ADVANCES IN DRUG RESEARCH

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ADVANCES IN

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PREFACE: ADVANCING DRUG RESEARCH

Drug research advances at a rate that never fails to amaze scientists who, like ourselves, are mature enough to discern a deep perspective and still fresh enough to experience awe and wonderment. As for drug researchers, they advance in their enterprise by a combination of expertise and creativity. These two statements may seem contradictory. However, they represent two sides of the same coin—drug research as a human endeavour in which scientists take both the part of actor and audience. In particular, writers of scientific reviews play such a dual role, on the one hand, observing and collecting, on the other, constructing and asserting,

> . . . because science consists not simply of a collection of true facts about the world, but is the body of assertions and theories about the world made by people who are called scientists. It consists, in large part, of what scientists say about the world whatever the true state of the world might be (Lewontin, 1993).

And when it comes to constructing and asserting, the present volume is rather unique. As will become rapidly apparent to the many faithful readers of *Advances in Drug Research*, it differs from all previous volumes in that none of the chapters focuses on a specific class of drugs. In other words, the present volume possesses the singular characteristic of containing only general chapters presenting conceptual and/or methodological advances. Such a feature would find justification, were any required, in the pregnant words of the philosopher Mary Midgley:

> We already have far more facts than we can handle. What we need most is to improve our ways of sorting and relating them—to work on the concepts, to philosophize (Midgley, 1991).

The book opens with a chapter by Kier and Testa whose subject is drug research as a whole. This is covered in an unconventional and even provocative way by the adoption of a stance few drug researchers will be familiar with, namely that of complexity and emergent properties. Some readers may be astonished by the thesis advocated in this chapter — that the now well-established science of synergetics and complexity allows chemical and pharmacological phenomena to be seen in a new perspective, thereby

procuring original ways to conceive, probe and interpret them. But whatever their reaction, our readers cannot remain indifferent to the new paradigm.

The second chapter carries the testimony of a scientist who has devoted most of his professional career to drug design. As a pioneer and successful drug researcher, Tute has much to tell us, and he does so with great elegance and authority while reflecting upon the present and future of drug design. Because his experience is both industrial and academic, Tute manages to blend the fundamental and applied objectives of drug design and to demonstrate their complementarity, and indeed their inseparability.

The third and fourth chapters stand at the very cutting edge of methodology, explaining and evaluating the present state of the art in transgenic animals and xenobiotic-metabolizing human cells, respectively, as pharmacological and toxicological tools. Both Bürki and Lederman in their chapter, and Crespi in his, manage to condense an impressive amount of information in a relatively limited number of pages. The clarity of their presentation, the critical and prospective tone of their message, will convince our readers of the interest and potential of these new biological tools.

The fifth and final chapter is quite a novelty for *Advances in Drug Research*, and a most welcome one. Compliance, pharmacovigilance and related issues have become important disciplines now that the role of pharmaco-socioeconomics is fully recognized as an essential aspect of drug research—in this case, research whose objective is to optimize the therapeutic use of existing drugs rather than to discover new agents. In his chapter, Urquhart places patient compliance in the broad context of an evolving health care environment. His contribution, written in an easy and almost oral style, will be an eye-opener to those numerous bench and computer workers who consider research to end, and development to begin, when a drug candidate enters clinical trials.

As Wolpert recently noted,

> . . . we may be thought of doing "science" in our everyday life by setting up hypotheses and testing them against experiment; but this is not science since there is no need for theory—only imaginative trial and error is required to achieve the right "taste" (Wolpert, 1993).

This is a decisive statement telling us that there is much more to science than merely setting up hypotheses and testing them. Creating theories is the crucial step from which hypotheses and then tests can emerge. To various extents, all chapters in this book give preponderance to theory, and then go on to consider hypotheses and facts. The editors are therefore proud to have

assembled, and the authors to have contributed to, a volume of noteworthy scientific content. May our readers share our *satis factum*, our satisfaction.

BERNARD TESTA
URS A. MEYER

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Complexity and Emergence in Drug Research

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1 General Background

1.1 INTRODUCTION

Over the past half century, scientists have become increasingly knowledgeable about interactions between drug molecules and biological systems. This has been a result of many major advances in methods of study, both experimental and computational, and in models of relevant systems. These advances include new applications of existing paradigms, technological developments enriching the data-gathering processes, and the creation of entirely new concepts to comprehend drug-related phenomena. As a consequence, we are now better equipped to move towards the elusive objective of "rationally" designing new drugs.

