REVIEW OF REVIEWS

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As I undertake the preparation of my tenth attempt to review various reviews of pharmacological interest for *Annual Review of Pharmacology,* I cannot avoid reflecting on the increasing difficulties of adequate reviewing of current scientific advance, as it comes bit by bit, whether in a narrow special area or over a broad expanse. Those who have tried it may agree that it is probably the most exacting intellectual effort in the whole scientific enterprise. Have I been honest, free from bias, and fair in my appraisal of the contributions others have made? Have I skipped anything worth while? Have I been wise in omitting what I think to be inconsequential reports? The answers to these questions are mildly, no. Yet, in regard to pharmacology, I have an abiding sense of learning trends of development of theory and of emerging generalities, and of appreciating the ever expanding complexity of the vast interactions of physico-chemical environments with living material, whether at molecular or ecological levels of biological organization and with all levels between. Thus, in learning there is rich compensation, as there is in trying to share with others what I have learned.

During the past year there has been a flood of pharmacological review material, not only in periodicals, but especially in the growing number of symposium volumes and monographs. Space limitation prevents more than passing notice of much of this material.

GENERAL

An important new general approach to technical pharmacology is the monographic review of principles of drug action by Goldstein, Aronow & Kalman (34). This considers molecular mechanisms in drug-receptor interactions, structure-action relations and conformation of receptor surfaces, analysis of graded dose-response, absorption, distribution and metabolism of drugs, time course of action, toxicity, pharmacogenetics, chemical mutagenesis, and drug screening. It is medically oriented, but could easily be extended to include applications in agriculture, sociology, and environmental contamination. It affords a well documented introduction to current trends in the development of pharmacology. LaVerne (49) introduced *Physicians' Drug Manual,* a monthly visual-chart reference for busy health professionals. It contains helpful bibliographies.

Using 108 references, Wand (87) reviewed our knowledge of pharmacological receptors, discussing types of drug interactions, their relation to effects, competitive antagonists, and classification. He reminded us of Paton's point (69) that response is governed by the rate of drug-receptor combination. An important symposium on the interaction of drugs with subcellular components was edited by Campbell (11), with reference to alkylating agents, antibiotics, mitochondria, protein synthesis, and lysosomes. Krüger-Thiemer (48) surveyed nonlinear dose-concentration relations. Using mathematical models, Wagner (86) as well as Loo & Riegelman (55) considered the intrinsic absorption rates of drugs, proposing methods for calculation. Wagner (85) also discussed drug dosage for infants, children, and adults on the basis of body surface in relation to body weight.

Weber (89) edited a considerable symposium on enzyme regulation, including discussions on control of carbohydrate and fat metabolism, mechanisms of action of steroids, action of vitamin K, activation and feed-back in enzyme effects, enzyme regulation in cancer, and a special session on ethanol effects on metabolic activities of livers. In considering facilitated proton transfer in enzyme catalysis, Wang (88) detailed the significance of zinc in carbonic anhydrase activity. Goldman (33) reviewed metabolic effects of fluoro analogues especially with regard to enzyme inhibition.

Drug interaction is attracting attention: Hartshorn (39) considered classes of drugs in relation to their interactions, especially in anti-infective agents, and also physiological states altering drug response. Morrelli & Melman (65) offered a clinical approach to drug interactions, using 61 references, and emphasizing that adverse reactions to drugs are proportional to the number of drugs given and the duration of administration, and that many mechanisms are involved.

A thorough analysis of prescription drugs and their economic impact was made by a USA task force in the Department of Health, Education & Welfare, under the direction of Lee & Silverman (51). This covered drug distributors, prescribers, and users, and concluded with the bureaucratic recommendation that the Social Security Administration have responsibility for "drug costs, average prescription prices, and drug use", and that there be a study to reappraise methods now used by various governmental agencies to evaluate the safety and effectiveness of drugs, with a registration and licensing system to assure drug production under quality standards. A more scientific approach to fundamental principles of drug evaluation was edited by D. H. & R. E. Tedeschi (80) for some 25 contributions on drug design, metabolism, receptors, action on tissues and organs, and on extrapolations from experimental animals to humans. In a practical way, Asperheim (1) discussed the pharmacologic basis of patient care. Zbinden (92) reviewed experimental programs relating to drug safety, especially as developed by the Food and Drug Administration. It was emphasized that drug toxicology is a living science and not an administrative procedure. Rickels (71) edited a discussion on placebo effects in relation to attitudes of physicians and pa-

tients, while Hartshorn (40) reviewed altered drug response in varying physiological states. In discussing drug allergies, Cruchaud & Frei (14) indicate that drug immunogenicity depends on protein-binding capacity, with wide and diverse clinical manifestations.

