

REVIEW OF REVIEWS¹

BY CHAUNCEY D. LEAKE

*Pharmacology Laboratory, University of California School of Medicine,
San Francisco, California*

A report of the President's Science Advisory Committee on "*Science, Government and Information*" (84) substantiates the opinion that critical reviews of scientific information may become more essential as the volume of scientific communication increases. Abelson (1) suggests that reviewers of scientific information be specially trained and supported by scientific communities. Wittily and wisely, Price (85) documents the shift from "little science" to "Big Science," with the resulting need for more and better reviews.

In pharmacology the rapid change in emphasis is indicated in Robson & Stacey's (86a) *Recent Advances in Pharmacology*. The first edition appeared in 1950. The third edition, in 1962, is quite a different book. The very chapter headings indicate the huge shift in point of view in pharmacology which has occurred in the past decade. It suggests that only by satisfactory reviews can the science retain reasonable unity. The authors of pharmacology texts are finding it increasingly difficult to maintain coherence in the face of the huge amount of accumulating factual information which must be analyzed, organized, and made digestible for unsophisticated readers if it is to be meaningful.

Good indices for pharmacology are essential. Special bibliographies are particularly helpful. Noteworthy therefore is the contribution by The Dow Chemical Company in reprinting the series of bibliographies in the 5th, 6th, and 8th editions of Torald Sollmann's (106) *Manual of Pharmacology*. These bibliographies cover the classic contributions in pharmacology cumulated to 1936, 1942, and 1957. The publishers point out that the 1st edition of Sollmann in 1917 listed some 3000 entries, while by 1936 the 5th edition contained more than 6000 entries.

Another bibliography of value, not only to pharmacologists, but to all experimentalists in biomedical fields, is the *Annotated Bibliography on Care and Use of Laboratory Animals* (16). A supplement of some 250 pages has appeared which brings the list of publications in this field to date.

Most satisfactory *New and Nonofficial Drugs* remains as a ready reference source for names and information on the identification, action and uses, administration dosage, precautions, and side-effects of new drugs (20). In addition, *Physicians' Desk Reference* (33) is a frequently used review of current pharmaceutical specialties and biologicals. Unfortunately, it is issued with information supplied by the manufacturers, and is not subject to critical editing. In it, uses are emphasized instead of actions, and the organization of the

¹ The survey of the literature pertaining to this review was concluded in July 1963.

volume features trade names and thus promotes commercial advantages. Yet, it is a helpful reference source for trade names and manufacturers. It is interesting that no information is given on any product regarding its patent specifications and claims. The current status of nonproprietary nomenclature of drugs is surveyed by Jerome (53).

New chemical entities put into the United States prescription drug market since 1941 total 542. The peak year of 1959 saw 63 new chemical preparations marketed in the United States. In 1962, the number of such new drugs fell to 28, and the welcome decline may continue. The revived importance of the A.M.A. Council on Drugs in evaluating drugs is indicated by its issuing 108 reports from July 1, 1962 to June 30, 1963 (4).

GENERAL PHARMACOLOGY

Cutting (22) has prepared a useful *Handbook of Pharmacology*. This gives essential information on important currently used drugs, with particular attention to chemical structure and with brief explanations of mechanisms of action. It is offered in outline form and is convenient for ready reference. Nevertheless, its arrangement seems almost haphazard. A more logically arranged method of organizing pharmacological information is needed. This might be on the basis of use: (a) drugs used for diagnosis of disease; (b) drugs used for prevention of disease; (c) drugs used for cure of disease; (d) drugs used for the alleviation of the symptoms of disease, and (e) drugs or chemicals involved in affecting individual or community health. The main group of drugs would come under the classification of those used for the alleviation of symptoms, and these might be referred in the conventional manner to the major systems of the mammalian body. With the increase in use of chemicals for their biological effects in many other ways in addition to human medicine, there should be increasing attention to the appropriate arrangement of this information.

The new regulations of the Food & Drug Administration are having a big impact on the development of new drugs. The Food & Drug Administration itself is swamped with files of data on new drugs which may take a long while to process. The basic purpose of getting effective drugs that are reasonably safe may be lost in the ever-growing mountain of red tape.

