REVIEWS OF REVIEWS[1]

By Chauncey D. Leake
Pharmacology Laboratory, The Ohio State University, Columbus, Ohio

In inaugurating a review of reviews of pharmacological information last year, it was pointed out that textbooks in pharmacology comprise more or less comprehensive reviews of the discipline as it appears when the text is published. More detailed comment is suggested by the recent issuance of new textbooks of pharmacology, as well as revised editions of older ones.

Textbooks are notoriously conventionalized. This is certainly the case in pharmacology texts. Most of them still follow the same general presentation of pharmacological information, orgaized by mammalian organ systems, as was offered by Meyer and Gottlieb decades ago. These follow the conventions established by Oswald Schmiedeberg (1838–1921), who in turn was influenced by his teacher, Rudolf Buchheim (1820–1879). Buchheim's *Lehrbuch der Arzneimittellehre* was first published in 1856.

Buchheim defined the task of pharmacologists as first determining where in the body a drug acts, and then explaining the response on the basis of physicochemical reactions between the cell constituents and the drug. Since the time of Schmiedeberg many theories of drug action have been proposed, only to be abandoned when subjected to critical experimentation. The result has been that, as I pointed out a quarter of a century ago (45), pharmacology is not yet a theoretical science, but merely an observational and empirical one. It has been largely concerned with classification of data, analyzing the action of chemicals on living material in whatever terms are convenient in current biophysics, biochemistry, and physiology.

Pharmacologists have usually been motivated by practical medical considerations. This has resulted in a stereotyping of their textbooks which are oriented almost entirely toward therapeutic purposes, and in a taxonomy based on drug effects on various mammalian organ systems. This reflects the continuing conventions in human physiology outlined by Albrecht von Haller (1708–1777), and it fails to take into account the broad implications of pharmacology as a scientific discipline covering many wide applications, not only in the various health professions, but also in agriculture, sociology, politics, warfare, and law.

Medical educators, practicing physicians, medical students, members of the various health professions, and indeed biologists and scientists generally, might welcome a textbook in pharmacology which would be comprehensive in its discussion of basic principles and which would organize the detailed information about individual drugs into some rational and widely applicable system. Textbooks, however, are commercial propositions. Publishers are very conservative in regard to standardized texts. It may well be that

[1] The survey of the literature pertaining to this review was concluded in July 1961.

publishers insist that pharmacological texts conform to the time-worn conventionalities of the trade.

Reviews of Basic Pharmacological Problems

Schueler (67a) offers a provocative volume on what he calls chemobiodynamics and drug design. This volume may annoy conventional pharmacologists, but it will be remarkably stimulating to some of the youngsters who are anxious to orient themselves scientifically in the discipline. This philosophical volume requires much thought. It is difficult to appreciate its value in furnishing practical detail for solving immediate practical problems. It considers, for example, frames of reference for scientific investigation as well as levels of drug action and relationships between chemical constitution and biological activity. There are discussions of primary and secondary drug effects and suggestions on the applications of physicochemical theory to pharmacological problems. The statistical basis for effective biological study is emphasized, and both structural and dynamic considerations are given to molecular systems and their pharmacological reflections. There is a survey of polymolecular systems and an appreciation of the levels of biological organization from cells to societies in affecting pharmacological action. Co-operation is stressed in drug design, with considerations of methods of variation and the designing of drug mixtures. A start is made toward a rational approach in the random search for new drugs. Isomorphism is discussed in relation to the unity of nature. Like an old-fashioned school book, this provoking volume contains "problems in exercises," which, like the balance of the book, require much independent thought.

De Jonge (20) edited the 1960 Leyden Symposium on *Quantitative Methods in Pharmacology*, dealing chiefly with detailed statistical procedures involving drug data. It contains discussions of sequential analysis, drug standardization, parametric or nonparametric statistical methods, drug screening, and drug mixtures. One wonders whether the precision of mathematical treatment discussed is warranted by the ordinary character of pharmacological data. One might suspect that an attempted therapeutic comparison of several drugs of widely differing molecular weight, administered in differing dosages without regard to the weight of the subjects, would yield information of dubious value. Certainly it would seem that different drugs, in order to be compared as to relative effectiveness, would have be to given in equimolar doses, so that there might be some correlation between the mass of the chemicals administered and the mass of the biological material on which the chemicals act. In this regard Mainland (50) has good advice on the use and misuse of statistics in medical publications. Along these lines also there has recently appeared an interesting little essay by Werner (83) on the measurement of uncertainty. Much wisdom from experience on the testing of new drugs is given by Starr (74) not only on animal and human experiments, and statistics, but also on the elimination of bias, the use of paired experiments, and the folly of elaborate experimental designs.

Biological membranes.—The passage of substances across biological membranes is reviewed by Kruhøffer (40). He classifies the processes into diffusion, where the rate is proportional to concentration differences and where water-oil solubilities may be involved; facilitated diffusion and penetration; reversible binding to membrane carriers; and unknown processes in which rates may be limited. Skou (72) reviews the effects of drugs on cell membranes with special reference to local anesthetics. He points out that undissociated bases block the permeability of nerves to Na^+ by molecular sticking in the lipid layer of membranes.

