REVIEW OF REVIEWS[1]

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Many current pharmacological reviews are significant for emphasizing molecular actions of drugs. Our understanding of mechanisms of drug action is enhanced as we think about molecules of drugs interacting with molecules comprising the awful complex of living material. This approach stimulates use of physicochemical concepts and techniques in our effort to realize how drugs truly act. It is from this molecular level that a chain reaction proceeds to evermore complex biological organizational levels from cells, through organs and tissues, to individuals, to societies, and to ecologies. The steps in this chain reaction remain dimly perceived, and are blurred by the persistency with which all living systems maintain their particular internal steady-states.

What is called "clinical pharmacology," on the human organismal level, attracts public attention where it is most vulnerable—in human experiments and in hallucinogenic drug abuse. These matters deserve discussion.

From Hippocratic times, it has been recognized that the prime obligation of physicians is to do no harm to any patient, and also that any treatment on any patient is an experiment in that its outcome is not fully predictable. Further, it was generally felt, until the 19th century, that patients should be managed medically solely for their own good—that is, treatment should be given or withheld on the basis of what was thought to be best for each patient.

This attitude changed with the clinical introduction of statistical methods for estimating the efficacy of therapy by Louis (59) in 1835. Now, clinical pharmacologists have developed "double blind" and other statistical ways of estimating the clinical value of new drugs, without prime regard for the welfare of each patient, but rather to try to guess the future potential usefulness of a drug, or other therapeutic procedure. This has now been called in question by Lear (53) popularly, and professionally by Beecher (6). The current discussion revolves around the question of "informed consent" of each patient or subject. The ethical and legal aspects of the problem were explored in a conference on human pharmacology arranged by Murphy & Parker (68). Moral problems of organ transplantation and associated drug use were reviewed by me (51).

Hallucinogenic drug abuse is getting much attention, largely due to sensational journalistic exploitation of the use of lysergic acid diethylamide (LSD). Ebin (19) compiled an anthology of first-person accounts of drug experiences, while LSD is the subject of two seriously popular paperbacks, one

[1] The survey of the literature pertaining to this review was concluded in July 1966.

edited by Blum (8), and the other by Solomon (95). Pollard, Uhr & Stern (78) have offered a short review, with 41 references, of hallucinogenic drugs with transcripts of subject responses to LSD, psilocybin, and phencyclidine.

Confusion and concern has arisen in scientific and industrial drug circles as a result of the new regulations and restrictive actions of our Food and Drug Administration. Increasing authoritarian bureaucracy has cut the number of new drugs being introduced from a total of 154 in the first half of 1961 to 39 in the first half of 1966.

Methodology and General

Scheuler (1921–1964) edited (88) an important symposium on molecular modification in drug design with regard to many types of therapeutic agents. Brand & Perry (10) critically reviewed methods of study of drugs for motion sickness. Petersdorf (75) described methods of testing of bacterial sensitivity to drugs.

A well-edited and indexed compendium of currently used drugs in all major categories was issued by Clegg (15). This supplements such now standard quick reference sources as Modell's *Drugs of Choice* and AMA's *New Drugs*.

Two compounds of wide pharmacological interest are histamine and 5-hydroxytyptamine. Both are covered in huge reviews which form part of the *Handbook of Experimental Pharmacology*, the former edited by Rocha & Silva (82) and includes antihistaminics, and the latter arranged by Erspamer (21) and includes related indole-alkylamines. Ungar (101) introduced a short symposium on histamine. A critical survey of serotonin, covering 3600 references, was made by Garattini & Valzelli (23). This has appendices giving serotonin concentrations in various tissues and reviews the effects of various drugs on serotonin activity and metabolism. Widely distributed compounds of potential pharmacological interest are the quinones, the biochemistry of which was reviewed by Morton (66).

