REVIEW OF REVIEWS[1]

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In his smiling account of "The Matthew effect in science," Robert Merton (63), the eminent sociologist of Columbia University, emphasizes the tendency of increasing recognition, and thus greater influence, of those who by good-will or early achievement attract the attention of their peers. This trend fulfills the Gospel according to St. Matthew: "For unto everyone that hath shall be given, and he shall have abundance; but from him that hath not shall be taken away even that which he hath." Even as a boy I thought this unfair. Reviews give a conscientious critic an opportunity to counteract this Matthew effect. Thus they can help to prevent the development of scientific dogma and authoritarianism.

The gap between molecular pharmacology and clinical pharmacology is widening, and reviews for cross stimulation and information may be all that can prevent a split that might be disastrous for both. The difficulty of lack of effective communication between pharmacologists in different phases of the discipline is compounded by the psychological disdain which even the most idealistic feel toward that with which they are unacquainted. Reviews, with critical analyses of the flood of bit-by-bit progress in verifiable pharmacological knowledge, thus are doubly helpful, both in bridging the communication gap between different intellectually oriented pharmacologists, and in breaking down the psychological barrier against the unfamiliar.

The problem goes deep: molecular pharmacologists feel that they are the real scientists in acquiring the basic knowledge of drug action, while clinical pharmacologists feel that they are the practical workers in determining actual status of drugs. Both tend to neglect significant applications of pharmacology in the health professions and services beyond medicine, as in agriculture, agronomy, sociology, ecology, warfare, law, and public policy. Pharmacology is a complex and broad scientific discipline and its applications are increasingly extensive. Pharmacologists must, if they are to justify their social responsibilities, increasingly broaden their general cultural and philosophical bases. Reviews of current progress help.

General

Currently there is much interest in drug compendia. The American Medical Association may aid greatly in clarifying commercial drug claims by its

[1] This review covers current publications to July 1968.

coming volume on *Drug Evaluation.* The Food and Drug Administration is considering a similar compilation which would have administrative authority. ***Physicians Desk Reference,*** a frankly biased drug manufacturers manual, is slowly being discredited, in spite of its slick appeal to busy physicians. An excellent loose-leaf drug monograph service has been developed by the American Association of Hospital Pharmacists. Under the title of *American Hospital Formulary Service,* it has been adopted by the U.S. Public Health Service, by the Veterans Administration, and by the American Hospital Association. It covers over 1000 old and new drugs, with nonproprietary as well as trade names, with full information on physico-chemical properties, absorption, fate, and excretion, local and general biological reactions, uses, toxicity, and preparations for dispensing. With a bit more careful editing and critical organization of information, this service could become quite satisfactory.

Many major American hospitals and health centers are developing efficient drug information centers. Many of these are well provided with skillfully arranged files of pertinent information on individual drugs as furnished by Paul de Haen of New York City. His concise annual *The New Products Parade* is an important statistical analysis of current trends in drug development and use.

For physical and chemical data on drugs, no reference source surpasses *The Merck Index,* now in its 8th edition, as edited by P. G. Stecher and colleagues (91). Covering more than 10,000 compounds, this gives clear information for identification, including tradenames and patent references. It is, unfortunately, skimpy on physiological and toxicological data, but indicates usage.

With regard to drug standards, Feldman (30), with 18 references, considers the influence of formulation on the biological activity of standardized drug products. Latiolais, Shoup & Thur (53) offer revised data on the stability of drug concentrates after reconstitution in various diluents. Some 360 drug preparations are included.

Evaluation of human experimentation with drugs continues, but with emphasis on technical details rather than with moral speculation. An historical perspective is offered by Dowling (25). The difficulties with placebos in clinical investigation are considered by Kirkendall (50). Nielsen (67) reviews correlations between animal and human findings in drug appraisal.

A critical survey of animal and clinical pharmacological techniques in drug evaluation has been edited by Siegler & Moyer (88). This comprehensive volume includes 83 contributions by 107 competent workers, and ranges from considerations of efficacy, through computer methodology, histo-chemical techniques, and measurement of pain, to details of evaluating different types of drugs for various clinical uses. The São Paulo review of clinical pharmacology was edited by Richards (81).

In a general survey of the molecular basis of drug action Mautner (60), using 150 references, discusses the physical nature of receptors and the use

of antimetabolites as tools for the study of drug-receptor interactions. He analyzes protein structure in relation to "structured water," and to "quaternary structure," which describes the arrangement of subunits within the make-up of macromolecules. Models are offered of flexible active-site mechanisms, as well as of regulatory changes in allosteric molecules in relation to molecules of substrate, of inhibitors, and of activators. Ariens (2) edited the São Paulo discussion on physico-chemical aspects of drug action.

