

Annual Review of Pharmacology and Toxicology. 2001, vol. 41. Arthur K. Cho (ed.). Annual Reviews, 4139 El Camino Way, P.O. Box 10139, Palo Alto, California 94303-0139, USA. 934 pp. Price not mentioned.

The book under review covers a broad range of topics dealing with issues of drug development, mechanisms of drug action, identification of drug targets and the wide array of signal transduction mechanisms mediated by receptors. One gets the distinct impression that an attempt has been made to highlight systems that are somewhat unique, less well-known and emerging. It is a welcome effort and the volume should prove very useful.

The introductory chapter 'Toxicology comes of age' by John Doull, besides providing a biographical sketch, makes the point that toxicology, like medicine, is both a science and an art. The observational or data-gathering part is science, whereas the predictive part is art. Thus, the fact that chloroform causes cancer in rodents is a fact, but that it can do so in humans, is a hypothesis. The new paradigm for risk assessment is based on the recognition that both time and dose are independent variables in exposure.

There are around 10 articles addressing the issue of drug development. Pharmacogenomics has become the password in drug companies and techniques to assess inter-individual genetic differences in drug disposition and effects are discussed by McLeod and Evans. There is hope that it will eventually be harnessed as a Public Health Tool, with adequate sensitivity to bioethical issues, to provide a strong scientific basis for optimal drug therapy and dosage for each patient, rich or poor. An important aspect here is ethnicity as a demographic variable. Xie *et al.* address this issue with specific reference to drug metabolizing enzymes (CYP2C9, 2C19, 2D6 and 3A4), drug transporter (P-glycoprotein), drug receptors and some functionally relevant proteins (e Nos and G proteins). Lin and Lu, once again discuss the inter-individual variability in drug interactions and highlight the inadequacy of the utility of data from *in vitro* metabolic studies. Lesko and Atkinson review the biomarkers and surrogate

endpoints used for predicting the efficacy and safety of a drug. Chan and Holford highlight the disease progress models combined with pharmacokinetic-pharmacodynamic models and hierarchical random effects statistical models to provide insights into understanding the management of degenerative diseases. Two other articles are specifically devoted to the cytochrome P-450 group of drug-metabolizing enzymes. Sueyoshi and Negishi address the issue of phenobarbitone-responsive elements in the cytochrome P-450 responding to this drug and highlight the involvement of NR-constitutive (CAR) and such other receptors in the process. Murray *et al.* review the regulation, function and tissue-specific expression of CYP1B1 with unique stereospecificity of hydroxylation, a recent addition to the human CYP1 family. The unique features of the metabolism of fluorine-containing drugs are discussed by Park *et al.*

Mechanisms of drug action focus on a wide range of rather less well-known molecules or less well-recognized drug effects. These include anaesthetics, L-arginine, nonpeptide vasopressin receptor antagonists, neurokinin receptor antagonists, nitric oxide, vitamin D and synthetic analogues, estrogen, lithium, thioredoxins, topoisomerase inhibitors and antisense oligonucleotides. It is proposed that the most plausible target for general anaesthetics among ligand-gated ion channel is the GABA_A receptor, although there are some exceptions (Yamakura *et al.*). L-arginine, not a well-known drug, can improve clinical symptoms of cardiovascular disease in man and the role of asymmetric dimethyl arginine, an endogenous molecule, needs to be studied in detail in this context (Boger and Bode-Boger). Davis *et al.* describe the non-3',5'-cGMP-mediated effects of nitric oxide through interaction of reactive N species with proteins, lipids and nucleic acids. Guyton *et al.* have focused on the role of cancer prevention by natural vitamin D and synthetic diltanoids, where dissociation between chemopreventive and toxic calcemic effects has been the problem. A similar narrow therapeutic window governs the therapeutic dose of lithium treatment for bipolar disorder and toxicity (Phiel and Klein). Estrogen, long identified as a female sex hormone, is now recognized to exert

neurotrophic and neuroprotective effects. Lee and McEwen review the mechanisms involved in the diverse effects, some of which do not involve the classical estrogen receptor element. The promise of oligonucleotides as a drug for gene regulation is yet to be realized. The difficulties in data interpretation, with particular reference to *bcl-2* gene expression in tumour cells are highlighted by Lebedeva and Stein. Thibonnier *et al.* review the pharmacological and clinical profile of orally active nonpeptide vasopressin receptor antagonists with consequences for arterial hypertension, congestive heart failure, liver cirrhosis, nephrotic syndrome, specific tumours, etc. Stout *et al.* review the status of research with nonpeptide antagonists of trachykinin receptors, neurokinin receptor antagonist in particular, that have potential antidepressant and anxiolytic properties. Recent advances on cellular events that respond to topoisomerase poisoning and following events leading to tumour cell death are reviewed by Li and Liu. Thioredoxins manifest a variety of functions and the elevation of thioredoxin-1 in many tumours has given hope for an inhibitor as an anticancer agent (Powis and Montfort).

Signal transduction pathways through receptor-mediated mechanisms and the ligands involved in the process offer new insights to develop drug targets. Dopamine is intimately associated with schizophrenia. Carlsson *et al.* review the evidence for a role, not only for dopamine and glutamate, but also for serotonin, noradrenaline and GABA in this disease. Ca²⁺ signalling, multiple Ca²⁺ messengers and Ca²⁺ store are an important arm of cellular signal transduction. The specific effects of the unusual nucleotides, cyclic ADP-ribose and NAADP, in this context are reviewed by Lee. Ca²⁺/calmodulin kinases, the multifunctional CAMI, II and IV, play pivotal roles from activation to function (HooK and Means). Another important aspect in signal transduction is the G-protein-coupled signalling pathways. The examples chosen are: lysophospholipid receptors that were elusive for a long time (Fukushima *et al.*), G-protein-coupled receptor (GPCR) polymorphisms and their implications for diagnosis and treatment (Rana *et al.*), the selectivity of prostanoid receptors in terms of ligand-

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binding and G-protein interaction (Breyer *et al.*), compartmentalization of cAMP action in cardiac cells via the G-proteins (Steinberg and Brunton), coupling of adenosine receptors and G-proteins, adenosine being a primordial signalling molecule (Linden), differential integration of GPCR signals through multiple isoforms of adenylyl cyclases (Hanoune and Defer) and the pharmacological complexity of the endothelin

system consisting of two G-protein-coupled receptors, three peptide ligands and two activating peptidases (Kedzierski and Yanagisawa).

Perhaps the article 'Pharmacology of the lower urinary tract' by de Groat and Yoshimura is an example meant to highlight the involvement of the complex set of ligands and mechanisms in understanding the pathophysiology of a complex disease such as voiding disor-

ders and the possible targets for drug therapy.

Pages 97–100 are missing in the volume!

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