

REVIEW OF REVIEWS^{1,2}

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While pharmacological search and research is proceeding increasingly in a strictly scientific way at a molecular level (molecules of drugs interacting with molecules, usually enzymes, of living material), the practical application of pharmacological information is increasingly focused empirically on clinical aspects of the health professions, on agriculture and agronomy, on pollution control, on criminology and law, on sociology and public health. Pharmacology and toxicology remain the scientific disciplines, while the applications of verifiable knowledge derived from them are becoming technologies.

Can the sciences and the technologies related to pharmacology and toxicology be handled or taught together? I believe that they can. One may appropriately follow chemical reactions at the various levels of organization of living material. One may begin with bioenergetics, or quantum reactions with atoms, going on to molecular effects, and thence to responses in subcellular units, in cells, in organs and tissues, in individuals, in societies, and in ecologies.

Annual Review of Pharmacology offers the most satisfactory medium for covering the overall advance of knowledge in pharmacology and toxicology, from strictly molecular interactions of drug molecules with molecules of living material, to whatever practical applications may be made of this vast and rapidly accumulating information. The editors of *Annual Review of Pharmacology* have been wise in recognizing the broad sweep of the discipline, and they have been remarkably effective in giving all who may be interested the opportunity to roll along with it.

GENERAL

John Krantz has issued 18 essays on *Historical Medical Classics Involving New Drugs* from digitalis to fluorinated anesthetic agents. These are delightfully anecdotal. A well-illustrated biobibliography of Corneel Heymans (1892–1968) was

¹This review was completed July 1, 1974, for material available at that time. References are cited at the end of the chapter, by author, without numbering. Names are arranged alphabetically for convenience. Titles may be inferred from author references in the text.

²This review is dedicated to the memory of Robert M. Featherstone 1914–1974.

prepared by his pupil, A. F. De Schaepdryver. This contains many reminiscent appreciations.

Human experimentation, a touchy subject, is well discussed by Barber and associates, with helpful guidelines. Goldberg and colleagues edit 33 informative essays on psychopharmacologic agents for the terminally ill and bereaved.

Methods

Ariens edits 9 reports on drug design. Costa & Holmstedt edit 13 articles on gas chromatography and mass spectrometry in neurobiology. Immunoassay methods are attracting attention. Yalow describes radioimmunoassay methods and their application to problems of the heterogenicity of peptide hormones, while Robinson & Frantz review radioimmunoassay of posterior pituitary peptides. La Du chaired a symposium on immunopharmacology dedicated to Solomon Berson (1918–1972), who developed radioimmunoassay methods. These are important in antibody studies on digitaloids, morphines, barbitals, prostaglandins, and in cancer immunotherapy.

Largely concerned with methods, the 21 important contributions edited by Robert M. Featherstone (1914–1974) constitute an admirable guide to molecular pharmacology and toxicology. The reviews range from models of cell membranes, through intermolecular forces and electron spin resonance, to optical activity and molecular orbital theory.

Advances

Collier reviews the experimental analysis of drug dependence. Davies & Prichard edit 19 reviews on the biological effects of drugs in relation to their plasma concentration. With 66 references, Demopoulos surveys the control of free radicals in biological systems with reference to various antioxidants. Dikstein edits 19 reviews on drugs influencing subcellular metabolism, adrenergic transmitters, synaptic components in central nervous systems, cell membranes, phagocytosis, and pinocytosis.

The prediction of pharmacological activity by reference to physicochemical-activity relationships is reviewed by Goodford. The mechanisms of drug-enzyme interactions are surveyed by Handschumacher & Hare. Heusghem & Lechat edit 33 reviews on undesired drug effects. These comprehensively include effects referable both to organ systems and to various types of drugs. Various antibodies to pharmacologically active molecules are well reviewed by Levine.

Fifteen reports on new concepts in metabolic regulation of neurotransmitters, including significance in drug abuse, are edited by Mandel. Rang edits 20 important reports on drug receptors, with much on allosteric enzyme regulation in regard to drug action. Zimmerman and colleagues edit reviews correlating drug action with cell cycles.