Drug transport.—This subject is attracting much interest. Harris (31) gives full consideration to the problems involved in transport and accumulation in biological systems. This basic discussion covers much physicochemical detail on membranes, movement of water, ion distribution, blood cells, muscle, mitochondria, nerves, plant cells, and yeast. Wilbrandt & Rosenberg (85) offer an excellent discussion of the concept of carrier transport and its corollaries in pharmacology. They emphasize that the carrier system involves a binding reaction between substrate and carrier, the diffusion of the complex, and a splitting reaction on the other side of the membrane; the kinetics depend on the velocity constants of these three steps. The review considers equilibria, steady states, counter-transport, metabolic factors, competition, and inhibition. Experimental studies reviewed include sugars, amino acids, inorganic ions, purines, glycerol, and serotonin; 477 references are given. It is clear that the identification of carriers will be a difficult problem.

Chelating phenomena.—The proceedings of a conference on chelation have been edited by Frederick (25). This conference considered chemical factors, including stability and selectivity; the biological significance of chelation, with examples from copper proteins, plant nutrition, the activation of muscle phosphorylase, iron and cobalt; medical applications, with reference to iron and calcium metabolism; the mobilization of lead; and industrial applications, as in catalysis and in maintaining food quality.

Ubiquinone.—An important Ciba Foundation conference on quinones in electron transport was edited by Wolstenholme & O'Connor and arranged by Folkers (89). It is an interesting example of good-willed international co-ordination and co-operation on a scientific as well as on an industrial level. Folkers indicates that nobody anticipated that the Liverpool studies on vitamin-A deficiency in rats (under Richard Morton) and the Wisconsin studies (under David Green and F. L. Crane) on lipid extracts of beef heart mitochondria, which function in the electron transport activities of certain particles would build a bridge into the field of photosynthesis in higher plants, as shown by Norman Bishop. Many quinones may be involved, but the important ones seem to be those which are structurally related to the A and K vitamins and which function as coenzymes. The most important one is sometimes designated as coenzyme Q_{10}. Because it is so widely distributed in living material, it is also called "ubiquinone." The symposium fully explored the chemistry and biological significance of these fascinating compounds.

Practical Sociological Aspects of Current Pharmacology

It is clear that some type of reform is coming in drug terminology. The confusion over names is ridiculous. The Committee on Advertising of the *New England Journal of Medicine* (15) emphasized the problem editorially. Miller (52), Director of Revision of the *U. S. Pharmacopeia*, well considers the various categories of drug names, the needs for nonproprietary names, and the standards that may be established for them. The American Medical Association Council on Drugs evaluated 51 new drugs in 1960, and established their public names (17).

Animals and humans.—A helpful annotated bibliography on the production, care, and use of laboratory animals has been prepared by Cass, Campbell & Lange (12). This lists 1518 references classified on the basis of anatomy, physiology, and psychology; diseases, abnormalities, and injuries; nutrition, food and water needs, and diets; breeding programs; design and operation of maintenance colonies; procurement and use; special techniques for handling for anesthesia or for euthanesia; administration with regard to costs; personnel and public relations; and periodical publications of interest in the field. In a survey of forecasting drug effects in humans from studies on laboratory animals, Litchfield (48) concludes that the predictive value is limited. Many of the most serious toxic reactions that may result when drugs are given to humans are not predictable from observations on dogs or rats. Fox (24), surveying 35 references, reviews social and cultural factors in our American society that are conducive to medical research on human subjects.

Social problems involving pharmacological factors.—In a recent interesting symposium (44) arranged by the Federation of American Societies for Experimental Biology, pharmacological factors were reviewed in the control of pollution of airs and waters (Stockinger), radiation protection (Patt), biological fertility (Millman), and insect pests (Burnett). Also considered were various aspects of the application of pharmacological information to problems of world-wide significance, with emphasis on some of the unsuspected occurances from such control attempts. Similar findings were reported in the symposium on biological problems arising from the control of pests and diseases, as arranged by Wood (90).

Pharmacological Aspects of Metabolism

Davis (18) opened a symposium arranged by the Federation of American Societies for Experimental Biology on the interaction of mineral elements in nutrition and metabolism. The survey considered calcium and phosphorus, zinc and calcium, magnesium, iron and copper, and molybdenum and sulfate sulfur. A thorough survey of copper metabolism, with 226 references, was made by Scheinberg & Sternlieb (65). In this review it is emphasized that the average human daily intake of copper in an ordinary diet ranges from two to five milligrams, which gives such an abundance of copper that there is no evidence of deficiency. The survey considers routes followed by ingested copper, with most being excreted in the feces; copper proteins, such as

ceruloplasmin, pyrosinase, erythrocuprein, cerebrocuprein, and cytochrome-C-oxidase; copper deficiency in relation to iron metabolism; phospholipid synthesis; osteoblastic activity; keratin and pigment formation; and copper toxicity on excessive ingestion, or in hereditary abnormality, such as Wilson's disease.

Modell (54) has recently surveyed the status and prospects of drugs that may be useful in the control of overeating. Young (91) chaired a Ciba Foundation Colloquium on the metabolic effects of adrenal hormones. This included consideration of adrenal hormone influence on protein synthesis.

Fishman (22b) surveyed the chemical aspects of drug metabolism, with well documented detail on conjugations and specific biochemical mechanisms.

Eichholtz and Alexander, (22a) in evaluating anti-rheumatic drugs, suggest that an increase in sugar metabolism in granulomatous tissue, with lytic effects, may be a better criterion for effectiveness than anti-edematous action. This review covers 109 references dealing with prednisolone, phenylbutazone, aminopyrine, and salicylates.

