REVIEW OF REVIEWS[1]

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Reviews are being increasingly recognized as the most satisfactory manner for effective interscience communication especially in the biomedical sciences, and indeed for making possible some reasonable understanding of the current status of the special fields for the specialists themselves who may be concerned. Significantly, Senator Hubert H. Humphrey has issued a series of statements on the problem, culminating in a memorandum dated May 14, 1962, on "An Action Program for Strengthening Medical Information and Communication," which calls for Federal support. Reviews of pharmacological progress continue to increase in number and significance.

Notable among new review media in pharmacology is *Advances in Pharmacology* edited by Silvio Garattini (Milan) and Parkhurst A. Shore (Dallas). The first volume, appearing in March 1962, has eight reviews of high quality which well reflect current interests.

In the discussion last year on the reviews in pharmacology, it was pointed out that texts often constitute helpful surveys of the current status of the science. Criticism was offered about the conventionality of pharmacological texts. Sicé (61) now offers a *General Pharmacology* which breaks with tradition to a considerable extent in utilizing more recent conventionalities, especially regarding the physico-chemical bases of pharmacodynamics. The volume also gives a short discussion of the scope of pharmacology from the laboratory to clinical use. The bulk of the volume, however, follows conventional organization of drug action largely on the basis of organ systems. The book is heavily oriented chemically, and this is an indication of the more recent conventional approach to pharmacological matters. On the other hand, the volume is not really general in its scope, since it is primarily oriented toward clinical use of drugs in humans.

Some aspects of the applications of pharmacological and toxicological knowledge are coming into public discussion. An interesting example is the series of articles (which have appeared in book form) by Rachel Carson (14) on "silent spring," an account of ecological pathology induced by pesticides and herbicides.

Similarly, the thalidomide affair has received wide public review, with resulting effort for more bureaucratic control over experimental and clinical research on new drugs and their possible introduction into clinical use. The issue has been clouded by sentimentality. Nevertheless, important problems

[1] The survey of the literature pertaining to this review was concluded in August 1962.

of practical medical ethics have been raised, and a clear challenge is before the great drug industry to conduct itself wisely with full consideration for the best public interest. Sheps (59) well discusses the problem of clinical evaluation of drug therapy.

In the case of thalidomide, it should be noted that ordinary reasonable toxicity studies at an experimental level would not have been likely to reveal potential intrauterine developmental defects in embryos to whose mothers the drug may have been given. From now on, careful toxicity studies on pregnant animals and their progeny are indicated in the preliminary appraisal of every proposed new drug.

Abstracts of the extensive professional discussion of thalidomide were made by Moser (45). Some 53 references to the pharmacology, clinical use, and toxicity of thalidomide from 1956 to 1962 were compiled in the September 1962 issue of *National Library of Medicine News*.

The case for stricter Federal (and thus bureaucratic) controls over the development of new drugs is offered by John Lear (*Saturday Review*, September 1, 1962, pp. 35 to 40). He had previously reported a shocking state of financial exploitation associated with the slickest sort of Madison Avenue manipulation in obtaining approval of certain antibiotics by the Food and Drug Administration. Lasagna voiced criticism of the proposed Federal legislation which might establish almost inhibitory control over clinical appraisal of new drugs (*Med. Trib.*, August 1962).

The answer to the abuses inherent in commercialized competition with new drugs is not more law and bureaucracy but more self-policing in the drug industry, with higher standards of public responsibility. Maybe drug companies would profit by submitting to periodic certification as to competency and responsibility, to be made by their own voluntary agency, quite as is the case with medical schools and hospitals.

General Pharmacology

In a brilliant and witty discussion of empiricism and logic in the discovery of new drugs, Keele (35) indicates that pharmacology is the most eclectic of all medical sciences. He points out that logic gives the direction to research, but that experience offers continual feedback control. Logic applied to chance observations may result in great advances in verifiable knowledge. His discussion is illustrated by references to the logic used by William Withering (1741 to 1799) in following up his observations on the relief of dropsy from a mixture of herbs given by an old country woman. Keele indicates that the same sort of empiricism and logic are current in the development of new drugs now.