Absorption and Fate

Ballard (4) reviews well the biopharmaceutical factors in sub-cutaneous and intramusuclar drug administration. In considering oral inhalation aerosols, Blaug & Karig (9) emphasize that absorption is more rapid with small particle size.

A comprehensive analysis of the movement of molecules across cell membranes was made by Stein (92), with a review of the anatomy of plasma membranes and the permeability properties of a bilayer of lipid molecules. Simple diffusion is related to "pore" models. The kinetics of facilitated diffusion are discussed, as well as co-transport and active transport. Pinocytosis is unwisely neglected as a factor in the ingestion of macromolescules into cells. The transport of inhalation anesthetics, carbon-dioxide, and glucose across red blood cell membranes was analyzed by Greene & Cervenho (39). Electrolyte transport and the pharmacology of diuresis were reviewed in the São Paulo symposium edited by Beyer (8).

Using 122 references, Dirheimer (24) succinctly reviews metabolic transformation of drugs with special reference to oxidations, reductions, methylation, demethylation, and desulfuration. An especially comprehensive and detailed review of the metabolism of drugs used in anesthesia was made by Greene (38). This covers 370 references, and ranges from enzyme induction and inhibition, through microsomal mechanism, and chemical reactions, to details of the metabolism of the whole gamut of specific drugs used by anesthetists. A special survey of the metabolism of vitamin A, with 184 references, is offered by Olson (70). This includes considerations of the conversions of carotenoids; the hydrolysis of retinyl esters; retinol absorption, transport, and excretion; and the function of vitamin A. For the latter there is no clear and simple explanation.

Enzymes

The pharmacological implications of microsomal enzyme induction are well reviewed by Conney (18), referring to 379 contributions. Some 200 drugs of all sorts, which are lipid soluble at pH 7.0 to 7.2, can stimulate the drug-metabolizing activity of liver microsomal enzymes. In particular, this occurs with halogenated hydrocarbon insecticides. Remmer and associates (80) report on reactions of drugs with microsomal liver hydroxylase.

De Matteis (21) carefully reviews drug-induced disturbances of liver porphyrin metabolism, with reference to barbitals, sulphones, estrogens, hy-

dantoins, and chlordane. Guroff and colleagues (40) survey hydroxylation, and the incorporation of atmospheric oxygen into a variety of substrates by oxygenases. A review of the origin and function of penicillinase is offered by Pollock (74).

Chemotherapy

The chemotherapy of viral infections was reviewed by Appleyard (1). Busch & Lane (11) prepared a comprehensive review of current chemotherapy with emphasis on penicillins, tetracylines, antiviral agents, sulfones, cancerostatics, protozoacides, anthelminthics, and fungicides. Martin & Wellman (59) offer a comprehensive review of clinically useful antimicrobial agents, while Fekety (29) appraises the clinical pharmacology of new penicillins and cephalosporins. Cohen (15) carefully considers drug treatment of tuberculosis, with attention to isoniazid, streptomycin, and para-ammino-salicylic acid, together with their derivatives, ethambutol, and antibiotics. The thiosemicarbazones are disappointing. The São Paulo session on mechanisms of action of anti-parasitic drugs was edited by da Silva & Ferreira (20). The chemotherapy of viral diseases is especially well covered by Prusoff (75), using 372 references, and giving details on methisazone, interferons, and amantadine.

A Ciba Foundation Symposium, edited carefully by Wolstenholme (100), was devoted to interferons on the 10th anniversary of their discovery, and was arranged by Alick Isaacs (1921–1967), their discoverer. It includes data on statolon as an inducer of interferons, on the production and purification of interferons, on the mode of interferon action, and on the effects of various carcinogenic agents on interferon production. Interferons of molecular weight around 30,000 have been highly purified, and are extremely active, but little of their protein structure can as yet be clarified.

Cancer chemotherapy seems to be turning toward immunotherapy and immunoprophylaxis. This trend is discussed by Southam (90). The São Paulo session on immunopharmacology is edited by Schild (85). Natural products are being explored for clues to cancer therapy. Hartwell (41) has surveyed plants used against cancer, and Bernard (7) has reviewed the treatment of leukemias and related diseases by natural products.

Hormones

The hormonal control of carboyhydrate and lipid metabolism with changes induced by various drugs, is discussed by Senft (87). A symposium on plant growth regulators was arranged by Fredrick (33), in which sessions were devoted to auxins, gibberellins, kinins, and flowering hormones.

