REVIEW OF REVIEWS[1]

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Pharmacology is maturing as a theoretical as well as an empirical science. Significant conceptual formulations are emerging by skillful induction from the huge mass of verifiable factual data accumulating from search and research on drugs. Much of this synthesis of theory is appearing in the increasing number of review articles dealing with various current problems of pharmacological interest. Surveys of pharmacological data-trends are thus becoming more and more helpful for orientation. Brodie and his group (12) agreed on the need for such reviews, especially in toxicology.

There are now several annual review volumes relating to pharmacology. Gordon (61) edited the first of a series of projected volumes on *Psychopharmacological Agents*, including reviews of monoamine oxidase inhibitors, meprobamate, and benactyzine. The second volume on *Molecular Pharmacology* was edited by Ariëns (2) with reviews of molecular factors in olfaction, molecular bases of cancer chemotherapy, and receptor theory in enzyme action. The third volume of *Advances in Pharmacology,* edited by Garattini & Shore (52), contains surveys of drug dependence, drug control of reproduction, antianginal agents, and pharmacological aspects of helminth infestations, the adrenergic system, and Parkinsonism.

General Aspects of Pharmacology

The proceedings of a Baltimore conference on Drugs in our Society were edited by Talalay (132). Some twenty-one contributors discussed past and present phases of therapeutics, drug effectiveness and safety, roles and responsibilities of the drug industry and government, drug advertising and economics, and various sociological, legal, and ethical considerations of drug use. The comments are largely explorative.

Potential chemical interactions with environments (ecological pharmacology and toxicology, as it were) are well treated as a basic problem in scientific integrity by Commoner and his associates (22). Their discussion concerns pesticides, pollutants, detergents, and radiation fallout. Air pollution as a major systems problem more challenging than moon-probing is well analyzed by Tilson (136).

Drug names remain crucial in exploitation. Nonproprietary drug names are well treated by Jerome & Alessandri (76). Confusing is the multiplication of trademark names for the same chemical substance. Drug manufacturers and distributors might be wise to identify their particular product by

[1] The survey of the literature pertaining to this review was concluded in July 1965.

adding their own company name to the public name, thus directly linking the drug to its source and to its quality control. This might help to curtail the growing black-marketing of counterfeit trademark drugs. Public names for drugs are now agreed upon by the USAN (United States Adopted Names) Council, a nomenclature committee sponsored by the American Medical Association, the American Pharmaceutical Association, and the United States Pharmacopeia. The designation USAN distinguishes such formally adopted nonproprietary names from other names. The USAN Cumulative List now contains 404 USAN's.

Problems of drug development were considered by Lasagna (87), in reference to interrelations of governmental agencies, the drug industry, universities, and the health professions. An important economic factor in drug development is the increasing legal tendency toward "strict product liability," which means that drug manufacturers are becoming increasingly liable for their products, in damage suits, whether the drugs are wisely handled or not by any intermediary.

Publicity releases in connection with the recent revision of the United States Pharmacopeia invite comment. Members of the United States Pharmacopeia Revision Committee seem to think it their duty to pass judgment on the efficacy and safety of drugs. Historically and practically, a pharmacopeia is a reference source for drug standards, designed to furnish reliable information for the identification and estimation of purity of any material offered as a drug with a public name. Such standards should be available for all drugs which are commonly used. Successive editions of United States Pharmacopeia might give such information for new drugs coming into common use, with cumulative index referring to drugs described in previous editions. Thus, standards could be continually maintained for the benefit of members of the health professions and of drug manufacturers.

As an aid in the identification of certain complex drugs, Tuch (137) reviewed electron-spin resonance spectroscopic methods. Whittet (146) surveyed factors affecting drug stability, listing 77 citations.

Principles of Experimental Pharmacological Research

Ther (134) evaluated over 2300 publications dealing with general and specific problems of pharmacological research. Toxicity tests are covered in detail, with much information on measuring and recording instruments, as well as with biochemical testing methods, operative procedures with experimental animals, and isolated organs. Accounts are given for studying embryonic toxicity, carcinogenesis, tolerance, addiction, and pathological effects. A comprehensive compilation of screening methods in pharmacology was also made by Turner (138).