Chemical Disinfection and Chemotherapy of Infectious Diseases

In a symposium on chemical disinfection, Jacobs (37) reviewed the dynamics of sterilization, showing that sometimes organic material may make bacterial colonies more sensitive to chemical destruction. In this same symposium, Cook reviews recent information on phenolic disinfectants, and Davis surveys industrial types of chemical sterilization.

Recent important studies have rendered possible an effective chemotherapy for systemic fungus diseases. This matter is reviewed by Harrell & Bocobo (30), with reference to 270 contributions. Factors affecting the absorption and excretion of erythromycin and two of its derivatives are reviewed by Hammond & Griffith (28). Biliary excretion in humans is emphasized. With reference to 121 contributions, Kunin & Finland (41) reviewed the clinical pharamcology of the tetracycline antibiotics.

Schnitzler (67) offers a valuable survey of the chemotherapy of leprosy and tuberculosis, with a comparison of chemotherapeutic response in the two diseases caused by acid-fast organisms to chaulmoogra, sulfones, streptomycin, and isoniazids, with combinations of these various types of drugs and with correlations of effectiveness in the two diseases. The antibacterial action of sulfonamides is reviewed by Neipp, Sackman & Tripod (56). The sulfur drugs cause both morphological changes and alterations in oxygen consumption in bacteria. This review considers various aspects of the pharmacological properties of sulfa drugs, their organ and tissue distribution, and their therapeutic effects in relation to blood concentration and toxicity.

Cancer chemotherapy.—The nomenclature of cancer chemotherapy agents is analyzed by Ihndris (34). Brockman (7) refers to 162 publications in reviewing the mechanism of resistance to metabolite analogues with anti-

cancer activity. LePage (46) reviews the use of combinations of antimetabolites in the chemotherapy of cancer. Holland (32) reviews 203 publications dealing with folic acid antagonists. Waksman (80) edits a conference discussion on actinomycins in regard to tumor treatment in animals and humans. This discussion includes chemical and microbiological considerations, as well as pharmacological and toxicological factors in relation to their clinical significance. In noting that it is 20 years since the isolation of actinomycin and its crystallization, Waksman suggests that its toxicity, which is too great for its use as an antibiotic, may parallel its antitumor action.

Autonomic Drugs

Important reviews have recently appeared on various aspects of the pharmacology of nicotine, on adrenergic mechanisms, and, quite significantly, on the character of autonomic drug receptors.

Nicotine and smoking.—Cattell (13) edited a conference discussion on the cardiovascular effects of nicotine and smoking. Actually the discussion covered wider aspects of the pharmacology of nicotine, such as its absorption and fate, its pharmacological action and the various factors involved in the biological effects of tobacco smoke, and chronic poisoning from nicotine or tobacco. Special consideration was given to the influence of nicotine from tobacco smoke on the peripheral circulation and on the heart and coronary circulation. Travell (79a) reviewed the absorption of nicotine and the effects of smoking on cardiovascular disorders. Larson, Haag & Silvette (42) reviewed 208 publications on the effects of nicotine and smoking on various metabolic functions.

An amazingly comprehensive study of the world's literature on experimental and clinical investigations on tobacco was also prepared by Larson, Haag & Silvette (43). This comprises an analysis of over 6500 scientific references. Here in one volume is all the pertinent information available on the effects of tobacco and its alkaloids on living material, and especially on humans. The analysis considers the absorption and fate of the alkaloids and other substances in tobacco which may be ingested by inhalation or other means; and the effects of tobacco and its alkaloids on special senses, the nervous system, skeletal muscle, blood, the cardiovascular system, the respiratory system, the urinary tract, the gastrointestinal tract, the oral cavity, metabolism, the endocrine glands, and the reproductive organs. Local actions of tobacco and its alkaloids are analyzed as well as their toxicity, hypersensitivity, tolerance, habituation, and immunology. Tobacco smoking is handled judiciously and fairly in relation to lung cancer and other specific diseases. There is a chapter on the medical uses of tobacco. Helpful appendices give information on biological and chemical methods for the estimation of nicotine, as well as notes on the pharmacology of nicotine derivatives. There is an excellent review of the use of nicotine in the physiological analysis of the components of the autonomic nervous system, as originally outlined by John Langley (1852–1925).

Adrenergic mechanisms.—Wolstenholme, O'Connor & Vane (88) have edited a comprehensive symposium on adrenergic mechanisms. Introduced charmingly by Sir Henry Dale, the book covers the formation and inactivation of adrenergic transmitters, the storage of catechol amines, the characteristics of the adrenergic neurone, adrenergic mechanisms in humans, the actions of epinephrine and norepinephrine on effector cells, the mechanism of action of other sympathomimetic amines, and central and peripheral adrenergic mechanisms. In this symposium Furchgott again discusses his concept of the various types of receptors for sympathomimetic amines: alpha for contraction of smooth muscle, beta for increases in rate and contractility of heart muscle and for relaxation of smooth muscle other than intestinal, gamma for glycogenolysis, and delta for inhibition of intestinal smooth muscle. Sutherland & Rall (76) survey 137 references in a discussion of the relation of catechol amines and other hormones to adenosine-3′-5′-phosphate and phosphorylase. The catechol amines increase cyclic 3,5-adenylate in tissues, with an increase in phosphorylase and glycogenolysis, which in the liver releases glucose, in the adrenal produces steroids, and in the heart gives inotropic effects. In a short, sharp review, Burn (10) discusses adrenergic reactions to reserpine, bretylium, and guanethidine.