CHEMOTHERAPY

Current interest in chemotherapy was well reviewed by Busch & Lane (8), with reference to antibiotics, sulfonamides, cancer control, mechanisms of actions, and the chemotherapy of tuberculosis, of protozoan diseases, and of worm and fungus infections. Goldin, Hawking & Schnitzer (32) edited reviews on statistical methods in chemotherapy, the role of lysosomes, the chemotherapy of trichomoniasis, cestode and trematode infections, and the antimitotic action of polyanions.

Antiparasitic drugs.—The treatment of schistosomiasis with a 2-hydroemetine was reviewed by Blanc & Nosny (4). Brown (6) offered a short review on new and old anthelmintics, using 59 references. Thiabandazole is effective in trichuriasis, strongyloidiasis, and trichiniasis.

Antibiotics.—Old and new penicillins were reviewed by Hoeprich (43), with 56 references. Chemical structures were included, with data on ampicillin and carbenicillin. Milne (63) chaired a conference on penicillamine, with much on its toxicity, including proteinurea, sensitivity, and the nephrotic syndrome.

Contraceptives.—Pointing out that we are still ignorant of causes of ovulation, Dodds (17) reviewed the past and future of oral contraceptives, tracing the current revolution in sexual mores to the brilliant studies of Gregory Pincus (1903–67). In another short review, Mental & Clem (60) note a remarkably active ring compound with NO in appropriate places, and with an unusual metabolic pathway.

Antimitotics.—Gedda, Cardinali & Parisi (31) edited a Rome symposium on hydroxyurea, alkylating agents, methyl-hydrazine, azathioprine, and vinca alkaloids. Taylor (79) opened a conference on vincristine, with discussions on its use in leukemia, Wilm's tumor, and malignant solid tumors in children.

General.—Hilleman (42) in reviewing the control of viral diseases, indicated that there is little promise for effective prophylaxis from interferon, but that much may result from careful study of its inducers. Campbell (10) edited a symposium with nine significant contributions on oral hypoglycemic agents, including structure-action relations, mode of action, and clinical uses. Scholer (73) surveyed the use of sulfonamides in experimental nocariosis, histoplasmosis and blastomycosis. Ernst & Doyle (20) reviewed the physico-chemical factors important in sterilization with gaseous ethylene oxide.

NERVOUS SYSTEM

In the important Paris symposium on pain, edited by Soulairac, Cahn &

Charpentier (77), there are well arranged sections on biochemical bases for analgesia and on psychopharmacology. Kelleher & Morse (47) ably reviewed determinants of specificity of behavioral effects of drugs. With 134 references, Oswald (68) well analysed the effects of drugs on sleep. One to two grams of barbitals are used per person per year in USA, Britain, Czechoslovakia, and Australia. These reduce rapid-eye movement slow-wave desynchronized sleep, as do alcohol and meprobamate, whereas reserpine, chlorpromazine, and imipramine increase this dreamy condition. An important symposium on the effects of drugs on sensory functions was edited by Herxheimer (41). This includes consideration of ototoxic drugs, anti-motion-sickness agents, chemicals which alter color vision and visual thresholds, drugs affecting taste and smell, hallucinogenic compounds, and drugs affecting dreams and sleep.

New information on aspirin action was reviewed by Melmon, Rowland & Morelli (59), with some facetious historical comment. Salicylates increase oxygen consumption and uncouple oxidative phosphorylation. They reduce inflammation in part by preventing kinin formation.

The big Puerto Rico conference on psychopharmacology was well edited by Efron (19). A comprehensive survey of psychopharmacological agents was edited by Gordon (35), with special bibliographies of phenothiazines and meprobamates. An important base from which to study the psychopharmacology of normal humans was provided under the editing of Evans & Kline (22). In this, Berger & Potterfield analyse with 207 references the effects of anti-anxiety tranquilizers on normal behavior. Meprobamate, they conclude, does not alter behavior in normals. Hollister (44), in surveying the current status of the clinical use of psychotherapeutic drugs, with 120 references, lists 53 such agents, giving structures and various names, with data on antidepressants, antianxiety agents, antipsychotics, and some drugs, such as lysergic acid diethylamide, nicotinic acid, and cannabis, in search of disorders in which they might be useful.

The pharmacology of thioxanthenes was reviewed by Lehmann & Ban (52). Related to phenothiazines (with CH_2 instead of NH in the central ring), these compounds, especially chlorprothixene, block autonomic effects of acetylcholine and adrenergics, and enhance tyrosine hydroxylase activity. They are sedative and disrupt active avoidance behavior. They also inhibit the vascular response to histamine.