An ambitious effort in "pharmacometrics" was organized by Laurence & Bacharach (89). This consists of 41 contributions, of which the first seven cover general principles of methodology and statistics, limitations of animal testing, toxicity testing, and drug dependence. The others deal with

drug actions on the basis of target organs and tissues. There is an appendix on organ-bath solutions.

Roberts (111) discussed ethical considerations in the use of animals for medical research. Kisch (81) organized a symposium on new drugs and their control by government, industry, and the health professions. Steinberg (128) edited a Ciba Foundation Symposium on animal behavior and drug action, with discussion of the dangers of extrapolation to humans. Lasagna (88) reviewed advances in drug research. Zaimis (148) edited much material on the evaluation of new drugs in humans. Feinstein (44) reviewed scientific methodology in clinical medicine with reference to therapeutic responses to drugs. Oberholzer (101) surveyed clinical testing of new drugs, and Herrick & Cattell (71) edited a symposium on the same subject, covering preclinical testing, the responsibilities of clinical investigators, clinical trials, and evaluation of results. Appendices give governmental regulations and points of view. Done (33) analyzed the influence of immaturity on drug effects and drug metabolism, referring especially to sensitivity factors. This review lists 417 publications on the subject.

Drug Absorption, Metabolism, and Excretion

Fisher & Griffin (48) surveyed pharmacogenetic aspects of gustation, pointing out that the bitter taste of drugs and poisons has survival value, and also indicating threshold taste variations in a population, with Gaussian distribution for such bitter-tasting substances as quinine. Finkelstein (46) offered a carrier model for active transport of ions across a mosaic membrane. Gibaldi & Kanig (55) reviewed the absorption of drugs through the oral mucosa. Schmidt (118) opened a considerable symposium on enteric resorption. Sögnen (124) surveyed calcium-binding substances in relation to intestinal absorption. Spencer (127) reviewed the variation of intestinal activity with age, indicating the significance of this factor in drug absorption from the gut.

Important in any pharmacological understanding of drug metabolism is information on biological oxido-reductions. This matter was well received by Eruster & Lee (41). The general metabolism of toxic substances was considered by Shuster (122). Randle (109) discussed the interrelations of hormones, fatty acids, and glucose in providing energy. Coons (24) analyzed current developments in understanding iron metabolism.

Biological secretion and excretion at cellular levels was treated in a symposium edited by Wohlfarth-Botterman (147). This included discussions on comparative aspects of vertebrate salivary glands, protein secretion in the pancreas, the function of the Golgi-apparatus, pinocytosis in amebae, the physiology of salt glands, and urinary excretion.

Mechanisms of Drug Action

Experimental models of drug-receptor binding were offered by Gero (53). Macromolecular systems incorporating reversible electrochemical

groups were reviewed by Lindsey (91). A symposium on cellular injury, edited by deReuck & Knight (31), included a discussion of the mechanism of cellular toxicity by alkylation of cell components, and consideration of the action of such endotoxins as "leucocidin."

Paintal (104) reviewed the effects of drugs on vertebrate mechano-receptors, referring to 335 reports. Included are discussions on local anesthetics, epinephrines, acetylcholines, veratrum alkaloids, general anesthetics, 5-hydroxytryptamine, histamine, bradykinin, and the action of guanides on nonmedullated nerve fibers.

Horowicz (74), with 178 references, reviewed the effects of anions on excitable cells. He discussed action potentials, mechanical responses, and excitation-contraction coupling of the lyotropic series in amphibian skeletal muscle. There is further analysis of the effects of substitutions for the chloride ion with reference to membrane conductance, chemoreceptors in nerves, and in cardiac and smooth muscle. Discussions of mechanisms of drug toxicity were given by Brodie and his colleagues (12).

Allergy

The relation of lysozyme to allergy was reviewed by Brown (13). Carr (19) arranged a symposium on allergic responses to drugs, in which there were discussions on contact hypersensitivity, circulating antibodies, and immunologic unresponsiveness. Penicillin hypersensitivity was considered along with immunological mechanisms involved in penicillin allergy. Hahn & Giertz (65) opened an extensive symposium on pharmacological aspects of allergy. In considering the pharmacology of immunity, it would be helpful to refer to Fischer's review (47) of theories of antibody formation.