Cholinergic receptors.—In a review of cholinergic receptors, Weser (84) raises the question of what is the substrate on which acetylcholine acts, and what is the change of this substrate by depolarization. The receptor substance may be a protein or a polysaccharide or a combination of both. By the use of radioactive carbon in curare and in muscarone, it appears that the receptor sites are pores in postsynaptic membranes, with anionic walls for quaternary nitrogen groups, and esteratic sites for ester groups, and thus with resulting permeability changes for sodium and potassium. Muscarone resembles acetylcholine but has no ester group to be hydrolyzed by cholinesterase and is ten times as active as acetylcholine in depolarizing ganglionic and neuromuscular synapses. Wilkinson (86) outlines the history and chemistry of muscarine in a helpful manner.

Other receptor problems.—An interesting theory of drug action, based on the rate of drug receptor combinations, is proposed by Paton (60). Winterstein (87) carefully reviews the problems involved in the surprising differences in the peripheral actions of many drugs depending on whether they are introduced into the circulation or into the cerebrospinal fluid. This discussion reviews intracranial chemoreceptors, pointing out that histological study is necessary to demonstrate their existence. Their presence is suggested by the fact that the surface and lateral parts of the fourth ventricle are sensitive to hydrogen ions and procaine, whereas the respiratory center is not. The presence of sensatory baroreceptors in the vascular supply to the brain seems likely in view of the appearance of headache after large doses of nitrates or vasoconstricutors or after increases or decreases of cerebrospinal fluid pressure. Schwarzacher (68) has edited an important Basel symposium on the histochemistry of cholinesterase and the distribution of this enzyme in various tissues.

Central Nervous System Stimulants and Depressants

A thorough review of analeptics is offered by Hahn (29). This begins with a consideration of the biochemorphology of the tetrazoles and gives much detail on pentylenetetrazol. Picrotoxin is discussed as well as glutarimides. There is further structure-action consideration of alkylated acid amides, with particular emphasis on nikethamide. The amphetamines are surveyed, as well as other stimulating drugs such as strychnine, camphor, the xanthines, and convulsant barbiturates.

Shideman (71) surveys 204 references on the clinical pharmacology of hypnotics and sedatives. Eckenhoff & Oech (22) review 262 contributions dealing with the effects of narcotics and narcotic antagonists on respiration and circulation in humans. Telford & Keats (79) review narcotic and narcotic-antagonist mixtures; they cite 143 references on this subject. In a detailed and skillful manner, Way & Adler (81) go over 338 references bearing on the metabolic fate of morphine and its surrogates. This important review considers methods of estimation; absorption, distribution, and excretion; metabolism by dealkylation and enzymatic mechanisms; conjugations; hydrolysis, tolerance, and analgesia in relation to the biologic disposition of these types of compounds.

Anesthesia.—The structure and function of the central nervous system in relation to anesthesia is considered in a symposium by Bowsher *et al.* (5). Johnstone (38), in reviewing the status of halothane as a general anesthetic, with reference to 243 contributions, concludes that it is excellent in all respects.

Pauling (58) offers a spectacular new molecular theory of general anesthesia. He attributes the interference with brain activity to the formation of minute hydrate crystals of the clathrate type by nonhydrogen-bonding anesthetics in the brain. His correlative evidence is impressive. Classic theories of anesthesia are discussed in relation to the new proposal, and Pauling is careful to point out that the hydrate microcrystal therory of anesthesia suggests that anesthetic agents act on all tissues in the same general way.

Pauling indicates that the striking correlation between the narcotizing partial pressure of the anesthetic agents and the partial pressure necessary to cause formation of hydrate crystals provides some support for the proposed theory. Nevertheless, he admits that any theory based on van der Waals attraction of the molecules of anesthetic agents for other molecules would show similar correlations. However, the proposed theory is sufficiently detailed to permit predictions and to devise experiments that may either prove or disprove it. One of its advantages is that it gives a common mechanism of action for such widely varying anesthetics as chloroform, xenon, and nitrous oxide.

Carbon dioxide is again attracting interest: Meyer and his associates (51) have surveyed carbon dioxide narcosis and Eckenhoff (21) has edited a

considerable symposium on the biological significance of carbon dioxide. This symposium also includes reviews on the production, storage, transport, and removal of carbon dioxide from mammalian bodies; its relation to organ systems, and its relation to anesthesia.

PSYCHOPHARMACOLOGY

Callaway & Stone (11) offer a critical review of psychopharmacologic theory. This review indicates the vast amount of specific information that is still needed before a satisfactory theory can be developed for explaining change of mood and brain activity as caused by drugs. Loranger, Prout & White (49) make a careful analysis of the placebo effect in psychiatric drug research. They point out that less than 10 per cent of published reports on tranquilizers and antidepressant drugs meet minimum standards of scientific acceptability. The double-blind technique is emphasized in the evaluation of psychopharmacological durgs.

Roth & Barlow (63a) review the penetration of drugs into the brain, using autoradiography. They point out that the anatomical boundaries of the brain are clearly reflected by the penetration and accumulation of all compounds studied, a finding confirming the proposition that whole brain homogenates are inadequate for the study of drug-brain relationships. Circulation as regional blood flow or volume of capillary blood flow is not decisive in the determination of the entry or accumulation of drugs in the brain. Thiopental, however, through its extreme fat solubility, may be circulation-dependent. Penetration is retarded by myelin. The blood-brain barrier is a complex anatomical, physiological, and biochemical phenomenon, and no unitary hypothesis is adequate to embrace all the observed events. The accumulation of a drug in the brain implies some sort of binding between drug and tissue. In general, this is nonspecific, but some drugs, such as the hydrazides, accumulate in the hippocampus, and acetazolamide accumulates in the hypothalamus. However, focal concentration of a drug in the brain does not necessarily imply the site of action. Correlations may be found between regional drug concentration and electrophysiological events, biochemical changes, and resulting pharmacological action.