Koppanyi & Avery (45) indicated that species differences level off on equalizing plasma drug levels, so that there is a tolerable risk in going from animal trial to human evaluation. Kalow (36) emphasized that all drug effects are subject to genetic variation, and that hereditary factors influence the development of enzymes for "regulator genes" and for "structural genes" for the formation of various polypeptides which modify drug action. Altered drug response in hereditary disease was reviewed by LaDu (46), with regard to inborn errors of metabolism, molecular disease, defects in protein synthesis and in structural anomalies. Hereditary resistance to coumarin types of anticoagulants was surveyed by O'Reilly & Aggeler (71), with evidence that it is transmitted by a dominant allele.

A thorough summary was given by Paoletti & Vertua (72) of radiosensitizing and protective drugs. Referring to 102 reports, Perry (74) reviewed drugs used in aerospace medicine with respect to effects of altitude, radiation, stress, and extremes of motion and temperature.

Veldstra (102) considered that competition for "sites of loss" (excretion)

constitutes the underlying mechanism of many observed synergistic drug effects. Gruneberg & Prince (28), with 55 references, analyzed factors in resistance to drug action. Wittenborn & May (107) edited discussions on predictions of response to pharmacotherapy.

Absorption, Metabolism, and Excretion

In reviewing drug kinetics, Levy (54) proposed that rate constants for drug absorption and removal can be estimated from pharmacological effects as well as from blood levels. With 120 references, Skou (92) reviewed evidence for an enzymatic basis for active transport of Na and K across cell membranes.

Much interest has been attached to the controversial penetrant solvent, dimethyl sulfoxide (DMSO). While the scientific facts about it are fairly well agreed upon, its clinical applications, even as an aid to absorption, remains doubtful, due largely to restrictions placed on its clinical study by our Food and Drug Administration because of alleged eye injury. It is a water-miscible, hydroscopic, and polar solvent, which readily crosses biological membranes without injuring them, and aids in transporting many compounds, such as steroids and large molecular complexes, across such membranes. It readily penetrates skin and tends to dissolve collagen. It is cryoprotective, mildly antiseptic, locally anesthetic, and has low toxicity on single or repeated doses. It is metabolized to dimethyl sulfide which may be excreted by the lungs, giving a garlic-like breath. It is claimed to be useful in acute and chronic musculoskeletal injuries and inflammations when applied locally in 70 per cent concentration with water. Kharasch & Thyagarajan (41) have analyzed publications on its chemistry. Reviews of pharmacological and clinical reports on DMSO have been edited by Laudahn (49) and by me (50). Schlenk (87) reviewed the metabolism of biological sulfonium compounds.

Polypeptides and Enzymes

Law (47), with 679 references, reviewed polypeptides of medical interest. With 470 references, Meldrum (63) surveyed actions of snake venoms on nerve and muscle, detailing the pharmacology of phospholipase A and of polypeptide toxins. Some eight venoms were discussed. Phospholipase A is heat stable, inhibits succinic dehydrogenase, and acts enzymatically to cause hemolysis.

The 1965 Florence symposium on hypotensive peptides was edited by Erdos, Back & Sicuteri (20). Including 57 reports, it deals chiefly with bradykinin, eledoisin, gastrin, kallidin, physalaemin, and trasylol. Using 229 references, Coon & Willis (16) reviewed side effects of heparin, heparinoids, and their antagonists, indicating that they may be caused by the high charge density of these macromolecules. They have some protective action, as in hyperimmune disease, and they increase coronary flow.

In reviewing the renin-angiotensin system, with 299 references, Peart (73) concluded that it comprises part of a hormonal control mechanism for water and electrolyte balance by means of a stimulating effect on aldosterone for-

mation and on renal action. It is part of the juxtaglomerular apparatus, with receptor sites in afferent arteriolar walls. Pinkerton (77) edited a London symposium on oxytocin. Innerfield (33) has considered quantitative aspects of oral enzyme therapy.