Within the past quarter of a century there has also been a revolution in science in regard to the way we view **systems** in general, their properties and global behaviour, and the components into which they can be decomposed. Such a view is contrary to the Newtonian concept that the whole can be defined as some simple, linear combination of its parts. In other words, a **post-Newtonian** view has emerged having at its core the belief that systems at every level of size and organization have exclusive properties that are indivisible attributes of the whole and which emerge from non-linear and dynamic interactions among the components of the system. A system exhibiting these characteristics is said to possess complexity, i.e. it is complex in a new meaning of the word. Furthermore, systems exist in a nested hierarchy where one system becomes part of the ingredients producing the emergent properties of the next higher complex system.

When we reflect on these prominent areas of development, several questions do arise which challenge drug researchers. For example, how have

the concepts of this post-Newtonian paradigm implicitly influenced the development of the current state of thinking in drug research? Do the concepts of complexity and emergence have a place in the methods and models of modern drug research? And are there some identifiable places in the hierarchy of systems investigated by drug researchers where these concepts should now play a recognized and explicit role?

We present these questions as an introduction to this writing. In the following pages, we will first outline the current concepts operating in drug research in general and medicinal chemistry in particular. Secondly, we will elaborate on some of the new concepts associated with complexity and emergent properties. Thirdly, we will see how we can answer some of the questions posed above, linking current and new concepts. And finally, we will explore possibilities for the enrichment of drug research from these post-Newtonian concepts.

1.2 PRESENT CONCEPTS IN DRUG RESEARCH

The evolution of methods and models in technology and theory has brought drug research to its current state. But what is this current state? We begin here with a brief answer by identifying the hierarchy of systems of interest to us in this activity and continue by describing the progress associated with each system.

1.2.1 Systems of Interest

Drug researchers have staked out a portion of the spectrum of systems in nature as focal points for studies and models. The full spectrum of systems now investigated by all branches of science, and defined by both size and complexity, begins at the level of "ultimate" particles (quarks, strings, etc.) and extends right through to the Universe. A hierarchy of physical systems thus exists which we feel incompetent to define, simply noting that a hierarchy of biological systems "branches" out of the sequence of inanimate systems, as discussed below.

We can say of the full spectrum of systems that each system is complex, i.e. itself composed of subsystems, and that it is an ingredient of a larger system. Each system loses characteristics in the development of the emergent properties of its next-up neighbour, those things lost being subsumed into the characteristics of the more complex neighbour. Perhaps only some philosophers of science would embrace this complete spectrum of nature's systems in their studies and models.

Drug researchers by contrast are interested in just that segment of the spectrum of complex systems where in their view the phenomena of drug

actions take place. With the advent of theories of chemical reaction mechanisms, the electron and the proton have become the least complex systems of interest in drug research, while the most complex systems studied would be populations and societies (as relevant for example in pharmacogenetics and pharmacovigilance). The spectrum of complex systems of interest in drug research, a subset of the totality of all existing systems, would thus be:

. . . subatomic particles . . . atoms . . . molecules . . . macromolecules . . . membranes and macromolecular assemblies . . . organelles . . . cells . . . tissues . . . organs . . . systems of organs . . . organisms . . . populations and societies . . .

We shall return later to some complex systems in this segment and detail some explanation.

1.2.2 Milestones of Progress

Associated with the segment of complex systems that are identified with drug research are the conceptual and technical advances that have illuminated these systems and that have brought us to our present state of understanding and skill. We identify some of these and show in Fig. 1 their relationship to some complex systems in our realm of interest.

These advances fall into two major categories. The first are those which produce an increase in understanding of a particular system without considering higher levels of complexity. Examples include quantum mechanics, a paradigm for describing the behaviour of electrons, and topological structure coding, a paradigm for describing molecules. The second category of advances are those which form a **bridge of greater understanding** between two systems in this hierarchy. Examples would include molecular orbital theory which links atoms and molecules, and enzyme and receptor theories which link molecules and biomacromolecules.

Drug design is one discipline within drug research that calls heavily upon information far from the complex systems that we directly manipulate to elicit changes. We employ for example information at the complexity level of cells or organisms in order to establish relationships with molecular structure. An in-depth understanding of this source of information is not the gift of all drug designers, who accept pharmacological data on faith as representing the measurable biological effects of chemical compounds as a function of their molecular structure (Testa, 1984).