Bures (9a) critically reviews the spreading depression phenomenon following the local application of salt solutions to various parts of the brain, as first described by Leao. Under the auspices of the Federation of American Societies for Experimental Biology, Davis (19) introduced a symposium on central nervous system physiology and drug action. In this symposium Goldring and O'Leary discussed the pharmacological dissolution of evoked cortical potentials; Bickford reviewed electroencephalographic analysis of drug action on the brain; Brazier surveyed the electrophysiological responses of the brain to anesthetics, and Hunt surveyed the behavioral implications of drug actions on the brain.

With regard to specific new psychopharmacological agents, Impastato

(35) introduced a critical symposium on nialamide. Another symposium was recently held on depression, (77) with special studies of a new antidepressant compound related to imipramine. At this symposium Vernier discussed the pharmacology of antidepressant drugs, and described the actions and characteristics of amitriptylamine, which is 5-3-dimethylamino-propylidene-dibenzo-1, 4-cycloheptadine hydrochloride. This has anticonvulsant action, an antihistaminic effect, some adrenergic blockade, and weak effects on the electroencephalogram. This compound is not a monoamine oxidase inhibitor.

Brill (6) introduced a symposium on chlordiazepoxide, a muscle-relaxing and spinal reflex-blocking agent. The pharmacology of this compound was reviewed by Randall. Although it has been used for relieving anxiety, the clinical studies are not well controlled. Toxic effects of drowsiness and vertigo occur at doses around 1 mg/kg/day, which is only slightly above the dose needed for clinical effectiveness.

Cardiovascular Drugs

Welt (82) is compiling a helpful compendium of information on cardiovascular drugs. The first two volumes include material published fron 1950 to 1955. This is organized by listing drugs which produce various cardiovascular effects, with references to the information, and also by listing all the various cardiovascular effects with reference to the drugs producing them. The value of the compilation lies in the fact that it is an exhaustive index analysis of publications in some of which the action of the drugs on the cardiovascular system may not be indicated from the title. In preparation now are similar volumes to cover the period from 1955 to 1960, and then there will come a volume to cover publications prior to 1950. It is anticipated that the project will be continued.

Bellet (3) surveys the clinical pharmacology of antiarrhythmic drugs. Charlier (14) carefully reviews coronary dilators. This review of 908 contributions deals with physiological factors in coronary blood flow, a critical analysis of methods of measuring changes in the lumen of coronary vessels, clinical methods for assessing antianginal medications, and then a consideration of specific coronary vasodilators such as the nitrites, the xanthines, and sympathomimetic drugs. Modell (53) surveys the chemical pharmacology of digitalis materials, correlating particularly the effects of digitalis as noted in animals with those noted in humans. A short review of drug therapy in hypertension is offered by Smirk (73). Grollman (27) edits a symposium on new diuretics and antihypertensive agents, which surveys guanethidine and bretylium, as well as benzothiadiazines, spirolactones, and phthalimidines. Price (62) again reviews 102 references dealing with the circulatory actions of general anesthetic agents and the homeostatic roles of epinephrine and norepinephrine in humans. Buckley (7a) briefly reviews the pharmacology of antihypertensive compounds.

Enzymes, Proteins and Hormones

Sherry & Fletcher (70) offer a therapeutic evaluation of proteolytic enzymes, reviewing 177 references. Folkers (23) edits a symposium on amino acids, peptides, and proteins, in which Du Vigneaud reviews his rich experiences with polypeptides from insulin to oxytocin. In this symposium there are discussions on ion-exchange chromotography and homogenecity studies on insulin and related substances.

Antoniades (2) edits an interesting symposium on hormones in human plasma, with special reference to their nature and transport. This considers methods of plasma fractionization and hormones of pancreatic, pituitary, steroid, thyroid, adrenal medulla, and placental origin. Levine & Berger (47) review orally active hypoglycemic substances and the rationale of their use. Selenkow & Callaco (69) with critical analysis go over 197 references on the clinical pharmacology of antithyroid compounds. In a symposium on neglected hormones (78), Lerner & Case deal with melatonin, Munson considers parathyroids, Farrell reviews the epiphysis cerebri control of steroid secretion, and Gann and his associates review aldosterone secretion.

Neurohypophysial hormones are broadly reviewed by Sawyer (64), with respect to their secretion and metabolism; their release, inactivation, and excretion; and active peptides such as oxytocin, vasopressins, and arginine vasotocin. He considers relations between structure and action, antidiuretic function, milk ejection, and saluretic action and suggests the growing knowledge of adenohypophysial function. There are 369 referencess. A survey of the metabolism of the neurohypophysial hormones is offered by Dicker (20a).

Graff helpfully classifies steroids and considers their nomenclature. Bunim (8) edits a review of a decade of antiinflammatory steroids from cortisone to desamethasone, from the standpoints of biochemical aspects, laboratory evaluation, enzymatic metabolism, effects on electrolyte and carbohydrate metabolism, and clinical effectiveness. Berczeller & Kupperman (4) review 97 references dealing with anabolic steroids. Streeten (75) analyzes the antimetabolic action of spirolactones. Kistner (39) discusses the use of steroidal substances in endometriosis.

