of the organization of his subject matter in an unambiguous a way as possible. Chemobiodynamics represents the concept of chemical control as it manifests itself in an orderly way through action on the molecular level of the fabric of living things upward and onward, level by level, through the hierarchy of organized processes that are the warp and woof of chemical, cellular, organismal, and interorganismal being. The emphasis in subject development in Part I is, therefore, upon the structural and functional relationship of chemistry to biology and its antecedents.

In so far as chemistry holds out enormous practical as well as theoretic involvement in matters not only biological but psychological and sociological as well, the philosophic foundations of science and its implication for the individual as well as for people at large are crucial. Therefore, a brief notion of the epistemologic basis of science is necessarily an introductory phase of this book. This seemed especially important since some students tend to forget that the mode of functioning of their own minds is at least as important as the test tubes in their hands during scientific investigation.

Part II entitled Drug Design represents the practical and creative open road that is a corollary of the idealistic and heuristic alter face

of chemobiodynamics. In this part, the objective is not so much passive learning and appreciation but rather active positive thought and things to be done. Yet it is as impossible to separate the contemplation and appreciation of the investigator from the thing investigated as it is to disentangle the artist from the love he holds for the things he paints. There is, therefore, no really fundamental *Schnitt* between Part I and Part II, and some may find it entertaining to start anywhere and work toward the end only to find that the final chapter of Part II serves as an introduction to Part I.

While, as indicated above, this book is aimed in a general way toward a very broad group, it is also designed for certain purposes. In particular, it has been the objective of the author to provide a volume which may serve as a textbook for students interested in the relationship between chemical constitution and pharmacologic activity, which today represents one of the most rapidly expanding fields of interest especially for pharmacologists, pharmaceutical chemists, and many organic chemists. As a text it is felt that the division of the book into two parts may serve appropriately the needs of graduate teaching in general pharmacology on the one hand and graduate teaching in pharmaceutical chemistry on the other. Thus Part I may be of greatest interest to those concerned with the nature of drug-initiated responses, while Part II emphasizes the nature of drug design as an activity preceding drug synthesis.

Finally, this book may serve in a supplementary way the needs of teachers in courses on medical, dental, or veterinary pharmacology who for particular students desire a reference or textbook concerning the fundamental nature of drug action not dealt with in conventional books oriented primarily toward therapeutics.

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Part One
Chemobiodynamics

INTRODUCTION AND PERSPECTIVES

I-1. Chemists and Physicians

It has become increasingly apparent to chemists and practicing physicians alike that, as the respective originators and final judges of new drugs, they are partners. Indeed, they have always been "partner-linked," but, unfortunately, "not always loving." Unfortunately for all of mankind, because the development of new therapeutic agents depends so much upon the existence of mutual understanding, communication, and cooperation between these two largest of scientific bodies in our time. It is, therefore, one general aim of the present volume to further this needed spirit of rapport by bringing into relief certain considerations that link the activities of chemists and physicians, these considerations being essential to a proper perspective for successful drug design.

It is not surprising that communication, much less understanding, between chemists and physicians should be difficult. The link which binds them is so enormous that it creates a problem in communication no less than that facing two friends who attempt to carry on a conversation across 42d Street at Times Square during a parade. Chemists and physicians must reach understanding through that colossal network of scientific activity which is the work of all other scientists who are building our knowledge of the processes and mechanisms that range from the nature of molecules to the nature of man as a complex organism. Since the design of a new drug for special therapeutic effects must be based on an appreciation of the interlocking sciences linking chemistry with medicine, it provides an excellent example of a field of inquiry in which the chemist and the physician can appreciate in detail the nature of their partnership. An appreciation of this relationship based on a multitude of scientific areas is the rational basis of drug design.

(In all that follows it must be understood that drug synthesis per se is a matter of purely chemical concern. It is the approach to the design of a drug *before* its synthesis that delimits this work.)

I-2. What Is a Design

To design something, anything, seems to be one of the main delights of mankind. Many creatures make things and in so doing carry out intri-

ate tasks which have yet to be recorded, much less understood. Yet man's fellow man is the only one with whom he may discuss what he *might* make—his designs.

There are many who are sufficiently satisfied with the development of designs per se so that they experience no desire toward their materialization. Perhaps it is as well, however, for what a chaos would exist if all designs were in reality possible.

If all the world were apple pie
And all the sea were ink,
What would we have to drink?

Certainly it is fortunate that nature limits to a degree man's ability to materialize all his designs while still permitting him the joys of poetic license. All this is to say that a design, in a general sense, may be thought of in two ways. The first connotation is of a thing *which is*—and all that remains for the individual is to appreciate the network of relationships embodied in it—the *deductive approach to design*. The second connotation is that of something which *might be*—and the individual so designing actively contributes to the network of relationships which is the design—the *inductive approach to design*. Clearly there is no obvious point of separation between these two connotations in practice, for everything of which one is aware presents itself as a tangle of relationships, in part objective in origin and in part subjective, as when a child sees his friend's face in the clouds.