A symposium on thyrocalcitonin was opened by Pecket (73). Here Copp (19) reviewed hormonal control of hypercalcemia, while Munson & Hirsch (66) evaluated the pharmacological data involved. Field (31) reviewed proposed mechanisms of action of thyroid-stimulating hormone. Vaes (94)

well surveyed biochemical mechanisms with cytological correlations in regard to bone resorption and the parathyroid hormone.

Much current interest centers in prostaglandins. Described three decades ago by U. S. von Euler, they occur in seminal fluids, and are formed from arachidonic acid. Reviewing them himself, von Euler (*27*) indicates that some 13 have been isolated and characterized. They are related to prostanoic acid formed in semen and also in lungs and brains. They are peripheral vascular relaxing agents, reducing blood pressure and relaxing uteri. In a short review, Hinman (46) suggests that the six primary prostaglandins are derived from essential fatty acids, and that they both potentiate and inhibit various enzymes and hormones. Bergström (5) has given the most satisfactory short reviews of the prostaglandins, one with 48 references, for scientists generally; the other, with Carlson / Weeks (6), with 344 references, for pharmacologists. The prostaglandins are tri, tetra, and penta eicosa-enoic acids, with high concentration in kidney and liver. Their activity on smooth muscle is coupled with oxidative metabolism. They disappear on circulating through lungs. A full book-length survey of the prostaglandins has been made by von Euler & Eliasson (28). The revelation of their structure and biosynthesis must rank as one of the great achievements of biomedical research.

Nervous System

With regard to central nervous system stimulants, Kosman & Unna (51) relying on 87 references, find that methamphetamine differs from *dl*- and *d*-amphetamine in that it depresses learning and performance. The central nervous system effects of analgesic drugs were thoroughly explored by Radouco-Thomas and his colleagues (76), with special attention to electrical responses, neuroendocrine effects, synergisms and antagonisms, influence on behavior dependency, and mode of action. The analgesic effects of morphine and codeine in tolerant and nontolerant animals were discussed by Johannesson (49). Way (95) continues his previous clear reviews of the distribution and metabolism of morphine and its surrogates. De Wied (*22*) well surveys the relation of chlorpromazine to endocrine function, with reference to pituitary glands, indicating that the pituitary effects are due to adrenergic action of the drug.

Opioid antagonists are carefully reviewed by Martin (58). This subject has developed broadly since the initial California reports of McCawley & Hart (61) in 1941 regarding N-allyl normorphine. Martin discusses data on chemical structures; metabolism; agonistic actions as analgesics; antagonistic effects; respiratory, cardiovascular, and neurophysiological actions; clinical uses; and diagnostic use to detect morphine or heroin dependency.

Increasing attention is being given to the pharmacology of anesthetic agents. Molecular forces operating in anesthesia are well reviewed by Schoenborn & Featherstone (86). Garfield and associates (34) offer a

pharmacological analysis of the ganglionic actions of ether, halothane, cyclopropane, and nitrous oxide. Ether has no effect on the response to post-ganglionic stimulation, but depresses the response to pre-ganglionic stimulation, an effect potentiated by atropine. Halothane and cyclopropane also depress response to preganglionic stimulation. Nitrous oxide has no effect of this sort. Krantz & Rudo (52) fully describe the fluorinated anesthetics, with particular attention to halothane. There are some 46 such compounds, of which many are mixed ethers. Krantz himself has been the pioneer in their study. Parbrook (72) reviews levels of nitrous oxide analgesia. Zipf (102) surveys proposed mechanics of action of local anesthetics. The São Paulo session on the pharmacology of pain was edited by Lim (55).

Regulations of metabolism by the sympathetic nervous system are fully reviewed by Himms-Hagen (44), with reference to 806 contributions. The calorigenic effect of catecholamines is analyzed, as well as the effects of epinephrine and norepinephrine on lipid, carbohydrate, and protein metabolism. The uptake and subcellular distribution of catechol amines, and their alphamethylated analogues is described by Lundborg (57). A short review of beta-adrenergic blocking agents is given by Slater (89), while Moran (64) edits a broad discussion of new adrenergic blocking agents. Ginsborg (35), in reviewing ion movements in junctional transmission, explains the action of many excitatory substances on the basis of opening pathways through membranes for N^+ ions, while inhibitory compounds seem to favor routes for K^+ and Cl^- ions. The São Paulo symposium on monoamine oxidase inhibitors was edited by Cheymol & Boissier (14).