Toxicology

An interesting symposium on general problems in toxicology has been edited by Coon & Maynard (16). This considers the accumulating toxic factors in airs and waters; the potential toxicity involved in foods, drugs, and cosmetics; agricultural and industrial toxicity; radiation toxicity; and toxicological aspects of submarine and space exploration. The symposium concludes with a consideration of toxicology as a discipline and gives suggestions for the training of toxicologists.

Nigrelli (57) arranged a conference on the biochemistry and pharmacology of compounds derived from marine organisms, most of which have toxic

action. Many marine organisms secrete pharmacologically active amines, and many involve extremely powerful poisonous substances. A sulfur-containing neurotoxin from anilid worms is described; a tetramine salivary poison occurs in gastropods; and there are special venoms from stone-fish, weaver-fish, and well-known highly poisonous Gonyaulix.

Drug-related forms of blood dyscrasia are analyzed and discussed by Huguley, Erslev & Bergsagel (33). They emphasize again the well-known problem confronting all clinicians in weighing the hazards of a drug against the hazards of the disease against which the drug may be used. The review notes pancytopenia, with particular references to chloramphenicol; thrombocytopenia, with such drugs as chloramphenicol, guanethidine, and chlorothiazide; and leukopenia with chlorpromazine. The phenothiazine derivatives are the more common causes of agranulocytosis.

The general pharmacology of heavy metals, with particular reference to toxic action, is reviewed by Passow, Rothstein & Clarkson (59). They note particularly the wide effect of heavy metals on enzyme systems, on surface films, and on all-or-none responses of cell membranes. They emphasize the time dependence of heavy metal action. The review gives special reference to uranium and mercury, with specific discussion on the action of these elements on permeability in transport.

Pizzalato & Mannheimer (61) review the histopathological effects of local anesthetics and related compounds.

Miscellaneous

Antian (1) offers a helpful review of plastics, their uses and problems in medicine and pharmacy. This review gives the characteristics of different types of plastics, the toxic reactions that may be associated with them, and a guide to their selection for various pharmaceutical and medicinal uses.

Burchenal & Ellison (9) review the experimental pharmacology and clinical use of pyridine and purine antagonists. They quote 81 references.

In a review of anticoagulant therapy, Ingram (36) discusses the mode of action of heparins and coumarin-indanediones, with indications for their use, dangers associated with their use, modes of administration, dose schedules, antidotes, and means of controlling their activity.

Moser (55) continues his reporting on diseases of medical progress with special attention to toxic reactions to various drugs. His review covers 112 references to antibiotic-induced diseases, 82 references involving cardiovascular drugs, 26 references on collagen diseases, 125 references involving hematologic reactions, 83 references to hepatic and gastroenteric conditions, 108 references regarding hormones, 81 references concerning radiation injury, and many other reports dealing with metabolic, neurologic, psychiatric, pulmonary, renal, surgical, and dermatological situations.

With reference to 140 contributions, Robinson (63) reviews lysolecithin. This glycerophosphatide with hemolytic action is probably a monopalmi-

toyl lecithin. It had already been shown to be lecithin from which one unsaturated fatty acid is missing. This toxic agent may be extracted from pancreas and salivary glands, and it is found in some bacteria and fungi, as well as in snake venom. It liberates histamine and causes hemolysis.

An interesting review is Schmidt's (66) discussion of pharmacology in relation to aviation medicine.

A general and comprehensive symposium on the efficacy of new drugs was edited by Conn (15a). This symposium includes a consideration of antibiotics, antitussives, oral hypoglycemics, cortico-steroids, fibrinolytics, diuretics, anti-ovulatory compounds and vaccines.

In Prospect

Reviews of pharmacological information are increasing in number and in significance. This is to be expected as the interdisciplinary relations of pharmacology are increasingly realized. Further, the increasing applications of pharmacological knowledge to so many widely diverse areas of practical endeavor are forcing greater reliance on reviews for the necessary background orientation. In divorcing itself from almost exclusive dependence on the medical profession, pharmacology has become an important basic science for all the health professions, as well as for agriculture, agronomy, sociology, politics and law, and warfare. In this widening of pharmacological influence, reviews are certain to become more and more necessary for the effective communication of pharmacological knowledge.

LITERATURE CITED

1. Antian, J., *Am. J. Hosp. Pharm.*, **18**, 329 (1961)
2. Antoniades, H. N. (Ed.), *Hormones in Plasma: Nature and Transport* (Little Brown & Co., Boston, Mass., 667 pp., 1960)
3. Bellet, S., *Clin. Pharmacol. Therap.*, **2**, 345–58 (1961)
4. Berczeller, P. H., and Kupperman, H. S., *Clin. Pharmacol. Therap.*, **1**, 464–82 (1960)
5. Bowsher, D., Magoun, H. W., Brazier, M. A. B., and Brock, J. C., *Brit. J. Anaesthesia*, **33**, 174–218 (1961)
6. Brill, N. Q., Randall, L. O., *et al.*, *Diseases of Nervous System*, [2] 22(7), 70 pp. (1961)
7. Brockman, R. W., *Clin. Pharmacol. Therap.*, **2**, 237–61 (1961)

7a. Buckley, J. P., *J. Pharm. Sci.*, **50**, 539–49 (1961)

8. Bunim, J. J. (Ed.), *Ann. N. Y. Acad. Sci.*, **82**, 797–1014 (1959)
9. Burchenal, J. H., and Ellison, R. R., *Clin. Pharmacol. Therap.*, **2**, 523–41 (1961)