A primary method by which modern man tries to sort out the maze of perceptions, conceptions, and preconceptions which is his total experience is the scientific method, and this itself is a design. That is to say, science has become his most fruitful method of understanding his world as a *rational* pattern of events. Since a rational approach to drug design must find its way by application of the scientific method, it is essential that the nature of the scientific method as understood by the author be clear.

I-3. Science

"By their fruits you shall know them." Application of this rule has unfortunately led to much misconception about the nature of scientists and especially about the nature of science. Unfortunately, because science is certainly not the sum total of ingenious devices or technical achievements ranging from the primitive lever through the chlorophyll deodorizer to the hydrogen bomb. Neither is it a collection of chemical or electrical apparatus or such objects of scientific study as atoms, molecules, cells, or brains, nor does it consist of the scientific writings that fill our great libraries. All these are, to be sure, the objects, products, or tools of scientific activity, and though, even among scientists, they are

all too often confused with science itself, they most assuredly are not science. Science is most characteristically a *method of thought*.

To confuse science with its tools and products is much like confusing a church, in the religious sense of the word, with a building and an assortment of prayer books. Like the concept of a church, science is an aspect of the mind and of the spirit, characterized by certain intellectual approaches to the understanding of our world. The great Danish physicist Niels Bohr defined science "as a method for placing limiting values on our preconceptions." That is, science is, in effect, a method for choosing which designs, among the many conceivable representations or interpretations of our experience, are the rational ones.

The objects of science, like those of art, are many and varied. The analogy here is quite close, for it is exactly due to a similar type of error in thinking that art is often confused with its products—sheets of music, paintings, sculptures, or a particular subject matter. Nor are the feelings and state of mind in the act of producing or appreciating objects of art so far removed from those that accompany invention and understanding in science. Certainly, it is in this freedom from their products that science and art are recognized as universal and limitless expressions of the minds of men!

I-4. The Scientific Method

What, then, is that mode of thought which characterizes science? The steps which characterize the scientific approach are easy to enumerate. They are

1. The gathering together of all manner of information available concerning a given problem.
2. The sorting or classification of the available information so that it makes sense to the person doing the sorting (or according to such schemes as have already been found to be useful in arranging information in that particular field of inquiry).
3. The formulation of a guess or (what may sound more dignified) a working hypothesis concerning some underlying principle that appears to express in a general way the relationships of the controlling factors.
4. From this point on, further observations are made either through setting up experiments, that is, a planned set of conditions, or, when this is not possible,¹ simply further observations to discover the necessary conditions.

¹ It is clear that, whereas a chemist may combine his materials in a prescribed way and thereby state that he has performed an experiment, such controlled types of observation are not possible in many scientific fields. Thus, geologists and paleontologists cannot return to the past to arrange their respective objects of interest for observation in the present, nor can the astronomer manipulate the heavenly bodies to

5. The last formal step, which never comes to an end, is comparing the observations, modifying the original working hypothesis in the light of the new observations, followed by more observations and further modification of the hypothesis, and so on.

By dint of much labor, the developing hypothesis may eventually become so effective in the prediction or correlation of observations that it is dignified by the term *theory* or, after many years of "success," nearly deified as a scientific "law." It is, however, still but a hypothesis (or guess) in long pants. Though transition from hypothesis to theory is gradual, as is the transition from boy to man, this change is always significant. Both represent transitions toward greater rationality.

Although satisfactory as a general guide to the formal steps of the scientific method, the above outline is little more than a crude map. A person memorizing these steps is no more acquainted with the process of scientific creation than the person who has learned that a musical composition is made up of notes played in a given rhythm and combined through certain rules of harmony and melodic line. Such formal knowledge, however important, is but the skeleton of science, and to see the skeleton and no more is to be satisfied with dry bones rather than living flesh.

A piano with its keyboard, a box of paints, a laboratory filled with instruments and chemicals—each represents the opportunity for combinations. Baboons may sit at the piano or dabble with paints, and (if one is a distance away) might be allowed free run in a chemical laboratory. One presumes, however, that the baboons would scarcely recognize any particular combination as more meaningful than any other, should they chance on striking a tune, form an interesting landscape, or crystallize by chance a wholly new chemical compound. Which would be the wiser unless it blew up in its face?¹ Certainly an important aspect of such activities is some capacity to recognize in large and small things alike, that which is meaningful or beautiful—in a word, *a design*. Indeed, is not the richness of personality largely an expression of the breadth and depth of one's capacity for seeing meaningful relationships among all manner of things and situations with which one comes into contact?

I-5. Science and Language

Everyone (scientists included, unless they are specialists in the given field) is out of his depth when reading original scientific papers because of

"see what will happen." We are also convinced that it is undesirable that people be shuttled about in an experimental fashion to test the theories of social science.

¹ Some human beings are like this—being unimpressed by a great idea unless it produces a hydrogen bomb, or a beautiful painting unless they are told it is worth \$100,000.