Each of the advances in Fig. 1 has its roots in an effort to describe the ingredients of a complex system, and is built upon the Newtonian concept of reduction to parts in an effort to understand the whole system. It is to this

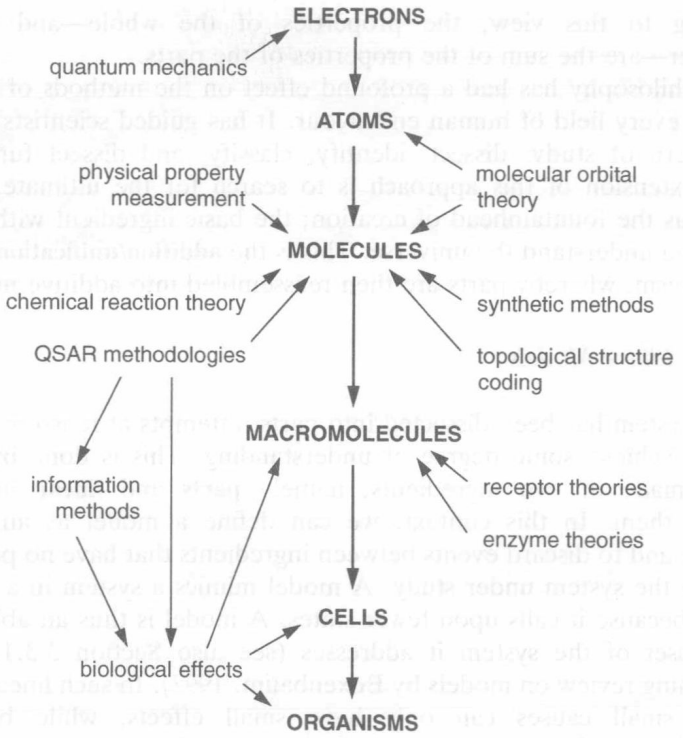

FIG. 1. The hierarchy of complex systems relevant to drug research, shown here associated with some of the theoretical and technical advances in this field.

Newtonian view of the world that we now turn our attention before introducing the post-Newtonian view.

1.3 NEWTONIAN PHILOSOPHY

1.3.1 Reductionism

The dominant philosophy in science for the last three centuries owes much to the epoch-making contributions of Isaac Newton (1643–1727). In regard to the nature of material objects, which we can generalize as systems, he viewed them as possessing properties that result from the **additive contributions** of their parts. This led to the belief that the route to the understanding of nature was through the dissection of a system to the parts followed by the study of these parts. This dissection is also performed in time, which is broken and sampled in a number of snapshots. Such a process is referred to as **analysis**, and the underlying philosophy as **reductionism**. In general then,

according to this view, the properties of the whole—and hence its behaviour—are the sum of the properties of the parts.

This philosophy has had a profound effect on the methods of inquiry in virtually every field of human endeavour. It has guided scientists to pursue the pattern of study: dissect, identify, classify, and dissect further. The logical extension of this approach is to search for the ultimate, ahistoric particle as the fountainhead of creation; the basic ingredient with which to model and understand the universe. This is the **addition/unification** sequel to reductionism, whereby parts are then reassembled into additive models.

1.3.2 Additive Models

Once a system has been dissected into parts, attempts at reassembly can be made to achieve some degree of understanding. This is done by building models made of two ingredients, namely **parts** and **linear interactions** between them. In this context, we can define a model as an effort to decouple and to discard events between ingredients that have no perceivable effect on the system under study. A model mimics a system in a simplified manner because it calls upon fewer states. A model is thus an abbreviation or a subset of the system it addresses (see also Section 3.3.1, and the enlightening review on models by Boxenbaum, 1992). In such linear additive models, small causes can only have small effects, while big causes necessarily elicit big effects.

The building of additive models begins with the portrayal of a system in an **equilibrium state**. This is true whether we are using a kinematic or a thermodynamic definition of equilibrium states. Each system is assumed to wind down to its lowest level of variable behaviour, a general statement that embraces a number of phenomena depending upon the level of complexity considered. This leads to a static model in which there is a sharp delineation between an event and its absence. There is a clear illumination of discrete events modelled to be cause and effect.

Along with the reduction–unification concepts, there have arisen ways to view nature using concepts such as thermodynamics and equilibrium. Forces such as enthalpy and entropy have been defined and invoked as integral parts of the consideration of ensembles of particles. Equilibrium states thus came to be regarded as the outcome of dynamic processes.