9a. Bures, J., *J. Comp. Physiol. Psychol.*, **53**, 558 (1960); *J. Neurophysiol.*, **23**, 225 (1960)

10. Burn, J. H., *Brit. Med. J.*, **1**, 1623 (1961)
11. Callaway, E., and Stone, G. C., *Clin. Pharmacol. Therap.*, **1**, 247–67 (1960)
12. Cass, J. S., Campbell, I. R., and Lange, L., *Federation Proc.*, **19**(4), Suppl. 6, 196 pp. (1960)
13. Cattell, M. (Ed.), *Ann. N. Y. Acad. Sci.*, **90**, 1–344 (1960)
14. Charlier, R., *Coronary Dilators* (Pergamon Press, London, England, 219 pp., 1961)
15. Committee on Advertising, *New Engl. J. Med.*, **263**, 21–23 (1960)

15a. Conn, H. F., *Med. Clin. N. Am.*, **45**, 779–1096 (1961)

16. Coon, J. M., and Maynard, E. A., (Eds.), *Federation Proc.*, **19** (3), Suppl. 4, 52 pp. (1960)
17. Council on Drugs, *J. Am. Med. Assoc.*, **177**, 45–49 (1961)
18. Davis, G. K., *et al.*, *Federation Proc.*, **19**, 635–77 (1960)
19. Davis, H., Goldring, S., *et al.*, *Federation Proc.*, **19**, 611–35 (1960)
20. De Jonge, H. (Ed.), *Quantitative Methods in Pharmacology* (Interscience Publishers, New York, N. Y., 411 pp., 1961)

20a. Dicker, S. E., *J. Pharm. Pharmacol.*, **13**, 449–69 (1961)

21. Eckenhoff, J. E. (Ed.), *Anesthesiology*, **21**, 585–766 (1960)
22. Eckenhoff, J. E., and Oech, S. R., *Clin. Pharmacol. Therap.*, **1**, 483–524 (1961)

22a. Eichholtz, F., and Alexander, K., *Arzneimittel-Forsch*, **11**, 515–21 (1961)

22b. Fishman, W. H., *Chemistry of Drug Metabolism* (Charles C Thomas Springfield, Ill., 252 pp., 1961)

23. Folkers, K. (Ed.), *Ann. N. Y. Acad. Sci.*, **88**, 533–770 (1960)
24. Fox, R. C., *Clin. Pharmacol. Therap.*, **1**, 423–43 (1961)
25. Frederick, J. F. (Ed.), *Ann. N. Y. Acad. Sci.*, **88**, 281–532 (1960)
26. Graff, M. M., *Clin. Pharmacol. Therap.*, **1**, 5–13 (1960)
27. Grollman, A. (Ed.), *Ann. N. Y. Acad. Sci.*, **88**, 771–1020 (1960)
28. Hammond, J. B., and Griffith, R. S., *Clin. Pharmacol. Therap.*, **2**, 308–12 (1961)
29. Hahn, F., *Pharmacol. Revs.*, **12**, 447 (1960)
30. Harrell, E. F., and Bocobo, F. C., *Clin. Pharmacol. Therap.*, **1**, 104–34 (1960)
31. Harris, E. J., *Transport and Accumulation in Biological Systems* (Academic Press, New York, N. Y., 282 pp., 1960)
32. Holland, J. F., *Clin. Pharmacol. Therap.*, **2**, 374–409 (1961)
33. Huguley, C. M., Jr., Erslev, A. J., and Bergsagel, D. E., *J. Am. Med. Assoc.*, **177**, 23–26 (1961)
34. Ihndris, R. W., *Clin. Pharmacol. Therap.*, **2**, 274–82 (1961)
35. Impastato, D. J. (Ed.), *Diseases of Nervous System*, [2] 20(8), 56 pp. (1959)
36. Ingram, G. I. C., *Pharmacol. Revs.*, **13**, 279–328 (1961)
37. Jacobs, S. E., Cook, A. M., and Davis, J. G., *J. Pharm. Pharmacol.*, **12**, Suppl., 9T-40T (1960)
38. Johnstone, M., *Anesthesiology*, **22**, 591–614 (1961)
39. Kistner, R. W., *Clin. Pharmacol. Therap.*, **1**, 525–37 (1961)