Lane-Petter (39) chaired a symposium on the influence of animal strain selection and conditioning in biological experiments and assay. In this symposium, Brown & Hughes (11) emphasized the importance of strain differences in variations of findings from different laboratories doing similar experiments. Brown (10) showed the wide extent of quantal responses in uniform

strains of mice and indicated the importance of standardizing each procedure in each experiment. D'Arcy (19) indicated the importance of housing and crowding on dose-response results. In the discussion, it was brought out that adequate and uniform diets are essential for obtaining satisfactory quantitative drug responses on experimental animals. Russell & Burch (53) give a thorough discussion of the principles of humane experimental technique. They indicate the importance of adequate care and of gentle and kindly treatment of experimental animals in all phases of experimental studies.

There is much current interest on the significance of enzymes in drug action. An excellent review on enzymes and drug action has been edited by Mongar & De Reuck (43). This comprises the discussions at a Ciba Foundation symposium. The review emphasizes the wide range of enzyme involvement in drug action. Many different types of chemicals may alter the complicated enzyme metabolic reactions at almost any point in the enzymatic cycle. To pinpoint the place of chemical interference is a scientific challenge of the first order, but it is being explored vigorously.

In the increasing discovery of new enzyme systems, it is becoming increasingly important to have satisfactory nomenclature. Thompson (64) discusses the classification and nomenclature of enzymes and co-enzymes. The matter has been approached by the Commission on Enzymes of the International Union of Biochemists (16). This Commission recommends a standard classification and nomenclature of enzymes with which it would be helpful to pharmacologists to become familiar. Uniformity in nomenclature is essential if there is to be satisfactory comparison of independent scientific studies and if there is to be reasonably satisfactory interscience communication.

There is increasing recognition of the action of drugs at macro-molecular levels with regard to genetic effects. A well-documented review on pharmacogenetics has been prepared by Kalow (34). This indicates the many surprising ways in which drug response may involve heredity. Huang & Bonner (33) describe histone as an agent capable of suppressing chromosomal ribonucleic acid (RNA) synthesis. It is likely that many other chemicals will be found that will interfere with RNA synthesis in chromosomes and thus produce developmental or genetic disturbances. It has become very important to determine the method by which thalidomide produces its developmental defects.

Comparative pharmacology has not been well advanced, and yet vast applications of pharmacological information are being made in respect to the control of insects and similar pests. The action of drugs on different classes of living material may vary remarkably but may also be similar enough to provide a background for experimental findings that may be widely applied. Fänge (26) reviews the pharmacology of poikilothermic vertebrates and invertebrates. This review considers the effects of drugs on various organs in both poikilothermic vertebrates and invertebrates, and then discusses preparations that are used for bioassay in each type of animal and concludes with a

consideration of the distribution of biologically active substances in poikilotherms and invertebrates. There is a vast amount of factual information in this review which offers 390 references.

Factors involving the absorption, metabolism, and excretion of drugs continue to be investigated vigorously. Schou (57) gives an interesting historical survey of the development of subcutaneous administration and then considers methods for studying the rates of absorption from subcutaneous injection. He indicates the importance of reporting postabsorptive symptoms, and of analyzing drugs quantitatively in circulating blood, as well as in excretions and secretions. He outlines tissue clearance methods. He reports on the mechanisms of subcutaneous absorption and then indicates various drugs which influence the rate of subcutaneous absorption. There are 147 references. Alcock & MacIntyre (2) review the inter-relation of calcium and magnesium absorption. Wilson (72) well surveys intestinal absorption with special reference to mechanisms and types of nutriments and drugs. Conney & Burns (17) review factors influencing drug metabolism.

Chemotherapy

Remington & Finland (51) survey the antibacterial activity of serum after oral doses of tetracycline, demethyl-chlortetracycline, and 6-methylene-oxytetracycline. Oral doses of tetracycline and 6-methylene-oxytetracycline are absorbed more rapidly than those of demethyl-chlortetracycline, but the antibacterial activity of the latter lasts much longer in the circulating blood stream. Demethyl-chlortetracycline and 6-methylene-oxytetracycline are equally bound by blood proteins and to a greater extent than tetracycline. In a review with 81 references, Shils (60) analyzes the metabolic aspects of the tetracyclines. He finds that these agents cause increased excretion of sodium and nitrogen, together with some diuresis. Their antimetabolic effect inhibits protein synthesis.