Polypeptides and Enzymes

Astwood & Beck (3) edited the proceedings of a conference on polypeptides and proteins with reference to pituitary hormones, hypothalamic peptides, corticotropin, angiotensin, and plasma kinins. Biological and medical studies on synthetic peptides of the neurohypophysis type were reviewed by Berde & Cerletti (7). Dahlström (28) edited a symposium on thrombolytic therapy with streptokinase and urokinase. Fitzpatrick & DiCarlo (49) reviewed 189 reports on "zymosan," a crude yeast-wall preparation consisting of protein-carbohydrate

The status of synthetic, physiologically active polypeptides was examined by Schwyzer (120).

Jorpes (78) revealed the early history of heparin, while Freeman (50) reviewed its structure and biological activity, and Engelberg (40) considered its relation to the removal of triglyceride from blood. Current knowledge of erythropoietin was reviewed by Keller (79). Practical aspects of enzyme preparations in clinical medicine were discussed by Hayaishi (68).

VITAMINS

Herbert (70) reviewed folic acid. With data from 166 reports, Johns & Bertino (77) discussed the absorption and metabolism of folates in relation to megaloblastic anemia, going over 19 natural folates as microbial growth factors. Olsen (102) arranged a symposium to consider the relations between vitamin K, coenzyme Q, and selenium. Olson (103) briefly reviewed the biosynthesis and metabolism of carotenoids and retinol.

Holtz & Palm (73) reviewed pharmacological aspects of vitamin B_6, giving 568 references. The active form is pyridoxal-5-phosphate, which acts as a coenzyme necessary for all nonoxidative metabolic reactions of amino acids, as well as for decarboxylation and transamination. It is a cofactor of phosphorylase. There are manifold effects from its deficiency. It is an active biocatylist by virtue of its high chemical reactivity. Many drugs interfere with its wide range of activity. It is readily inactivated by hydrazides.

CHEMOTHERAPY

Schwartz (119) reviewed the chemotherapy of immunologic disease with regard to possible mechanisms. Stuart-Harris & Dickinson (129) offered an extensive monograph on an approach to the chemotherapy of virus disease. The status of anticalculus agents was analyzed by Weinstein & Mandel (143). Deter & Liebelt (32), citing 112 reports, suggest gold-thioglucose as an experimental tool for chemotherapeutic studies on inhibiting sulfhydryl.

Antibiotics.—Darken (29) reviewed puromycin inhibition of protein synthesis, giving 102 references. This antibiotic localizes at ribosomal sites, and blocks the formation of polypeptide chains. Brumfitt & Williams (15) edited the proceedings of an international conference on new penicillins, opening with a discussion on their biological characteristics, and going on to details of therapy.

It is interesting that the only significant recent review of a drug used for diagnosis should involve an antibiotic. Sandlow & Necheles (115) described the use of tetracycline in detecting cancer of the stomach. Oral doses of 500 mg, four times daily, are given for two days, with gastric washings taken 26 hours later. The smallest pinpoint of bright yellow fluorescence is positive for malignancy.

Cancer.—Tannenbaum (133) offered a monograph on the use of urethane in studying carcinogenesis. Bun-Hoi (16) surveyed recent studies on chemical carcinogenesis by polycyclic and heterocyclic hydrocarbons. Cromwell (26) well analyzed chemical carcinogens, carcinogenesis, and carcinostasis.

Brown (14), citing 387 references, reviewed nitrogen mustards and related chelating agents with regard to protein synthesis and glycolysis. The toxicity and clinical use of sulfur mustards, sulfonic esters, ethylene im-

ines, and ethylene oxides were discussed. Henderson & Mandel (69), with 320 citations, considered purine and pyrimidine antimetabolites in cancer therapy. They discuss toxicity, metabolism, resistance, and the mechanism of action by inhibition of nucleotide synthesis, protein synthesis, and the action of coenzymes. Cyclophosphamide ("Cytoxan") and its use in cancer therapy and in the suppression of cellular immunity were well reviewed by Fairly & Simister (42), who gave over 800 references.