40. Kruhøffer, P., *J. Pharm. Pharmacol.*, **13**, 193–203 (1961)
41. Kunin, C. M., and Finland, M., *Clin. Pharmacol. Therap.*, **2**, 51–69 (1961)
42. Larson, P. S., Haag, H. B., and Silvette, H., *Clin. Pharmacol. Therap.*, **2**, 80–109 (1961)
43. Larson, P. S., Haag, H. G., and Silvette, H., *Tobacco: Experimental and Clinical Studies* (Williams & Wilkins, Baltimore, Md., 944 pp., 1961)
44. Leake, C. D. (Ed.), *Federation Proc.*, **19**, 541–61 (1960)
45. Leake, C. D., *Univ. Calif. Publs. Pharmacol.*, **1**, 1 (1938)
46. LePage, G. A., *Clin. Pharmacol. Therap.*, **2**, 121–29 (1961)
47. Levine, R., and Berger, S., *Clin. Pharmacol. Therap.*, **1**, 227–46 (1960)
48. Litchfield, J. T., *J. Am. Med. Assoc.*, **177**, 34–38 (1961)
49. Loranger, A. W., Prout, C. T., and White, W. A., *J. Am. Med. Assoc.*, **176**, 920–25 (1961)
50. Mainland, D., *Clin. Pharmacol. Therap.*, **1**, 411–22 (1961)
51. Meyer, J. S., *et al.*, *Neurology*, **11**, 524 (1961)
52. Miller, L. C., *J. Am. Med. Assoc.*, **177**, 27–33 (1961)
53. Modell, W., *Clin. Pharmacol. Therap.*, **2**, 177–90 (1961)
54. Modell, W., *J. Am. Med. Assoc.*, **173**, 1131–36 (1960)
55. Moser, R. H., *Clin. Pharmacol. Therap.*, **2**, 446–522 (1961)
56. Neipp, L., Sackman, W., and Tripod, J., *Antibiotics and Chemotherapy*, **9**, 19–82 (1961)
57. Nigrelli, R. F. (Ed.), *Ann. N. Y. Acad. Sci.*, **90**, 615–950 (1960)
58. Pauling, L., *Science*, **134**, 15 (July 7, 1961)
59. Passow, H., Rothstein, A., and Clarkson, T. W., *Pharmacol. Revs.*, **13**, 185–224 (1961)
60. Paton, W. D. M., *Proc. Roy. Soc.*, (*London*) *B*, **154**, 21–69 (1961)
61. Pizzalato, P., and Mannheimer, W., *Histopathological Effects of Local Anesthetics* (Charles C Thomas, Springfield, Ill., 108 pp., 1961)
62. Price, H. L., *Clin. Pharmacol. Therap.*, **2**, 163–76 (1961)
63. Robinson, N., *J. Pharm. Pharmacol.*, **13**, 321–54 (1961)
63a. Roth, L. J. and Barlow, C. F., *Science*, **134**, 21 (1961)
64. Sawyer, W. H., *Pharmacol. Revs.*, **13**, 225–78 (1961)
65. Scheinberg, J. H., and Sternlieb, I., *Pharmacol. Revs.*, **12**, 355–81 (1960)
66. Schmidt, C. F., *Aerospace Med.*, **32**, 577 (1961)
67. Schnitzler, R. J., *Antibiotics and Chemotherapy*, **9**: 145–90 (1961)
67a. Schueler, F. W., *Chemobiodynamics and Drug Design* (McGraw-Hill, New York, N. Y., 638 pp., 1960)
68. Schwarzacker, H. G. (Ed.), *Histochemistry of Cholinesterase* (S. Karger, Basel, Switzerland, 261 pp., 1961)
69. Selenkow, H. A., and Callaco, F. M., *Clin. Pharmacol. Therap.*, **2**, 191–219 (1961)
70. Sherry, S., and Fletcher, A. P., *Clin. Pharmacol. Therap.*, **1**, 202–26 (1960)
71. Shideman, F. E., *Clin. Pharmacol. Therap.*, **2**, 313–44 (1961)
72. Skou, J. C., *J. Pharm. Pharmacol.*, **13**, 204 (1961)
73. Smirk, F., *Clin. Pharmacol. Therap.*, **2**, 110–20 (1961)
74. Starr, I., *J. Am. Med. Assoc.*, **177**, 14–22 (1961)
75. Streeten, D. H. P., *Clin. Pharmacol. Therap.*, **2**, 359–73 (1961)
76. Sutherland, E. W., and Rall, T. W., *Pharmacol. Rev.*, **12**, 265–300 (1960)
77. Symposium on Depression, *Diseases of Nervous System*, [2] **22**, Suppl., 56 pp. (1961)
78. Symposium on Neglected Hormones, *Federation Proc.*, **19**, 590–610 (1960)
79. Telford, J., and Keats, A. S., *Anesthesiology*, **22**, 465–84 (1961)
79a. Travell, J., *Ann. N. Y. Acad. Sci.*, **90**, 13 (1960)
80. Waksman, S. A. (Ed.), *Ann. N. Y. Acad. Sci.*, **89**, 283–486 (1960)
81. Way, E. L., and Adler, T. K., *Pharmacol. Revs.*, **12**, 383 (1960)
82. Welt, I. D. (Ed.), *Index-Handbook of Cardiovascular Agents*, **2** (Publ. 821, Natl. Acad. Sci.—Natl. Research Council, Washington, D. C., 1568 pp., 1960)
83. Werner, G., *Clin. Pharmacol. Therap.*, **2**, 143–46 (1961)
84. Weser, P. G., *J. Pharm. Pharmacol.*, **12**, 577–94 (1960)
85. Wilbrandt, W., and Rosenberg, T., *Pharmacol. Revs.*, **13**, 109–84 (1961)
86. Wilkinson, S., *Quart. Revs.* (*London*), **15**, 153–72 (1961)

87. Winterstein, H., *Pharmacol. Revs.*, **13**, 71 (1961)
88. Wolstenholme, G. E. W., O'Connor, C. M., and Vane, J. R. (Eds.), *Adrenergic Mechanisms* (Little Brown & Co., Boston, Mass., 652 pp., 1961)
89. Wolstenholme, G. E. W., and O'Connor, C. M., with Folkers, K., *Quinones in Electron Transport* (Little Brown & Co., Boston, Mass., 453 pp., 1961)
90. Wood, R. K. S. (Ed.), *Biological Problems Arising From the Control of Pests and Diseases* (Inst. of Biol., London, England, 120 pp., 1960)
91. Young, F. G. (Ch.), *Metabolic Effects of Adrenal Hormones* (Little, Brown and Co., Boston, Mass., 108 pp., 1960).

CONTENTS