Hoffer & Osmond (47) recapitulate their ideas on the chemistry, pharmacology, and toxicology of all known hallucinogens, with much emphasis on lysergic acid diethylamide. Cole (16) moderated a discussion on butyrophenone compounds showing promise in treating schizophrenia. A broad symposium on amines in relation to schizophrenia was edited by Himwich, Kety & Smithies (45), in which aberrant transmethylation of catecholamines and indoles was considered. The urines of schizophrenics seem to contain dimethoxy-phenylethylamine.

Livingston (56) offers much detail on a wide variety of anticonvulsant drugs, with much on metabolism and untoward reactions. With 175 references, Wittenborn (99) analyzes the clinical pharmacology of anxiety, with careful critique of the use of clinical data, taking experience with oxazepam as an example.

Miscellaneous

Cardiovascular drugs.—Page (71), to whom the initial award of the important AMA Sheen award was deservedly made, summarized well a symposium on renin mechanisms and hypertension. The São Paulo symposium on vaso-active polypeptides, chiefly bradykinin and its relatives, was edited by Rocha e Silva & Rothschild (83). This included discussions on structure,

precursors, activation, biological activity, and pathological significance. Mercer & Osborne (62) surveyed the current status of diphenylhydantoin in heart disease. Reid & Chan (79) discussed a difibrinating anticoagulant, from Malayan Pitviper venom, the pharmacology and toxicity of which were reviewed by Ashford, Ross & Southgate (3). Wenzel (97) reviewed drug induced cardiopathies. Born (10) edited the São Paulo discussion on drug effects on blood coagulation and thrombosis.

Histamine.—Rocha e Silva (82) uses an historical approach in editing a comprehensive survey of the chemistry, metabolism, and biological effects of histamine. Green (37) uses 99 references in reviewing histamine uptake and binding. Colldahl (17) edits a symposium on inhalation tests in allergy diagnosis.

Anti-inflammatory drugs.—Erdös (26) considers the effects of nonsteroidal anti-inflammatory drugs in endotoxin shock, while Goth (36) appraises the interaction of these agents and carbohydrates with mast cells. Jacob & Wood (48) offer a brief review of the pharmacology, toxicity, and clinical use of dimethylsulfoxide (DMSO). Using 108 references, O'Brien (69) surveys clinical trials with indomethecin, and concludes from the severity of side-effects that there is no clear reason for preferring it over aspirin in rheumatoid arthritis. Whitehouse (98) reviews possible mechanisms of anti-inflammatory drug action at biochemical levels.

Metals.—Chenoweth (13), with 251 references, reviews the clinical use of metal-binding drugs, recommending dimercaprol for prompt systemic treatment of As and Hg poisoning, and Ca disodium edetate to relieve chronic Pb symptoms. There are no available antidotes for cadmium, thallium, beryllium, or manganese. Strontium metabolism, with special reference to fallout, is thoroughly surveyed in the discussions of the Glasgow symposium edited by Lenihan, Loutet & Martin (54).

Singles.—Fisher (32) edits a comprehensive symposium on erythropoietin, with 71 contributors, covering assay, standardization, chemistry, sites of production, kinetics of red blood cell production, immunology, and effects of drugs thereon. Diczfalusy (23) reviews well the mode of action of contraceptive drugs and edits the São Paulo Symposium on the pharmacology of reproduction. The action and metabolism of insecticides is fully discussed by O'Brien (68). Experimental carcinogenesis from tobacco and tobacco smoke is reviewed by Wynder & Hoffman (101). The São Paulo session on the pharmacology of growth was edited by Welch (96).

Toxicity

Oxygen therapy and oxygen toxicity are receiving much attention as a result of clinical interest in hyperbaric technology. Haugaard (42) carefully reviews cellular mechanism of oxygen toxicity, particularly in regard to its inhibition of a variety of enzymes, and its oxidation of sulphyldryl and other co-enzymes. Morgan (65) indicates that there is no threshold to

oxygen toxicity, and that it favors free radicle formation. Using 257 references, Hedley-Whyte & Winter (43) offer a comprehensive review of oxygen therapy.

Carbon tetrachloride hepatotoxicity is well reviewed by Recknagel (78) using 351 references. This drug depresses protein synthesis, and results in lipoperoxidation. Chen & Kovarikova (12) survey the toxicity of toad venoms, while Russell (84), with 196 references, surveys the broad range of venomous snakes, arthopods, and marine animals. A discussion on carcinogenic hazards from drugs was edited by Truhaut (93). Raskova (77) edited a survey of mechanisms of toxicity.

In Prospect

As pharmacological review articles increase in significance and interest, it might be wise for a few pharmacologists of wisdom and library skill to consider the preparation of such articles as a worthy professional vocation. Helpful reviews of drug action and use may soon command appropriate recompense. May review writers ever remember that they may become the most satisfactory offset to the Matthew effect.

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