PHARMACOKINETICS

Biological transport processes and rates of transport continue to be vigorously explored. Callingham edits a London symposium of 23 discussions on drugs and

transport processes. Jollow & Brodie review bioavailability via the alimentary tract, and find it is related to membrane absorption and/or solubility. With 50 references, Longshaw reviews factors inhibiting hepatic drug metabolism. Painter analyzes biodegradability.

Rowland, Benet & Graham discuss clearance concepts in relation to pharmacokinetics. Scheline, with 454 references, reviews the metabolism of foreign compounds by gastroenteric microorganisms. The many and diverse methods are mostly hydrolytic and reductive, with some toxic degradations, as with steroids to carcinogens.

A comprehensive discussion of pharmacokinetics is given in 22 reviews edited by Teorell, Dedrick & Condliffe. With 56 references, Thron reviews linearity and superposition in pharmacokinetics. Urquhart & Yates edit 11 discussions in an Alza conference on temporal aspects of therapeutics, pointing the way to controlled drug delivery.

CHEMOTHERAPY

The continuing search for antiviral drugs is surveyed by Bucknell. Garattini & Franchi edit well-organized reports on the chemotherapy of cancer dissemination and metastasis. With 397 references, Haddow well reviews biological alkylating agents from nitrogen mustards to chlorambucil, showing their many and diverse actions. Joyner & Brocklesby survey the chemotherapy of anaplasmosis, babesiasis, and therileriasis. Oliverio reviews pharmacology and toxicology of nitrosoureas, now being studied for cancer chemotherapy. The immunotherapy of cancer is well reviewed by Parker. Mechanisms of action of antiviral agents are described by Prusoff & Goz, using 93 references. Ryley & Betts review the chemotherapy of chicken coccidiosis. Cavier & Hawking edit 5 reviews of the chemotherapy of helminthiasis.

NERVOUS SYSTEM

Autonomic

A symposium of 11 reviews on the neurochemistry of cholinergic receptors, with the isolation and molecular properties of these proteins, was edited by De Robertis & Schacht. With 232 references, Fuller reviews the control of epinephrine synthesis and secretion, mostly on the enzyme phenylethanolamine N-methyl transferase. Using 328 references, Higgins, Vatner & Braunwald survey parasympathetic control of hearts. They show that baroreceptor reflexes give parasympathetic stimulus to hearts attenuated by general anesthesia, exercise, and hypertension. These reflexes are depressed in heart failure.

Central

Dawson & McGaugh discuss drug facilitation of learning and memory. Phenothiazines and structurally related drugs are fully reviewed in 67 reports edited by

Forrest, Carr & Usdin. In an important review on drugs, neurotransmitters, and schizophrenia, Snyder and his associates show how phenothiazines block dopamine receptors by mimicking preferred catecholamine configurations, while amphetamines activate schizoid symptoms by mediation of catechols in brains. Phenothiazines are optimal antidotes for amphetamine psychoses. With 182 references, Severs & Daniels-Severs show that angiotensin has central hypertensive effects in humans; it is present in brains and increases fluid intake.

Hemp (bhang, hashish, cannabis, marijuana) continues to attract interest. Mechoulam edits 7 reports on its pharmacology, while Nahas gives the most detailed and informative account to date. This is due largely to his historical account, but he is also full on the botany, chemistry, pharmacology, toxicology, and clinical and social aspects. The chemistry and pharmacology of mescaline analogs is reviewed by Shulgin.

Narcotics and Analgesics

Braude and her colleagues edit 46 reports on narcotic antagonists, from history through chemistry to mechanisms of action, pharmacokinetics, and long-acting preparations. The original report of Hart & McCawley on N-allylnormorphine still deserves attention. DuPont & Greene carefully examine dynamics of the Washington DC heroin epidemic, which peaked in 1969, with deaths peaking in 1971 to total 60 for heroin and 17 for methadone. Eddy & May detail search for better analgesics. Drugs inhibiting prostaglandin synthesis are analgesic, and as reviewed by Flower, with 166 references, include arachidonic acid analogs and salicylates. McQueen surveys mechanisms of action of anti-inflammatory drugs.

