CHIMIA 46 (1992) Nr. 7/8 (Juli/August)

New Swiss Chemical Society, Section of Medicinal Chemistry
European Federation for Medicinal Chemistry (EFMC)
American Chemical Society, Division of Medicinal Chemistry (USMC)

XIIth International Symposium on Medicinal Chemistry

Basel, Switzerland
September 13–17, 1992

Chimia 46 (1992) 297–299
© Neue Schweizerische Chemische Gesellschaft
ISSN 0009–4293

Medicinal Chemistry: A Teacher's and Worker's Perspective

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Abstract. This personal commentary aims at offering a description of the origin, purpose, and methods of medicinal chemistry, and a delineation of its fields of activity in connection with related sciences. Directions of future development of medicinal chemistry as a science are suggested.

1. Introduction

Defining medicinal chemistry is both easy (yet tautological) and difficult (yet obvious). A hasty approach is to define medicinal chemistry as the (study of the) chemistry of medicines, but this statement is a circularity and as such affords no information. And when one is bold enough to venture a definition, one quickly realizes that the number of divergent opinions is equal to the number of interlocutors. Yet, all of us self-proclaimed medicinal chemists never fail to acknowledge the existence of a multidisciplinary, dynamic, and fuzzy science to which our professional life is devoted, and which we call medicinal chemistry [1].

Rather than offering a disputable definition, the author draws from two decades of experience as a teacher of and researcher in medicinal chemistry, and proposes in the present commentary a personal perspective that may broaden the perception of some readers.

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2. Where from? A Historic View

A number of terms such as pharmaceutical chemistry, medicinal chemistry, and pharmacochemistry are commonly used and sometimes confused. Schematically, it can be said that medicinal chemistry evolved from *pharmaceutical chemistry*, as summarized in *Table 1*. Most influencial in this evolution is the significance gained by two fields, namely *a*) drug design and structure-activity relationships, and *b*) the biochemical reactivity of drugs.

Drug design in its broadest sense and *structure-activity relationships* are central and essential to medicinal chemistry, and it is the creation and development of this field of research that has made medicinal chemistry the modern and enormously productive science it has become in the last two or three decades. While the earlier pharmaceutical chemists prepared drugs, medicinal chemists essentially *design and/or prepare drugs*.

Table 1. *The Evolution from Pharmaceutical Chemistry to Medicinal Chemistry.* Main fields of activity are in italics.

Pharmaceutical Chemistry
Drug synthesis
Pharmaceutical analysis
Chemical stability and reactivity of drugs
Medicinal Chemisty (*ca.* 1950)
(= pharmacochemistry = chimie thérapeutique)
Drug synthesis
Drug design and structure-activity relationships
Biochemical reactivity of drugs
Chemical stability and reactivity of drugs

Table 2. *What for and how?* The purpose, aims, and methods of medicinal chemistry (adapted from *Spilker* [2]).

Mission (overall purpose)
- To provide drugs

Objectives (non-quantifiable, long-term aims)
- To prepare drugs
- To discover new drugs
- To create knowledge leading to new drugs
- To contribute to an understanding of the molecular mechanisms of interaction between drugs and biological systems

Goals (quantifiable, time-limited endpoints)
- To discover and prepare a drug with specific activity, *e.g.*, a new antiviral agent

Strategies (plans, concepts and principles of how goals will be achieved)
- *Lead generation* by, *e.g.*
  - Mass screening
  - Testing of metabolites
  - Isolation and testing of natural products
  - Lead generation based on biological hypotheses
  - Serendipity
  - Intuition
- *Lead optimization* by, *e.g.*
  - Mass synthesis (molecular modifications)
  - Quantitative information analysis
  - Pharmacophore disclosure
  - Drug design based on hypotheses
  - Prediction

Tactics (detailed methods and plans used to implement a given strategy), *e.g.*
- Synthetic methods
- Structural determinations
- Assessment of physicochemical properties
- Quantitative structure-activity relationships
- Molecular-graphics methods
- Metabolic studies

The *biochemical reactivity of drugs* (*i.e.*, biotransformation reactions, biochemical mechanisms of activation, deactivation, toxication, and detoxication) is a field that, while not specific to medicinal chemistry, has become important to it and is actively investigated by a number of medicinal chemists (see also *Sect. 4*).

Note that *pharmacochemistry* is taken by many to be synonymous with medicinal chemistry. The correct French translation is '*chimie thérapeutique*', a term coined in France in 1966 with the creation in this country of a '*Société de chimie thérapeutique*'.

3. What for and how? Purpose, Aims, and Methods of Medicinal Chemistry

What purpose, lay-persons may ask, does medicinal chemistry serve? This question, naive as it may sound, is repeatedly directed at those pharmacochemists who venture out of the comforting security of academic ivory towers or industrial strongholds and take it as a duty to confront and inform the public. Even among practioners, opinions may differ.

Based on definitions and illustrations given by *Spilker* [2] in another context, an application to medicinal chemistry of his 'five concepts' is presented in *Table 2*. Schematic as it may be, this conceptualization into mission, objectives, goals, strategies, and tactics has the advantage of separating the short term from the long term, the fluid from the stable, the particular from the general.

4. Where? The Relation of Medicinal Chemistry with Connected Sciences

One important way of delineating a given science is to identify areas of overlap with connected sciences. Medicinal chemistry obviously belongs in its totality to the chemical sciences, from whence it draws its tools, *e.g.*, synthetic, analytical, physical, structural, quantum, and mathematical chemistry (*Fig.*). There is some overlap with *biochemistry*, a distinct chemical science, as exemplified by the study of drug-enzyme interactions or the characterization of the structure of receptors and other relevant macromolecules.