An important report on the symposium on amebiasis and other intestinal infections, held at the Central Drug Research Institute, Lucknow, has recently come to hand. It is edited by Mukerji (46). This is an extremely important symposium and covers all aspects of the chemotherapy of amebiasis. There is included various considerations of experimental studies together with therapeutic trials, and then a rather detailed consideration of specific amebicides. In the symposium, Druey (23) gives an excellent review of antiamebic drugs. Some of the new drugs considered are entamide, paromomycin, neoviasept, entobex, various phenanthroline compounds, various quinolinols, and a new synthetic emetine-like compound.

A more general symposium on chemotherapy was held at the Central Drug Research Institute, Lucknow, and the proceedings have been separately published. This symposium was held under the direction of Mukerji (47), and includes a wide series of reviews on general aspects of chemotherapy, including cancer, tuberculosis, various sulfones, and a variety of antibiotics. There are also reviews on the chemotherapy of malaria and of amebi-

asis. There are also discussions of various anthelmintics, and even a consideration of drug screening against animal viruses. All together this symposium represents the relatively high level of chemotherapeutic studies which are being vigorously promoted at the Lucknow Central Drug Research Institute.

Recent reviews on cancer chemotherapy include Delmonte & Jukes' (21) discussion of folic acid antagonists with reference to 300 reports. It is their careful analysis of the chemistry and action of these antagonists which makes this review useful. Rutman *et al.* (54) evaluate chemotherapeutic agents against a variety of mouse ascites tumors, and Leiter and co-workers (40) give anticancer screening data on plant extracts.

Wheeler (69), with 538 references, comprehensively reviews the mechanisms of action of various cytotoxic alkylating agents. His discussion considers various types of nitrogen mustards, ethyleninimes, sulfonic esters, epoxides, and N-alkyl-N-nitroso compounds not preferentially localized in tumor systems. He finds that certain of the critical reactions occurring with these compounds have greater effect in neoplastic tissue than in normal tissue. It seems that the effects are due to the alkylation of nucleoproteins. This interferes with mitosis, and alters the rate and character of desoxyribonucleic acid (DNA) replication. This in turn alters RNA, and thus produces the shift in the gene structure. DNA is most sensitive to alkylation and the sensitivity seems to be localized at the seven position of the guanine moiety. Witten and his associates (73) are studying enzyme alterable alkylating agents, which are sulfur mustards containing enzyme-susceptible amide bonds. Ross (52) more generally discusses biological alkylating agents.

A significant discussion of the biochemorphology of amidine ($-C.NH_2:NH_2$) derivatives is given by Fastier (27) from the standpoint of blood pressure, smooth and skeletal muscle tone, and metabolism. He indicates the extent of pressor, depressor, vasoconstrictor, hypoglycemic, and antibacterial activity among these compounds. The factors which determine activity are extent of basicity. The characteristic properties of amidine derivatives are those of amidinium cations. These cations are considered to compete with physiological cations for anionic sites on or in cells. Molecular size is also a factor of importance, as well as the characteristics of the drug receptors. The ability of many amidine derivatives to exert direct chemotherapeutic effect implies that little specificity of structure is needed to permit interaction with various receptors.

Autonomic Drugs

Koelle (37) is editing a comprehensive survey of cholinesterases and anticholinesterase agents. This *Supplement 15* to the great *Heffter-Heubner Handbuch* should give detailed informaton on all aspects of the subject. Koelle (38) himself has developed a new general concept of the neurohumoral function of acetylcholine and acetylcholinesterase. There is evidence of storage of acetylcholine in the synaptic granules. Acetylcholinesterase is found along the entire length of cholinergic neurons. Its function is the hydrolysis of

acetylcholine after the production of the localized depolarization. Is there any evidence that acetylcholinesterase may be involved in the resynthesis of acetylcholine as the local chemical equilibria shift?

Koelle's review is an excellent one. He points out the significance of the cytological localization of acetylcholinesterase and describes differences in the properties of various sites where it is found. He considers that acetylcholine and its associated enzymes may play a role in sympathetic ganglia. The general working hypothesis proposed by Koelle is that the acetylcholine liberated along a nerve by the nerve action potential, acts initially at the same presynaptic terminals to bring about the liberation of additional amounts of acetylcholine, and it is this secondarily released increased amount of acetylcholine which acts at the postsynaptic site to effect transmission.