Anesthetics

Andersen & Amaranath, considering a fluid mosaic structure to cell membranes, claim anesthetic agents have nonspecific physical effects thereon. Cascorbi reviews biotransformations of drugs used in anesthesia. Cohen analyzes effects of anesthetics on mitochondrial function. Dorsch and associates offer a generalized hydrate mechanism for gaseous anesthetic action with theoretical and experimental discussion. Fink & Haschke discuss anesthetic effects on cerebral metabolism. Using 221 references, Merin concludes that inhalation anesthetics have negative inotropic effects on heart muscle. Rosner & Clark, with 181 references, find different inhalation anesthetics produce distinctive sequences in neuroelectric human recordings.

CARDIOVASCULAR-RENAL

With 262 references, Davies & Withington find that adrenalin and noradrenalin, with tyramine, contract splenic smooth muscle, while isoprenaline is a splenic vasodilator. Doherty & Kane give a review of the clinical pharmacology of digitalis glucosides. Mason and associates review antiarrhythmic agents, their ways of acting and their rational uses. Rosen & Hoffman also survey the mechanisms of action of antiarrhythmic drugs. Smith & Haber describe radioimmunoassay of digitalis glycosides.

TOXICOLOGY

Browder, Joselow & Louria consider the growing problem of lead poisoning, while Hicks reviews air-borne lead as an environmental toxin. Jukes considers risk-value of insecticides. Maugh reports on wide evidence of effects of trace elements on health, while Schroeder fully reviews their toxicity. Miescher introduced a session on drug-induced blood dyscrasias, with reference to alcohol, chloramphenicol, and drugs causing anemia or methemoglobinemia. Oakley surveys the neurotoxicity of hydroxyquinolines. Perry considers delayed toxicity to hydralazine resembling systemic lupus or rheumatoid arthritis. Sasner surveys comparative studies on algal toxins. Tappel reviews evidence that ascorbic acid and tocopherol reduce lipid peroxidation damage to cell components due to free radicals. Tu reviews the neurotoxicity of snake venoms.

CLINICAL

Austen & Lichtenstein edit 18 discussions on the immunopharmacology and treatment of asthma. Bonica edits a remarkably comprehensive series of 92 discussions on various aspects of pain and its relief from acupuncture, hypnosis, to surgery and many diverse drug uses. Brogden, Speight & Avery review the clinical pharmacology, ways of action, and therapeutic use of streptokinase. Fann & Maddox edit 14 discussions on drug uses in geropsychiatry. Giusti reviews the clinical use of cephalosporins in renal and hepatic insufficiency. Greenblatt & Shader review the use of benzodiazepines in clinical practice with extensive bibliographies.

Prostaglandins come into clinical interest: Katz & Katz, using 219 references, consider their scientific and clinical aspects; Weeks introduces a comprehensive symposium, with many references, on the various 20-carbon unsaturated lipid acids and their diverse uses from renal, autonomic, and reproductive functions to interactions with thyroid, calcium metabolism, and cancer, and Wilson edited a symposium on the broad clinical aspects of their activity.

McCrory introduced an important symposium on fetal drug effects, with much on fetal metabolism. Prange edited 15 reviews relating to the thyroid axis, drugs, and behavior, including thyroid enhancement of imipramines and lithium. Seelig surveys role of copper-molybdenum interaction in iron deficiency and iron storage disease. Vinar opens a conference on "trazodone," a triazolopyridine complex from Italy, as useful in psychiatric disorders.

MISCELLANEOUS

Dluhy, Lauler & Thorn review the chemistry and pharmacology of adrenal glucocorticoids. With 393 references, Fain reviews drug and hormone activity on adipose tissue, showing that there are adrenergic receptors in fat cells, and that many drugs alter lipolytic enzyme action. Hüttenrauch surveys physicochemical factors involved in the effectiveness of steroids. Irwin & Kienholz review studies on the calcium needs of humans. Thomas & Singhal edit 10 reviews on molecular mecha-

nisms of gonadal hormone action, including effects of prostaglandins and cyclic 3'-5'-adenosine monophosphate. In reviewing the regulation of iron absorption from gut, Van Campen concludes that it is not yet clear how iron homeostasis is maintained. Weinberg surveyed iron in bodies in relation to susceptibility to infectious disease. He found that hypoferrremia is advantageous to hosts and disadvantageous to invading microorganisms. The Weisburgers review the pharmacology, toxicology, and pathological properties of hydroxylamines.