In addition to these 'intra-chemical' connections, medicinal chemistry is also strongly related to pharmacology, and particularly *molecular pharmacology*. This applies to *pharmacodynamics* (defined as the study of pharmacodynamic events, which are the effects of drugs on biological systems) as well as to *pharmacokinetics* (defined as the study of pharmacokinetic events, which are the effects of biological systems on drugs) [3]. There is certainly no need to belabour the point that pharmacochemistry and pharmacodynamics share common interests and goals, *e.g.* studying processes of drug-receptor recognition and molecular mechanisms of action of drugs. In contrast, not all medicinal chemists are ready to acknowledge the connections between pharmacochemistry and drug metabolism, in particular the bioreactivity of drugs as outlined in *Sect. 2*.

5. Where to?

The *Figure* not only describes a current situation, it also suggests some likely developments of medicinal chemistry. Indeed, existing connections with neighbouring sciences can be expected to intensify and expand, while new connections are being or will be created. In the coming years, the growth of medicinal chemistry can safely be predicted to be sustained by

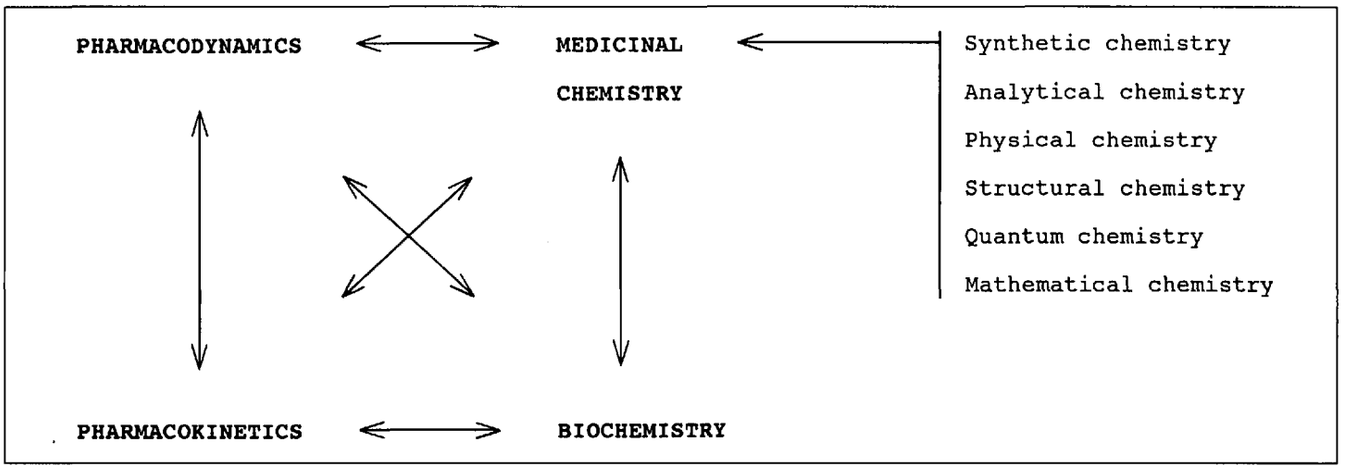

Figure. *The relation of medicinal chemistry with connected disciplines*

discoveries in the chemical sciences (*e.g.* synthetic chemistry), but the major contributions to progress should come from molecular biology and mathematics.

Molecular biology is having a major impact on molecular pharmacology and enzymology, and this in turn has begun to deeply affect the thinking and work of medicinal chemists. For example, the cloning of new receptor subtypes and of mutant receptors and enzymes obtained by site-directed mutagenesis has brought us closer to understanding the structure and functioning of these macromolecules. The impact on molecular-graphics studies and on lead generation and optimization is overwhelming.

It is not in the least fortuitous that the development of medicinal chemistry should parallel advances in *mathematical and computational sciences* and their applications. These theoretical advances, coupled to the fast technological evolution of computing machines, will continue to offer to pharmacochemists tools of ever increasing sophistication and efficiency.

In the longer run, however, the molecular level of conceptualization may reveal its limits. At this point, continued progress in medicinal chemistry may call for input from *systemic pharmacology*, in other words from a highly integrated and organismic pharmacology which may well be the clinical pharmacology of the future. In such a perspective, medicinal chemistry would become more 'therapeutic', thus providing a belated vindication of the French label 'chimie thérapeutique'.

The author is deeply indebted to Prof. *Lemont B. Kier*, currently holder of the Chair of Honour at the University of Lausanne, for many stimulating discussions and for his insightful correction of the text.

Received: June 12, 1992

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Chimia 46 (1992) 299–303
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ISSN 0009-4293

Hydrogen-Bonding Capacity and Brain Penetration

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Abstract. Brain penetration has been reported to correlate with Δlog P, defined as log P (octan-1-ol/H_2O) – log P (alkane/H_2O). Another recent development, describing log P as the sum of a cavity or volume contribution and H-bonding capability, the latter expressed by $A_{solvent}$ values, prompted us to reinvestigate the properties accounting for brain penetration. It was found that A_{alkane} and the hydrophilic part of the *van der Waals* surface both correlate well with brain uptake. These findings offer new opportunities for the design of compounds which either should or should not be active at sites located in the brain.

1. Brain Uptake and Physicochemical Properties

1.1. *The Δlog P Concept*

Numerous QSAR studies on CNS drugs have demonstrated that besides p*K*a and molecular size, lipophilicity is a highly significant contributor to brain penetration [1][2]. Partition coefficients measured in the octan-1-ol/H_2O system are mostly used as experimental assessment of the lipophilicity of a compound. However, it has been observed that neither octan-1-ol/H_2O (log P_{oct}) nor cyclohexane/H_2O (log P_{chex}) partition coefficients are predictive for brain penetration of H_2-

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