While the first volume of Webb's *Enzyme and Metabolic Inhibitors* dealt with general principles, including kinetics, mechanisms, and effects of various factors, the second and third volumes (105) offered detailed coverage of metabolic inhibitors whose effects are due to structural relationships to naturally occurring substances which react with enzyme sulfhydryl groups. They include reviews of mercurials, arsenicals, quinones, malonates, and various oxidants.

Chemotherapy

Antibiotics continue to be well reviewed. Goldberg (24) surveyed antibiotics affecting nucleic acid and protein synthesis. Lorian (58) has described antibiotics in laboratory use. Martin (60) surveyed the complications of antibiotic therapy. Reich (81) considered actinomycin in regard to nucleic acid function. Schwank & Kandracova (89) have reviewed side effects of antibiotics as allergic phenomena. Seelig (90) discussed mechanisms by which antibiotics increase the incidence and severity of candidiasis and alter immunological defenses. Stewart (97) offered a comprehensive review of penicillins.

General cancer chemotherapy was well reviewed by Larionov (48). Jellife & Marks (35) have edited the Cambridge symposium on benzmethyzin as a cancer chemotherapeutic agent. The Millers (65) skillfully reviewed the mechanisms of chemical carcinogenesis, and, using 223 reports, considered the nature of proximate carcinogens and their interaction with macromolecules. Roe (83), with 248 references, reviewed the relevance of preclinical assessment of carcinogenesis from alkylating agents, antibiotics, metallic carcinogens, hormones, and viruses, concluding that carcinogenic risk from drugs is a graded matter of balance between risk and benefit. The Paris symposium on anticancer effects of vinca alkaloids was edited by Sproston (96).

Malaria is again attracting chemotherapeutic interest as a result of our problems in Viet Nam. Its current status was reviewed by Powell (80). Saz & Bueding (86) analyzed relationships between anthelmintic effects and biochemical and physiological mechanisms. Antiviral chemotherapy was reviewed by Massarani & Nardi (61) with evidence that guanidines are effective against RNA viruses, while 5-halo-deoxyuridines are active against DNA viruses, with some thiosemicarbazones as modifiers of vaccinia virus. Kaufman (38) reviewed problems of virus chemotherapy.

Autonomic Drugs

The proceedings of the 1965 Milan catecholamine conference was edited by Acheson (1), with sections on enzyme factors, metabolic effects, measure-

ment and detection, adrenergic transmission, modification of adrenergic function, and relations to the nervous and circulatory systems. The pharmacology of cholinergic and adrenergic transmission was well reviewed by Koelle, Douglas & Carlsson (43). Triggle (100) summarized chemical aspects of the autonomic nervous system, with emphasis on receptors.

Using 174 references, Volle (103) reviewed drug modification of synaptic mechanisms in autonomic ganglia. In an important survey of DOPAmine-β-hydroxylase, with 173 references, Kaufman & Friedman (39) concluded that catalytic activity involved ascorbate as the electron-donating cofactor, copper as part of the active site, and fumarate as the moderator of action. They discussed catecholamine vesicles and rate factors in norepinephrine synthesis. Potter (79) described norepinephrine storage in sympathetic nerves. Von Euler (104) recorded the striking history of norepinephrine.

Central Nervous System Drugs

Using 385 references, Curtis & Watkins (17) reviewed the pharmacology of amino acids related to γ-aminobutyric acid, noting synaptically released CNS transmitters or those associated with energy metabolism and inhibitory transmitters at Purkinje cell axonal terminals. Hornykiewicz (31) carefully surveyed the significance of 3-hydroxytyramine (DOPAmine) for brain function. McGaugh (62), with 123 references, reviewed drug effects on memory and learning.

Haase & Janssen (29), with 351 references, described the action of various neuroleptics. Leake & Silverman (52) gave data on composition and differential effects of various alcoholic beverages. Lieber (55) analyzed hepatic and metabolic actions of alcohol, using 148 references. Klerman & Cole (42), with 341 references, surveyed the clinical pharmacology of imipramine and related antidepressants. Drug therapy for epilepsy was reviewed by Livingston (56) with respect to usage, metabolism, and undesired reactions of various anticonvulsants. Longo (57) correlated the behavioral and EEG effects of atropine and related compounds. Nakajima (69) did the same for biochemical interactions of psychotropic drugs with their pharmacological effects, referring to 120 reports.