1.4 POST-NEWTONIAN PHILOSOPHY

1.4.1 The Need to Outgrow Reductionism

The limitations of the reductionistic philosophy became apparent near the end of the 19th century. The recognition of the diversity of life following the

contributions of Charles Darwin (1809–1882) called attention to the great difficulty in describing living systems with additive, linear models based on ingredients. At the turn of the century, Henri Poincaré (1854–1912) concluded that the accurate prediction of the trajectory of three or more interacting bodies was impossible, revealing further limitations of reductionism.

In this century, prodigious conceptual leaps were made with quantum uncertainty, Kurt Gödel's incompleteness theorem, and deterministic chaos, all of which are irrevocably incompatible with the clockwork universe of Newton and Laplace. The recognition of self-organization of states far from equilibrium as pioneered by Ilya Prigogine has dispelled any remaining belief that the reductionistic approach should offer a route to understanding a system in its globality and complexity. The concept of fractional dimensions (fractals) has brought with it a genuine revolution in our manner of viewing and describing a diversity of phenomena, and has now found many applications in the pharmaceutical sciences (Koch, 1993).

1.4.2 The Concepts of Complexity and Emergence

There has evolved over the past three decades a set of general concepts that have revolutionized the way we regard and study systems in nature. Their basic premises run counter to the Newtonian reductionistic approaches and might thus be labelled post-Newtonian concepts. The central theme of this new philosophy is the recognition that the behaviour and properties of a system are **non-linear combinations of the subsystems**. Such a system is endowed with complexity and displays specific properties that emerge from **dynamic interactions** between the subsystems. We discuss briefly complexity and emergence as the two pillars of post-Newtonian thought.

We define **emergent properties** of a system as those that are possessed by the system itself in its globality, but are neither properties of the components nor linearily derivable from them. Emergent properties arise from the interactions between the constituents of a system, when these transactions are of such a nature and magnitude that the individuality of the parts is subsumed in an unrecognizable form within the larger system. In other words, emergent properties are seen in systems whose component parts interact with such intricacy that they cannot be predicted by standard linear equations.

As an example, the ingredients of a photograph are dots arranged in some characteristic pattern. A study of individual dots may be of interest and will tell us something about them. It will, however, tell us nothing about the object having been photographed. The picture portrayed in the photograph is an emergent property of the dots. The individuality of the dots is lost; only the ensemble of dots has significance as a recognizable picture.

Closer to home, and as discussed in detail later, we can cite the properties of a molecule as being emergent and not predictable from a linear combination of atomic properties. The identity of the individual atoms in a molecule is lost in the extensive electronic interactions that occur when a molecule is formed. The physical properties of the atoms are no longer of significant value in understanding the molecule. Other steps must be taken if we are to achieve some understanding.

Emergence, in other words the existence of emergent properties, is the specific characteristic of, and the necessary condition for, systems said to display **complexity**. Emergent properties and complexity are thus two manifestations of the same phenomenon and have come to be recognized as characteristics of nature at every level. But whether emergent properties are also the sufficient condition for complexity remains to be clarified.

1.4.3 The Study of Complex Systems

The Newtonian approach to understanding nature is based first on the reduction of a system to its parts and second on the study of these parts, in the belief that the information so obtained can be reassembled additively to understand the whole. In post-Newtonian philosophy this is an incomplete procedure. Dissection of a complex system to the ingredients will give us the basic building blocks but will not reveal how they are ordered or organized in developing the emergent behaviour of the original complex system. To approach this goal one must attempt to **model the organization *per se*** in a process called **synthesis**.

As outlined above, model building is also performed in the Newtonian paradigm, but the differences with the post-Newtonian paradigm are worth restating. In the reductionistic approach, analysis into parts is by far the more important and informative step, with unification considered as an accessory and "downhill" task. Within the post-Newtonian paradigm, analysis remains an essential undertaking, but only insofar as it is the obligatory precursor to synthesis, the decisive step which justifies analysis and will bring forward understanding and knowledge. As expressed by Sheldrake (1989) in another context, one way of thinking about creative synthesis involves looking from below, from the bottom up, seeing the emergence of ever more complex forms. The other approach is to start from above, from the top down.

In post-Newtonian research, both analysis and synthesis are thus essential in order to complete a circle of research with any possibility of enhancing our understanding of a complex system. This is illustrated in Fig. 2, which shows the circle of research in the understanding of the emergent behaviour of a complex system such as an aeroplane. We can study in great depth the components of this complex system, revealing vast amounts of information