Popular interest in drugs grows apace. The ten billion dollar drug industry, with its vast production and promotion of drugs, is critically examined by Silverman & Lee. They evaluate the role of clinical pharmacists, and of the Food and Drug Administration. There are many tables and references. This is a useful book. Di Cyan issues a useful book on vitamins and micronutrients, with much helpful information, and many references.

IN PROSPECT

Evermore bit by bit pharmacological and toxicological information accumulates, with proliferation of pharmacologists and pharmacology periodicals; evermore this vast amount of information yells for critical examination, evaluation, classification, comparison, and synthesis into working generalities; evermore are critical reviews needed so that people may stay abreast of the deluge, and gain some idea of what it is all about. *Annual Review of Pharmacology* is increasingly necessary for the maintenance of the discipline.

Literature Cited

- Andersen, N. B., Amaranath, L. 1973. *Anaesthesia* 39:126-52.
- Ariens, E. J., Ed. 1973. *Drug Design*. New York: Academic. 489 pp.
- Austen, K. F., Lichtenstein, L. M., Eds. 1974. *Asthma: Physiology, Immunopharmacology and Treatment*. New York: Academic. 348 pp.
- Barber, B., Lally, J. J., Makarushka, J. L., Sullivan, D. 1973. *Research on Human Subjects*. New York: Russell Sage Found. 272 pp.
- Bonica, J. J., Ed. 1974. *International Symposium on Pain*. New York: Raven. 858 pp.
- Braude, M. C., Harris, L. S., May, E. L., Smith, J. P., Villarreal, J. E., Eds. 1974. *Narcotic Antagonists*. New York: Raven. 485 pp.
- Brogden, R. N., Speight, T. M., Avery, G. S. 1973. *Drugs* 5:357-445.
- Browder, A. A., Joselow, M. M., Loria, D. B. 1973. *Medicine* 52:121-140.
- Bucknell, R. A. 1973. *Advan. Pharmacol. Chemother.* 11:100-51.
- Callingham, B. A., Ed. 1974. *Drugs and Transport Processes*. Baltimore: Univ. Park Press. 356 pp.
- Cascorbi, H. F. 1973. *Anaesthesia* 39:115-25.
- Cavier, R., Hawking, F., Eds. 1973. *Chemotherapy of Helminthiasis*. Oxford: Pergamon. 537 pp.
- Cohen, P. J. 1973. *Anaesthesia* 39:153-64.
- Collier, H. O. J. 1972. *Endeavor* 31:123-30.
- Costa, E., Holmstedt, B. 1973. *Gas Chromatography-Mass Spectrometry in Neurobiology*. New York: Raven. 192 pp.
- Davies, B. N., Withington, P. G. 1973. *Pharmacol. Rev.* 25:373-414.
- Davies, D. S., Prichard, B. N. C. 1973. *Biological Effects of Drugs in Relation to Their Plasma Concentration*. Baltimore: Univ. Park Press. 260 pp.
- Dawson, R. G., McGaugh, J. L. 1973. *Physiological Basis of Memory*, ed. J. A. Deutsch, 78-114. New York: Academic.
- Demopoulos, H. B. 1973. *Fed. Proc.* 32:1903-8.
- De Robertis, E., Schacht, J., Eds. 1974. *Neurochemistry of Cholinergic Receptors*. New York: Raven. 146 pp.