A conference on anesthetic effects on metabolism and cellular function was edited by Bunker & Van Dam (13), with regard to experimental models, phosphorylation, membrane phenomena, effects on liver and heart, role of endocrines, and anaerobiosis. Moya & Smith (67) considered the uptake, distribution, and placental transport of anesthetics. They also (93) reviewed drugs used in resuscitation of anesthetically depressed newborn. Black (9) surveyed the pharmacology of halothane, and Conway (15a) reviewed anesthetic ethers. Shephard (91) edited a session on neuroleptic-analgesic agents, such as phenoperidine, as aids to anesthesia. Beckett (5) considered analgesics and their antagonists.

Cardiovascular and Endocrine Drugs

The pharmacology of the coronary circulation was reviewed by Kaverina (40). Rowe (85) considered the effects of various drugs on the coronary circulation in human beings. Wigle (106) reported on cardiovascular drugs in muscular subaortic stenosis. Gross (27) edited the Sienna symposium on antihypertensive therapy.

Kolpakov (44) surveyed the influence of the hypophysis and adrenals on biochemical changes in dying and resuscitation. Drews (18) discussed mechanisms of action of steroid hormones. In short reviews, Armaly & Becker (2) noted a genetic factor in the intraocular response to topical corticosteroids, and Ashboe-Hansen (3) considered the hormone content of connective tissue.

Toxicity

Teratogenicity remains a topic of interest. Beck & Lloyd (4) discussed the teratogenic action of azo dyes. In reviewing drug responses of fetus and newborn, Nylan & Lampert (70) considered teratogenesis and various aspects of perinatal pharmacology. Smithells (94) surveyed drugs in relation to human malformations. A comprehensive monograph on malformations was prepared by Stolle & Maraud (98).

Bisset (7) described arrow and dart poisons of southeast Asia in regard to species of *Strychnos* used. Kao (37) recommended as tools for study of excitation such purified marine toxins as tetrodotoxin and saxitoxin, which are guanidine compounds blocking Na channels in excitable membranes. Meyler (64) added much to his continuing study of side effects of drugs. Rostenberg & Coulston (84) edited substantial reports on cutaneous toxicity. Hartl (30) reviewed drug allergic agranulocytosis, and Horowitz (32) discussed drug-induced purpura. In reviewing trends in therapy of acute poisoning, Gosselin & Smith (26) noted enhancement of excretion by dialysis.

Brown (11) helpfully described the identification, pharmacology, and therapeutics of pesticides encountered in clinical practice. Chichester (14) edited remarks of 40 discussants at the Davis conference on pesticide research.

Miscellaneous

Bulbring (12) edited a session on pharmacology of smooth muscle, with emphasis on calcium ion motility and contractile proteins. With 117 references, Taylor & Nedergaard (99) reviewed the biochemorphology of quaternary ammonium neuromuscular blocking agents. Friedman (22) surveyed the effects of various drugs on uterine contractility.

Oral contraceptives are much discussed. Goldzieher & Rice-Wray (25) reviewed the mechanisms and management of oral contraception, including hazards. More broadly, Jackson (34) considered antifertility compounds in male and female insects, animals, and human beings. Pincus (76) summarized

evidence showing that the benefits of oral contraceptives are not offset by adverse effects.

In Prospect

Reviews of pharmacological interest are becoming more oriented toward molecular aspects of mechanisms of drug action, and toward strict control in human applicability. There is danger that paternalistic governmental bureaucracy may block drug research, both scientifically and clinically, and inhibit the free interests of pharmacologists in studying drug action and drug development in response to the needs of members of the health professions. Pharmacologists must strive to deserve public support for their scientific endeavors free from unwise bureaucratic restrictions.

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CONTENTS