In many types of noncholinergic neurons, it is equally likely that a similar mechanism is involved in which the initial liberation of acetylcholine promotes the release of another neurohumoral transmittor from the same nerve endings. It is also suggested that at peripheral sensory receptors, the specific stimulus may activate the release of acetylcholine from either the accessory cells or the axonal terminal itself, and that it then acts on the latter to initiate indirectly the sensory impulse.

Waser (65) reviews much detail, from 104 reports, on the chemistry and pharmacology of muscarine and related compounds. Some 87 derivatives are tabulated for structural and pharmacological data. Nothing is known about the metabolism of muscarine or muscarone. Maximal muscarinic action depends on the cationic nitrogen with 3 methyl groups and a nucleophilic group (ether- or carbonyl-oxygen) at a distance of 4Å. Nicotinic action depends on the polarizability of the nucleophilic part of the molecule and another electron-dense part symmetrical with the polar group relative to the quaternary nitrogen. These considerations indicate possible structural aspects of cholinergic receptors.

Burn & Rand (12) offer a new approach to adrenergic nerve fibers. Eger (25) reviews the actions of atropine, scopolamine, and related compounds, with particular reference to methantheline bromide and oxyphenonium bromide, with regard to their quaternary nitrogen curare effects. Some 294 references are included.

Coleman, Little & Bannard (15) study cholinolytics for treating anticholinesterase poisoning, but find few agents better than atropine sulfate. D'Arcy & Taylor (20) offer a comprehensive review of quaternary ammonium compounds in medicinal chemistry. Silvette and his associates (62) consider the actions of nicotine on the central nervous system. Naturally occurring active tissue amines are surveyed by Haverback & Wirtschafter (31).

It is interesting that study of autonomic drug action is revealing much information on the chemical characteristics of receptor sites. This is well confirming the faith expressed over a century ago by James Blake (9) in his pioneer investigation of the over-all action of inorganic salts on mammals. One important contribution to the discussion on receptors is the Ciba Foun-

dation Group Study on curare, edited by De Reuck (22). Chagas, in whose honor the group met, indicated that acidic mucopolysaccharides are part of the generalized system of sites for binding curare and curare-like agents. In the discussion were considerations of drug-receptor interactions at neuromuscular junctions (by Paton and Want), and of structure-action relations indicating receptor characteristics (by Cavallito).

Central Nervous System Stimulants and Depressants

Sadove & Wallace (55) give a full account of the practically useful fluorinated anesthetic, halothane. This includes 365 pages of abstracts of articles relating to the drug, and a 24-page index.

It is interesting that anesthesia has always included a consideration of various aspects of inhalation therapy. Maestro Baruch (4) appropriately gives an historical background for a comprehensive symposium on inhalation therapy. This symposium includes a consideration of tests for ventilation adequacy and a broad review of oxygen therapy as well as of aerosols, bronchodilators and mucolytic agents. It further offers a review of oxygen toxicity (24) as well as a consideration of the effectiveness of inhalation therapy in chronic lung disease. Spence (4) offers an outline of emergency treatment in acute respiratory failure.

In a detailed consideration of the neuropharmacology of morphine and morphine-like analgesia, Carroll & Lim (13) indicate that analgesia results from blockade at synapses of nociceptive afferents first, in the thalamic sensory relay areas, and later in the brain stem and spinal internuncials. There is also a block in the suppressor system in the reticular formation causing postural changes accompanying the analgesia. In a review based on 201 references, Murphree (48) discusses the clinical pharmacology of potent analgesics, concluding that morphine is still among the best. He says, "The array of compounds now available is made labyrinthine by the doubtful virtuosity of trademark inventors." He shows that it is not likely that any of the newer compounds, including meperidine, have any significant advantage over morphine. A practical classification of potent analgesic agents depends on the degree of analgesia and its duration. He concludes by indicating that the safe use of analgesic agents is increased by the development of such morphine antagonists as nalorphine.