Autonomic Drugs

Catecholamines in the urine may be used quantitatively to judge mental stress, according to a short review by von Euler (142). Kosterlitz & Lees (84) offered a pharmacological analysis of intrinsic intestinal reflexes. They cite 225 references in explaining actions of ganglion-blocking drugs, local anesthetics, catecholamines, 5-hydroxytryptamine, atropine derivatives, morphine compounds, adrenocortical hormones, anoxia, and cooling. Nickerson (99) discussed adrenergic regulation of cardiac performance.

Autonomic drugs and enzymes.—Haugaard & Hess (67) analyzed the effects of autonomic drugs on phosphorylase activity and function, referring to 220 reports. They indicate the significance of this enzyme in muscle and heart action and in brain function. Ellin & Wills (36) reviewed oximes antagonistic to inhibitors of cholinesterase, giving 143 references, and data on the metabolism of these compounds. Kopin (83), with 86 citations, analyzed factors in the storage and metabolism of catecholamines. Substrates for monamine oxidase are involved in deamination of many amines. Epinephrine is inactivated by catechol-O-transferase, while tissue stores of norepinephrine include many bound forms. A short review of monamine oxidase inhibitors, using 49 reports, is offered by Goldberg (59), with special reference to adverse reactions.

Specific autonomic drugs.—Von Euler (141) edited a comprehensive monograph on alkaloids derived from tobacco, including their chemistry, their action on cells and organs, their distribution and metabolism, and their effects on catecholamines. Thomas (135) surveyed the history and uses of curare. Sokoloff (125) reviewed the biological activity of serotonin. Green (64) opened a discussion on histamine and the nervous system, with consideration of histamine as a chemical mediator for cutaneous pain. Belleau & Lacasse (6) analyzed complex-forming mechanisms between acetylcholinesterase and compounds related to acetylcholine. The active surfaces of the latter are nonpolar, allowing the operation of hydrophobic forces in binding of substrates and inhibitors. Stereochemical studies indicate that acetylcholinesterase is nearly identical with the muscarinic receptors for acetylcholine.

Central Nervous System

Gaddum (51) introduced a symposium on the pharmacology of the central nervous system, which included discussions of drug actions on single neurons in spinal cord and thalamus by Curtis (27), on single neurons in

the brainstem by Bradley & Wolstencroft (10), and on single neurons in cerebral cortex by Krnjevic (85). The pharmacology of central inhibitory synapses was analyzed by Eccles (34), while cholinergic mechanisms in the cerebellum were discussed by Phillis (106). Feldberg & Fleischauer (45) described the uptake of drugs from brain ventricles, and indicated that amine release in the hypothalamus is involved in body temperature control. Quastel (108) concluded that many amines, including ammonia, play a role in neuronal function, so that substances affecting their metabolism have significant effects. Vogt (140) discussed DOPAmine and antimetabolites of catecholamines. The action of alpha-methylDOPA in the brain was reviewed by Sourkes (126), while Richter (110) covered brain protein metabolism. Gamma-aminobutyric acid and other inhibitory substances on brain action were surveyed by Elliott (38).

Millichap (97) related anticonvulsant drugs to clinical indications as reflected by electroencephalography. Göres (62) detailed ethanol effects on proteins, enzymes, bacteria, cell, spermatozoa, and organs, and considered its metabolism, toxicity, sensitivity, and effects on other drugs such as insulin. There are 389 references. The pharmacology of chloralose has been reviewed by Balis & Monroe (5). Seevers (121) checked data on the abuse of barbitals and amphetamines. Elliott and his associates (37) concluded that the nalorphine pupillary reaction is a useful method for screening possible ingestion of morphine or its derivatives.

Anesthetics.—Adriani (1) appraised current concepts in anesthesia, covering 45 topics including statistics. Van Dyke & Chenoweth (139) reviewed the metabolism of volatile anesthetics, citing 67 reports. Ether is metabolized by microsomes to ethanol and acetaldehyde. Halogenated hydrocarbons are dehalogenated by enzymes and detoxified to glucuronides. Uptake of anesthetics was analyzed by Paton & Speden (105), who also examined the kinetics of onset and offset of anesthesia. Little & Whetstone (90) reviewed anesthetic effects on the liver. Gordh (60) opened a symposium on cardiovascular relations of anesthesia. Citing 220 reports, Rossi (113) discussed synergism between analgesics and anesthetics, with much information on phenothiazines.