- De Schaepdryver, A. F., Ed. 1973. *Corneel Heymans: A Collective Biography*. Ghent: Heymans Found. 307 pp.
- De Schaepdryver, A. F. 1973. *Arch. Int. Pharmacodyn.* 202:11-282
- Di Cyan, E. 1974. *Vitamins in Your Life*. New York: Simon and Schuster. 223 pp.
- Dikstein, S., Ed. 1973. *Fundamentals of Cell Pharmacology*. Springfield, Ill.: Thomas. 548 pp.
- Dluhy, R. G., Lauler, D. P., Thorn, G. W. 1973. *Med. Clin. N. Am.* 57:1155-66
- Doherty, J. E., Kane, J. J. 1973. *Drugs* 6:182-221
- Dorsch, R. R., DeRocco, A. G., Distefano, V. 1973. *Physiol. Chem. Phys.* 5:209-36
- DuPont, R. L., Greene, M. H. 1973. *Science* 181:716-22
- Eddy, N. B., May, E. L. 1973. *Science* 181:407-15
- Fain, J. N. 1973. *Pharmacol. Rev.* 25:67-118
- Fann, W. E., Maddox, G. L., Eds. 1974. *Drug Issues in Geropsychiatry*. Baltimore: Williams & Wilkins. 122 pp.
- Featherstone, R. M., Ed. 1973. *A Guide to Molecular Pharmacology-Toxicology*. New York: Dekker. 811 pp. in 2 parts
- Fink, B. R., Haschke, R. D. 1973. *Anaesthesia* 39:199-215
- Flower, R. J. 1974. *Pharmacol. Rev.* 26:33-67
- Forrest, I. S., Carr, C. J., Usdin, E., Eds. 1974. *Phenothiazines and Structurally Related Drugs*. New York: Raven. 720 pp.
- Fuller, R. W. 1973. *Fed. Proc.* 32:1773-81
- Garattini, S., Franchi, G., Eds. 1973. *Chemotherapy of Cancer Dissemination and Metastasis*. New York: Raven. 430 pp.
- Giusti, D. L. 1973. *Drug Intel. Clin. Pharmacol.* 7:252-62
- Goldberg, L. K., Malitz, S., Kutscher, A. H., Eds. 1973. *Psychopharmacologic Agents for the Terminally Ill and Bereaved*. New York: Columbia Univ. Press. 339 pp.
- Goodford, P. J. 1973. *Advan. Pharmacol. Chemother.* 11:52-99
- Greenblatt, D. J., Shader, R. I. 1974. *Benzodiazepines in Clinical Practice*. New York: Raven. 325 pp.
- Haddow, A. 1973. *Perspect. Brit. Med.* 16:503-24
- Handschumacher, R. E., Hare, L. E. 1973. *Anaesthesia* 39:165-77
- Hart, E. R., McCawley, E. L. 1944. *J. Pharmacol.* 82:339-48
- Heushgem, C., Lechat, P., Eds. 1973. *Les Effets Indésirables des Médicaments*. Paris: Masson & Cie. 884 pp.
- Hicks, R. M. 1972. *Chem. Biol. Interactions* 5:361-90
- Higgins, C. B., Vatner, S. F., Braunwald, E. 1973. *Pharmacol. Rev.* 25:119-55
- Hüttenrauch, R. 1973. *Pharmacie* 28:84-102
- Irwin, M. I., Kienholz, E. W. 1973. *J. Nutr.* 103:1019-96
- Jollow, D. J., Brodie, B. B. 1972. *Pharmacology* 8:21-32
- Joyner, L. P., Brocklesby, D. W. 1973. *Advan. Pharmacol. Chemother.* 11:321-70
- Jukes, T. H. 1974. *Naturwissenschaften* 61:6-17
- Katz, R. L., Katz, C. J. 1974. *Anaesthesia* 40:471-93
- Krantz, J. C. 1974. *Historical Medical Classics Involving New Drugs*. Baltimore: Williams & Wilkins. 139 pp.
- La Du, B. N. 1973. *Pharmacol. Rev.* 25:157-361
- Levine, L. 1973. *Pharmacol. Rev.* 25:293-308
- Longshaw, R. N. 1973. *Drug Intel. Clin. Pharmacol.* 7:263-70
- Mandell, A. J., Ed. 1973. *New Concepts in Neurotransmitter Regulation*. New York: Plenum. 316 pp.
- Mason, D. T., Amsterdam, A. N., Zelis, R., Massumi, R. A. 1973. *Drugs* 5:261-317
- Maugh, T. H. 1973. *Science* 181:253-54
- McCrory, W. W. 1973. *Clin. Pharmacol. Ther.* 14:621-769
- McQueen, E. G. 1973. *Drugs* 6:104-17
- Mechoulam, R., Ed. 1973. *Marijuana*. New York: Academic. 409 pp.
- Merin, R. G. 1973. *Anaesthesia* 39:216-55
- Miescher, P. A. 1973. *Semin. Hematol.* 10:179-279
- Nahas, G. G. 1974. *Marihuana-Deceptive Weed*. New York: Raven. 325 pp.
- Oakley, G. P. 1973. *J. Am. Med. Assoc.* 225:395-401
- Oliverio, V. T. 1973. *Cancer Chemother.* 4:13-20
- Painter, H. A. 1974. *Proc. Roy. Soc. B* 185:149-58
- Parker, C. W. 1972. *Pharmacol. Rev.* 25:325-42
- Perry, H. M. 1973. *Am. J. Med.* 54:58-72
- Prange, A. J. Jr., Ed. 1974. *The Thyroid Axis, Drugs, and Behavior*. New York: Raven. 205 pp.
- Prusoff, W. H., Goz, B. 1973. *Fed. Proc.* 32:1679-87
- Rang, H. P., Ed. 1973. *Drug Receptors*. Baltimore: Univ. Park Press. 328 pp.

