Sugared pill

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Comprehensive Medicinal Chemistry. The Rational Design, Mechanistic Study and Therapeutic Application of Chemical Compounds. Editor-in-chief Corwin Hansch. *Six volumes. Pergamon: 1990. Pp. 5,494. £1,145, $1,995.*

UNTIL the development of synthetic organic chemistry in the latter part of the past century, our stock of medicinal chemicals came largely from plant sources, usually used impure in the form of herbal preparations. Such sources provided drugs such as morphine, codeine, quinine, cocaine, ergot, curare, ephedrine, reserpine, salicin, digitoxin and, from microbes, many antibiotics. Progress in synthesis put at the disposal of the medicinal chemist an enormous range of structures, together with the means for modulating their design. It is of course one thing to have available lots of chemicals, and quite another to select useful medicinal compounds from among them. In the early days, this process was often a matter of guesswork and luck. Naphthalene, thought to be useful as an internal disinfectant, was tried for the eradiction of worms, for example. Fortunately, a dispensing error was made and acetanilide was administered to a patient suffering from a fever as well as from worms. The drug abated the fever, and the value of the closely related phenacetin and the much used paracetamol is derived from this observation. It was noticed that the antisyphilitic mercurial drug merbaphen produces a striking increase in urine flow; this observation led to the use of diuretics to treat congestive heart failure.

Although sharp observation is as important as it ever was, the design and evolution of medicinal compounds is now a highly sophisticated business involving enormous expenditure. It is also highly interdisciplinary, covering chemistry, biochemistry, physics and many areas of biology and pharmacy, as well as requiring knowledge of patents, regulations and similar topics. This complex amalgam of interests directed towards the specific aim of producing new and better medicinals is the theme of the six volumes entitled *Comprehensive Medicinal Chemistry*, which describe common ground for those engaged in this endeavour. Despite the massive nature of the work (as well as the vast number of pages there are more than 230 authors and editors from 15 countries) organic synthesis, which occupies much of a medicinal chemist's time, is not discussed. But this omission is reasonable as organic synthesis is a large topic with well-established sources of information of its own. Starting with a candidate drug structure, rather than discussing how it may be made, also makes the work more accessible to those in other disciplines.

In many ways the second and third volumes provide the core information on new drug discovery. Volume 2, *Enzymes and Other Molecular Targets*, covers agents acting on oxygenases, electron-transport systems and pyridoxal-dependent systems, on metabolic processes, on hydrolases and peptidases, on cell walls and on nucleic acids. Volume 3, the largest of the set, deals with membranes and receptors, covering neurotransmitters, peptidergic and intracellular receptors as well as drugs acting on ion channels and membranes. These are excellent comprehensive volumes.

Healing plant — *Trachelospermum jasminoides* or Chinese star jasmine. Traditional uses include treatment of rheumatic pains, muscular spasm and injuries. This is one of the 150 most commonly used plants in traditional Chinese medicine catalogued in *Medicinal Plants in China*. Publisher is the World Health Organization, price is $40 (pbk). *Plants for Medicines: A Chemical and Pharmacological Survey of Plants in the Australian Region* gives details of the phytochemical testing of nearly 2,000 species of Australian flora. Published by CSIRO, price is $70.

Quantitative structure–activity relationships are considered in volume 4. The idea of factorizing drug activity into physical contributions (hydrophobic, electronic, steric and so on) has been central to the Hansch approach and has shown how important hydrophobicity is to drug transport. Application of structure–activity data assists the optimization of 'lead' compounds to form effective drugs with economy of effort by aiding the selection of the most significant structures for synthesis. The burgeoning subjects of molecular modelling and computer graphics are also covered in this volume. Volume 5 deals with biopharmaceutics — drug delivery, distribution, absorption and related topics. Analytical methods are also covered, although this will be familiar ground to well-trained organic chemists.

Volume 1 seems to me to be of the most general interest. Not only does it give historical perspective, it treats, in relatively uncomplicated form, areas that the medicinal chemist should know something of — human physiology, cell architecture, the immune system, genetic engineering, process development and similar subjects. Socio-economic topics are also considered — government control, toxicological evaluation, clinical testing, patents, trademarks, post-marketing surveillance, sources of information and 'orphan' drugs (drugs that are useful yet, for various reasons, cannot be expected to make any financial profit). There is a good cumulative subject index in volume 6, though there is no author index relating to the many references cited. An unusual feature is the drug compendium — a collection of 5,500 structural formulae of drugs that have been used or studied in man, together with log P and pK_a data.

Although appreciating the constraints involved in producing a work of this nature, I would like more attention to have been paid to stereochemistry, optical resolution and other methods for producing drugs in optically pure forms. Frequently, only one stereoisomer of a drug is active, other isomers merely adding to the body's burden of excretable material. In some cases, the matter is much more serious, thalidomide being a classic example. The R(+)-isomer has the desired sleep-inducing effect, but the S(−) is teratogenic. As spatial arrangement is so important in medicinal chemistry, I was surprised that this parameter is not indicated on many natural product formulae illustrated in the otherwise admirable "Chronology of Drug Introductions" in volume 1.

This major work has been well planned, and the high proportion of practising industrial authors (many from the United States and the United Kingdom) has given the result authenticity. Despite its size, the work is really very readable and the organization helps to remedy one's lack of knowledge in some areas. One of the contributors writes, overmodestly, "it is unlikely that anyone will be reading this volume from cover to cover. But in that improbable event..." My riposte is "why not?". This is exciting stuff for an organic chemist keen on medicinal chemistry.

The main barrier to potential readers will be that the volumes will be non-loan, to be read only in the library rather than, as they should be, in the comfort in an armchair at home. A serious pharmaceutical company should consider providing one or more loan sets. Compared with the cost of developing a saleable drug, expenditure would be minute and the return in terms of education of its staff would repay it many times. Sadly, most universities and polytechnics in Britain at least will be lucky to have sight of a non-loan set. □

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