Anxiety and mild tranquilizers.—Meduna (1896–1964) edited the proceedings of a conference (96) on anxiety and the use of mild tranquilizing agents. Meprobamate, some diphenylmethanes, and benzodiazepines were differentiated from more powerful antipsychotic drugs such as the phenothiazines and reserpines, as well as from such central nervous system depressants as alcohol, anesthetics, sodium bromide, and the barbitals. Quantitated EEG records were suggested for estimating central nervous system depression or stimulation. Berger & Ludwig (8) surveyed meprobamate and related compounds. Svenson & Gordon (130) reviewed clinical uses of diazepam.

Antidepressant agents.—The American Medical Association's Council on Drugs (25) reviewed the therapeutic efficacy of antidepressants, indi-

cating that amitriptyline, imipramine, and tranylcypromine are more active than placebos and safer than monamine oxidase inhibitors. Cole (21), using 72 reports, collected clinical data on various antidepressant drugs. Kline (82) offered suggestions on the practical management of depression.

Psychotomimetic drugs.—Giarman & Freedman (54), citing 168 reports, reviewed biochemical aspects of psychotomimetic activity. Many metabolic products are implicated. N-methylation of serotonin and tryptamine yields bufotonine, while mescaline probably forms indoles. 6-Hydroxylation of indole-alkyl-amines is slight in humans, as is O-methylation. Mescaline, as well as lysergic acid diethylamide, may interact with 5-hydroxytryptamine and brain neurohormones, as well as with cholinolytic compounds.

Hoffer (72) summarized the present status of lysergic acid diethylamide, with reference to its possible sources in comparison with other ergot alkaloids. Its pharmacological, psychological, and toxicological actions are reviewed. Subjective reactions are considered and clinical uses are suggested. There are 411 references. Key (80) surveyed the effect of LSD on potentials evoked in specific sensory pathways, concluding that the drug does not act directly at these points, but rather within more complicated integrating mechanisms. Ludwig & Levine (92) fully described patterns of hallucinogenic drug abuse.

Cardiovascular-Renal Agents

Welt (144) supervised the preparation of the first volume of the *Index Handbook of Cardiovascular Agents*, covering publications from 1931 to 1950. This is a huge compilation of over 2000 pages with systematic cross-indexing. It gives detailed information on the cardiovascular effects of an enormous variety of drugs. It is an indispensable bibliographical instrument for retrieval of information on cardiovascular agents.

Beznak (9) reviewed hormonal influences in the regulation of cardiac performance. Gifford (56) reviewed new oral diuretic agents and their clinical application. Whelan (145) surveyed the control of peripheral circulation in humans.

Glynn (58), citing 211 references, analyzed the action of cardiac glycocides on ion movement. The movement of sodium and potassium ions is activated by adenosine triphosphatases. A review of the clinical use of digitalis is offered by Braunwald & Klocke (11). Conn & Luchi (23) surveyed the cellular basis for the regulation of the circulation by digitalis and quinidine. Nordström-Öhrberg (100) discussed the effect of digitalis glucosides on electrocardiography in regard to exercise tests in healthy subjects. Schott (117) gave a short but pertinent review of digitalis intoxication.

Hormones

Malinow (94), referring to 320 citations, discussed the relation of hormones to atherosclerosis, with special reference to the gonads, the pancreas, the thyroid, and the adrenals. Lukens (93) reviewed information on

the relation of insulin to protein metabolism. Money (98) considered the influence of hormones on sexual behavior. Ross (112) surveyed aldosterone and its antagonists, with reference to 384 reports. The metabolism and actions of aldosterone, as well as of factors in the control of its secretion, are discussed. Its therapeutic uses are well reviewed, as well as various antagonists to its effectiveness. Schlagel (116) reviewed the comparative efficacy of topical anti-inflammatory corticosteroids. Gray and his colleagues (63) reviewed the action of steroid hormones at cellular levels.