In the discussion edited by DeBold & Leaf (16) on lysergic acid diethylamide, it was emphasized that effects in humans from this drug are unpredictable from animal studies. Claims that LSD promotes creativity are not demonstrated scientifically or aesthetically, but it seems to cause changes in social attitudes related to those caused by the great religions. Eveloff (23) noted consensus that most subjective manifestations of LSD relate to predrug expectation, hypersuggestibility in group reactions, and loss of characteristic modes of perception and cognition. Predictions of psychotropic drug responses were analysed in a symposium edited by May & Wittenborn (57).

Some predictability seems to result from successive screening, and drug and placebo response seems to be a function of physician-patient type and relationship. The remarkable 1951 outbreak of possible LSD poisoning in Pont-Saint-Esprit was surveyed by Fuller (28), with indication that fermentation in bakers' flour produced by *Claviceps purpurea* was responsible. The biochemistry and pharmacology of methyldopa was reviewed by Stone & Porter (78) and with reference to related compounds.

Anesthesia.—Vandam (84) edited a comprehensive symposium on anesthesia in relation to the autonomic nervous system, in which there are many excellent reviews, such as those on beta-adrenergic blocking agents; on anesthetic-adrenergic arrhythmias, and by Zaimis (91) on vasopressors and catecholamines. An example of worthy clinical pharmacology is the review by Michenfelder, Gronest & Rehder (61) with 359 references on anesthesia for neurosurgery. Siegel (74) with 234 references offered a good review on the relation to anesthesis to myocardial contraction. Greene (36) edited a comprehensive monograph on halothane. Fink (24) edited 26 reports on various aspects of the toxicity of anesthetics as discussed at the Seattle conference.

Alcohol.—The pharmacology of alcohol was reviewed by Forney & Hughes (25) and then in combination with other depressants, with caffeine and amphetamine, with anticoagulants, and with hypoglycemic agents. A short review on the biochemical pharmacology of alcoholism was made by Truitt & Walsh (83). Large amounts of ethanol cause metabolic shifts in brains and livers, with resulting accumulation of acetaldehyde, the unpleasant effects of which may be temporarily concealed by ingesting enough more alcohol to depress sensation, thus setting up a vicious cycle.

Amphetamine.—Those vigorous organizers, Garattini & Costa (29) edited a very comprehensive Milan symposium of 59 contributions to knowledge of amphetamines and related compounds. This dealt with the biochemorphology of such agents, including those halogenated; their distribution and metabolism; their interaction with biogenic amines and the significance of such interaction; effects on the cardiovascular system, on food intake and lipid metabolism, and on the central nervous system, both experimental and clinical. Very disconcerting has been the amazing extent of recent abuse of methamphetamine ("speed", by vein). The warnings I made (50) in 1958 were mild in the face of the realities now. Smith (75) has reviewed high dose methamphetamine abuse, and Meyers (62) has offered general recommendations for treatment and research facilities for studying drug abuse, with special reference to methamphetamine.

Autonomic nervous system.—Costa, Cote & Yahr (13) edit a review volume on the biochemistry and pharmacology of the basal ganglia, with reference to cholinergic and adrenergic functions, while Trendelenburg (82) discussed advances in the pharmacology of autonomic ganglion cells. Wurtman & Zigmond (90) reviewed the use of pharmacological tools in autonomic nervous system research. The actions of sympathomimetic amines and their

antagonists on skeletal muscle were well reviewed by Bowman & Nott (5). Epinephrine has a direct effect via beta-receptors. There are 358 references in this important review. The beta-receptor blocking action of propranolol was well surveyed by Fitzgerald (26), using 64 references. In comparing the potency of 11 related compounds, oxprenolol was found to be twice as effective as propanolol in inhibiting a standard isoproterenol tachycardia in dogs. Nayler, Chan & Lowe (67) surveyed beta-adrenergic antagonists in relation to the control of cardiac arrhythmias.

Cardio-vascular-renal Drugs

The clinical pharmacology of digitalis glucosides was reviewed by Doherty (18). In reviewing the site and mechanism of action of mercurial diuretics, Cafruny (9), with 191 references, concludes that these agents block sodium reabsorption at all sites where this ion is actively transported, and that the mechanism involves mercury effects on sulfhydryl renal enzymes, none of which have been identified. The local regulation of blood flow is controlled by metabolically linked vasoactive chemicals, according to Haddy & Scott (38), quoting 216 references.