- Robinson, A. G., Frantz, A. G. 1973. *Metabolism* 22:1047-58
- Rosen, R., Hoffman, B. F. 1973. *Circ. Res.* 32:1-9
- Rosner, B. S., Clark, D. L. 1973. *Anaesthesia* 38:564-82; 39:59-81
- Rowland, M., Benet, L. Z., Graham, G. G. 1973. *J. Pharmacokinet. Biopharmaceutics* 1:123-36
- Ryley, J. F., Betts, M. J. 1973. *Advan. Pharmacol. Chemother.* 11:221-94
- Sasner, J. J. 1973. In *Marine Pharmacognosy: Action of Marine Biotoxins at Cellular Levels*, 127-78. New York: Academic
- Scheline, R. R. 1973. *Pharmacol. Rev.* 25:451-524.
- Schroeder, M. A. 1973. *Essays Toxicol.* 4:108-218
- Seelig, M. S. 1973. *Am. J. Clin. Nutr.* 26: 657-72
- Severs, W. B., Daniels-Severs, A. E. 1973. *Pharmacol. Rev.* 25:415-49
- Shulgin, A. T. 1973. *Lloydia* 36:46-58
- Silverman, M., Lee, P. R. 1974. *Pills, Profits & Politics*. Berkeley: Univ. Calif. Press. 403 pp.
- Smith, T. W., Haber, E. 1973. *Pharmacol. Rev.* 25:219-28
- Snyder, S. H., Banerjee, S. P., Yamamura, H. I., Greenberg, D. 1974. *Science* 184:1243-53
- Tappel, A. L. 1973. *Fed. Proc.* 32:1870-74
- Teorell, T., Dedrick, R. L., Condliffe, P. G., Eds. 1974. *Pharmacology and Pharmacokinetics*. New York: Academic. 370 pp.
- Thomas, J. A., Singhal, R. L., Eds. 1974. *Molecular Mechanisms of Gonadal Hormone Action*. Baltimore: Univ. Park Press. 450 pp.
- Thron, C. D. 1974. *Pharmacol. Rev.* 26:3-32
- Tu, A. T. 1973. *Ann. Rev. Biochem.* 42:235-58
- Urquhart, J., Yates, F. E., Eds. 1973. *Temporal Aspects of Therapeutics*. New York: Academic. 213 pp.
- Van Campen, D. 1974. *Fed. Proc.* 33:100-5
- Vinar, O. 1973. *Curr. Ther. Res.* 15: 743-810
- Weeks, J. R. 1973. *Fed. Proc.* 33:37-86
- Weinberg, E. D. 1974. *Science* 184:952-56
- Weisburger, J. H., Weisburger, E. K. 1973. *Pharmacol. Rev.* 25:1-66
- Wilson, D. E., Ed. 1974. *Arch. Intern. Med.* 133:29-146
- Yalow, R. S. 1973. *Pharmacol. Rev.* 25:161-78
- Zimmerman, A. M., Padilla, G. M., Cameron, I. L., Eds. 1973. *Drugs and Cell Cycles*. New York: Academic. 331 pp.