Toxicity

Burns (17) chaired an extended discussion on the evaluation and mechanisms of drug toxicity. The first part of this symposium considered the basis of selective toxicity. The second section dealt with metabolic aspects of drug toxicity. Genetic factors in drug toxicity comprised the third section, while drugs in relation to mammalian embryology was the subject of the fourth part. The fifth section considered applications of new knowledge to toxicity tests in animals, and the concluding discussion reviewed clinical aspects of drug toxicity with reference to the blood-forming organs, kidneys, the nervous system, cardiovascular effects, and the skin. Cahen (18) cited 262 references in evaluating the teratogenecity of drugs. This is an important review with an excellent bibliographical survey covering thalidomide, antimetabolites, steroids, hypoglycemic agents, and vitamin deficiencies. Screening methods are considered as well as possible mechanisms. High doses of vitamin A are proposed as reference standards for comparative purposes.

Zbinden (149) offered an extensive consideration of experimental and clinical aspects of drug toxicity, relying on 500 references. He discussed the frequency and organ distribution of drug toxicity in humans, outlined designs for toxicity experimentation, considered the factors not relating to drugs which may affect the outcome of animal toxicity studies, and concluded with a consideration of the economics of evaluation of safety.

Kurland (86) introduced a comprehensive symposium on the toxicity of cycads, with reference to amytrophic lateral sclerosis. There were special discussions on the neurotoxic amino acids of certain species of lathyrus and vetch, as well as the potential carcinogenic effects of cycad meal. Simkiss (123) reviewed phosphates as crystal poisons for calcification processes.

Halstead (66) surveyed fish poisoning from the standpoint of diagnosis, pharmacology involved, and treatment, citing 59 references. Fish toxins include nine different sarcotoxins, hemotoxins, and various venoms which are not satisfactorily characterized.

Pesticides

An extensive symposium on carbamate insecticides was opened by Back (4). Egler (35) reviewed the significance of pesticides in our ecosystem.

Rudd (114) gave a carefully documented report on the price we pay for trying to control our environment in a consideration of *Pesticides and the Living Landscape*. Casida (20) reviewed esterase inhibitors as pesticides, indicating their favorable biological properties.

Jacobson & Beroza (75) gave an important short review on insect attractants which have been successfully synthesized for the purpose of congregating insects for destruction by physical means or by concentrated chemical processes, reducing the need for the widespread use of insecticides.

Clinical Therapy

Dennis & the Lanes (30) gave a quick survey of useful drugs for skin disorders. Glaser (57), with 260 references, surveyed pharmacological considerations in the treatment of myasthenia gravis. This survey included a consideration of the clinical features of the disease, as well as its pathogenesis and diagnosis. Pharmacological tests are described and therapy is considered in relation to anticholinesterases with oximes for use in therapy crises.

Miscellaneous

Elworthy & MacFarlane (39) analyzed the physical chemistry of some nonionic detergents. Fairbairn (43) described anthracene derivatives from medicinal plants. Pinder (107) gave a chemical review of lactonic alkaloids covering carpaine and compounds containing simicidine, which are insecticidal. Phthalide-isoquinolines are considered as well as drugs containing indole groups and quinolizidine compounds.

The Tabors (131), with reference to 479 citations, carefully reviewed the nonprotein nitrogenous bases exemplified by spermidine, spermine, and related amines. 1-4-Diaminobutane is the compound once called "putresine," while 1-5-diaminopentane is what was once called "cadaverine." These relatively simple amines are to be found in all tissues and may function in part as growth factors. They protect against bacteriophage inactivation, and have a mild antimicrobial action. However, they also show some effect against certain antimicrobial agents such as flavines and streptomycin. They are toxic for kidney cells and have a biphasic effect on blood clotting. There is little toxicity associated with them.

Mann (95) offered an interesting survey of biological aging and its modification of drug activity.

In Prospect

Analytical surveys and reviews of current subjects of pharmacological interest will continue to provide quick means of orientation in the wide expanse of pharmacological advance. There is an increasing trend to develop

general principles regarding the interrelations of the chemical constitution of drugs and their overall biological activity. There are also significant trends toward greater emphasis on detailed studies of drug effectiveness and safety. Various sociological and economic factors in regard to drugs are certain to get more attention. In all of pharmacological and toxicological development, reviews will continue to have increasing significance.

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