Jenden & Fairhurst (46) well review the pharmacology of ryanodine, using 155 references. This is a five membered ring compound with a single tertiary nitrogen, obtained from *Ryania speciosa Vail,* the roots and stems of which are used as insecticides in Trinidad. It inhibits creatine phosphoryltransferase, causes irreversible contracture of skeletal muscle, and has a negative inotropic effect on mammalian heart muscle in low concentrations. In a full review of the control of resistance, exchange, and capacitance in the peripheral circulation, Mellander & Johansson (58) indicate that relaxation of large arteries, dilation of capacitance vessels, and venodilation can lead to an unloading of the heart, which may explain the effects of nitrites in relieving angina pectoris. This suggests that the pain in this condition may be due to pericardial stretch rather than to cardiac ischemia, and that the nitrites relieve acute anginal pain by unloading the heart and reducing pericardial stretch. Torrance (81) edited the efforts of 40 contributors to a symposium on arterial chemoreceptors. This includes discussion of their structure and responses, their biochemical, biophysical and circulatory aspects, and of the reflex effects they cause.

Hormones

In an exceptionally informative review, Berde & Boissonnas (3) with 161 references tabulate 146 analogues and homologues of neurohypophysial hormones derived from the seven naturally occurring ones. These occur from fish to mammals and range in molecular weight from 966 in ichthyotocin to 1084 in arginine vasopressin. Synthetic derivatives range from 739 to 1435 with varying degrees of oxytocin and vasopressin activity. Deane & Rubin (15) edited a volume on adrenocortical hormones, covering aldosterone se-

cretion, control of ACTH secretion, hypersecretion of sex steroids and of glucocorticoids. In reviewing the pharmacological alteration of steroid hormone function, Gaunt, Steinetz & Chart (30) using 160 references conclude that there are many vulnerable sites for such action but that the number of safe and effective drugs for such effects are small. Interference with steroid hormone function is common with insecticidal types of drugs, but interference with gonadal steroidogenesis is rare.

Levine & Pfeiffer (54) edited the Milan conference on insulin secretion. Margoulies (56) edited the Liege symposium on protein and polypeptide hormones, considering assay by radio-immunology, effects on cellular metabolism, biochemorphology, and mode of action on transport of ions, glucides, amino acids and lipids. In reviewing effects of sex steroids on pregnancy and development, Saunders (72), with 398 references, concludes that endogenous estrogens and progestins must be kept in balance for normal course of pregnancy. The review considers estrogens, androgens, progestins, and corticoids in relation to interruption of pregnancy, antifertility, prolonged gestation, fetal masculinization and feminization, and teratogenesis.

Miscellaneous

Bull, Culvenor & Dick (7) fully review the pyrrolizidine alkaloids, rejecting the idea that they are hepatocarcinogens. In a survey of the pharmacokinetics of heparin, Estes, Pelikan & Krüger-Thiemer (21) conclude that its uptake by the reticulo-endothelial system makes reliable dose schedules difficult. Foa (27) well reviewed information on glucagon. James (45) analyzes data on antilymphocytic antibody. In a comprehensive review of the pharmacology of amino-acids, Milne (64) offers analyses of absorption, transport, distribution, excretion, deficiencies, and toxicities. LD_{50} estimations in rats run from 8 m.mols per Kg for tryptophan to 57 for alanine. Smith (76) edited a symposium on the use of drugs in animal feeds.

Toxicology

In reviewing drug-induced hemolytic anemia, Bentler (2) with 188 references reveals the wide range of drugs which may produce this situation as a result of possible deficiency of glucose-6-phosphate dehydrogenase, a condition found in a few sensitive people. The various adverse effects (unsought action, often toxic) which may come from the use of a very wide range of chemicals in many medical procedures were thoroughly explored in a comprehensive symposium volume edited by Moser (66). Haberman (37) explored the biochemistry, pharmacology, and toxicology of the active principles of the various hymenoptera poisons. Christenson (12) helpfully reviewed the stability of bis(4-hydroxy-imino-methyl-1-pyridinomethyl) ether dichloride ("Toxogonin"), the most efficient antagonist of organophosphorus cholinesterase inhibitors in various insecticides and "nerve gas" chemical warfare agents. The Utah sheep-poisoning episode and the attempt

to move large amounts of chemical warfare agents for dumping into the Atlantic Ocean have aroused much public concern over the whole problem of chemical warfare.

In Prospect

Looking back on the rapid progress of pharmacology with its trends for future development can best be done through critical reviews. Increasingly, inspiration can be obtained from historical and biographical accounts of great pharmacologists. Autobiographical essays give much insight into ways of thought which can be very stimulating to younger research workers, as illustrated by the fine writings featured in each issue of *Annual Review of Pharmacology*. The great influence of Otto Loewi (1873–1961) in pioneering in cholinergic nervous activity has been fully documented by a notable biography prepared by Lembeck & Giere (53). With its reviews, histories, and biographies, pharmacology is reaching a lasting plateau of maturity which assures its increasing dignity among the major sciences.

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