Maynert & Kaji (42) discuss the relation of brain levels of γ-7-aminobutyric acid to convulsions. Benson & Schiele (5) analyze and classify tranquilizing and antidepressive drugs. Their useful little book includes an appendix of such drugs, giving the trade name, the public name, the over-all action, and dosage. Shepherd & Wing (58) review pharmacological aspects of psychiatry. Himwich (32) neatly abstracts information on tranquilizers, barbituates, and brains. Bickerman (8) reviews the clinical pharmacology of antitussive agents. Empirical cough remedies seem to act largely by central effect. There is, however, a peripherally acting benzonatate which inhibits peripheral receptors.

Killam (36) analyzes drug action on the brain stem reticular formation with evidence chiefly for general anesthetic agents and the amphetamines. Weiss & Laties (67) survey the problem of increasing human performance by caffeine and amphetamines. Gyermek (30) has reviewed 5-hydroxytryptamine antagonists, covering 200 references. With evidence for different hydroxytryptamine (HT) receptors, many types of HT antagonists are to be expected. Anti-HT agents include ergot alkaloids and derivatives, indoles, antihistaminics, phenothiazines, adrenolytic drugs, atropine and derivatives, local anesthetics, morphine and derivatives, and sympathomimetic amines.

Various Types of Drugs

Applezweig (3) offers a comprehensive and detailed review of steroid drugs. This is the most complete coverage of these compounds that has yet appeared. Berliner & Dougherty (6) consider hepatic and extrahepatic regulation of corticosteroids. Their review, covering 127 references includes biosynthesis and biotransformation, the influence of ACTH, thyroid and estrogenic hormones, and the metabolism of cortisol by target cells. Alauddin & Martin-Smith (1) well review the biological activity of steroids containing nitrogen atoms. These nitrogenous steroids reflect the biological properties of steroids in general; there is anabolic action in steroidal Schiff's bases, and there is hypotensive action in steroidal enamines. The ceveratrum ester alkaloids are widely used as pharmacological tools with which to study biological phenomena.

Page & Bumpus (50) review the extensive data on angiotensin. Pharmacology in relation to cardiovascular reflexes is discussed by Schmidt (56). Weisman (66) considers the wide misuse of quinidine in auricular fibrillation. Green (28) offers a critical review of antihypertensive drugs. Wiener (70) discusses various pharmacological considerations of antithrombic therapy. With the increasing use of antithrombic agents, this review may be of increasing importance as a guide for the clinical therapeutic use of these agents. Steinberg (63) suggests various chemotherapeutic approaches to the problem of hyperlipidemia.

Levitt & Goldstein (41) review mercurial diuretics. Beyer & Baer (7) consider physiological factors in the action of diuretic agents, including carbonic anhydrase in renal electrolyte transport, biochemorphology of thiazides and chlorthalidone, modulation of $K^+ - Na^+$ exchange by inhibition of aldosterone synthesis or by aldosterone antagonists such as the spirolactones, and inhibition of distal $K^+ - Na^+$ exchange by organomercurials, chlorazanil and triamterene.

Pharmacological Aspects of Disease Conditions

Mongar & Schild (44) survey cellular mechanisms in anaphylaxis. Nickerson (49) well reviews the drug therapy of shock. He emphasizes the use of adrenal steroids and vasoconstricting sympathomimetic amines, as well as the importance of vasodilation in some aspects of hypovolemia. Adrenergic blockage by dibenzylene may be helpful in patients failing to respond to

blood volume replacement. Wilhelm (71) considers the mediation of increased vascular permeability in inflammation.

Toxicity

Wide concern over drug toxicity has resulted from the thalidomide episode. It is to be emphasized that none of the usual procedures of toxicity estimation, which were thoroughly explored before the introduction of thalidomide to clinical use, were applicable in that instance. In addition to the toxicity of specific drugs, there is growing interest in ecological toxicity resulting from the extensive use of insecticides and herbicides. Dalgaard-Mikkelsen & Poulsen (18) fully explore the toxicity of various herbicides. Welsh (68), in reviewing 440 various articles, discusses skin eruptions as possible hazards of modern therapy with a wide variety of new drugs. He also (68a.) discusses the toxic hazards of anti-obesity drugs. DuBois (24) briefly reviews oxygen toxicity, a matter often disregarded.

In Prospect:

There will be more and better reviews of significant pharmacological developments.

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