Modell (66) is trying heroically to maintain some degree of reasonable perspective in the evaluation of new drugs. He emphasizes the protean character of clinical pharmacology with special reference to the difficulties of providing adequate control. He discusses the estimation of hazards of new drugs (67). A basic problem confronting every physician is whether the risk in the use of a drug is justified by the hazards of the disease. This calls for sound judgment, and is a matter which can be decided in general terms only vaguely. The problem comes down to the specific circumstances inherent in each particular individual case. It is from this standpoint that every sick patient confronting a physician offers a specific and unique research problem which may tax the physician's judgment to the limit.

The ethics of drug research on human subjects is analyzed by Greiner

(38), while Schreiner (100) surveys liability in use of investigational drugs. Laurence (56) emphasizes the importance of careful selection of patients and their grouping for therapeutic trials. It is important to detect small differences in the therapeutic effects of the drugs being tested, and the tests should be on relatively homogeneous groups.

An interesting important recent pharmaceutical development in the administration of drugs is the search for ways to delay absorption and thus to prolong action. The principles involved in developing pharmaceuticals for prolonged action are discussed by Nelson (72).

Review articles relating to general problems in pharmacology include Van Rossum's (111), on the relation between chemical structure and biological activity, as well as the symposium introduced by Lowry (59) on methods for studying pharmacological effects at cellular and subcellular levels. Ottoson (78) reviews the relation between olfactory stimulating effectiveness and the physical-chemical properties of odorous substances. Of broad interest is the review of Opie (76) on the pharmacology of inflammation.

Enzymes continue to command pharmacological interest. Webb (114) issued the first volume of a comprehensive summation of enzymes and metabolic inhibitors. This deals with general principles of inhibition and offers much information of new methods of analysis. Hayaishi (45) edited a general review of oxygenases. This considers the scope of this type of enzyme, with reference also to oxygen isotopes. Mehler (45) reviews phenolytic oxygenases, and Hayano (45) discusses aromatic hydroxylation oxygenases in lipid and steroid metabolism. There is included a survey of peroxidase, phenolase, and cytochrome oxidase.

ABSORPTION, METABOLISM, AND EXCRETION OF DRUGS

Schanker (99) reviews the passage of drugs across various body membranes. There is little on pinocytosis, which may be a factor in the absorption of large molecules into those cells where there is not so much of an actual membrane as there may be a phase boundary. Schanker (80) also reviews the penetration of drugs into the central nervous system. Fishman (30) opens a significant symposium on plasma membranes with an appropriate tribute to Homer Smith (1895-1962). An important symposium on the active transport of ions was introduced by Mommaerts (68).

Soloman (80) surveys the transport of solutes across biological membranes. This review is part of a symposium on the uptake and distribution of anesthetic agents, edited by Papper & Kitz (80). This contains much information of general significance on the absorption, metabolism, and excretion of drugs. Thus, Featherstone reviews binding on proteins and fats, while Schanker reviews the pharmacologic implications of drug ionization. In this, also, Severinghaus discusses the role of lung factors in anesthesia, and Eger gives a mathematical model of uptake and distribution of anesthetic agents, which is further considered by Landahl. Further, Bern surveys the role of biotransformation, and Perl analyzes large-scale diffusion between body

compartments, while Prockop reviews the exit of drugs from the central nervous system.

Williams (117) continues his important surveys of detoxication mechanisms, most recently with reference to humans, citing 84 references. With regard to the metabolism of specific drugs, Fleischer & Wakim (31) give a helpful survey of the fate of enzymes in body fluids, with special reference to transaminase. Maloof & Soodak (61) review the intermediary metabolism of thyroid tissue with relation to the action of drugs. Outstanding is the well-documented review by Way & Adler (113) on the biological disposition of morphine and some of its surrogates. Iron metabolism is well analyzed by Bothwell & Finch (12), with special reference to isotopic methods, transferrin, ferrokinetics, tissue storage and overload. The metabolism of barbiturates in humans is reviewed by Mark (62).

NUTRITION

Before his untimely death, Arild Hansen (1899–1962) reviewed with his colleagues (42) the value of linoleic acid in infant feeding. He also opened an important symposium (43) on nutrition and nutritional problems. Holden (48) edited a significant survey of amino acid pools, in which there was broad consideration of the distribution, formation, and function of free amino acids. Gross (39) edited a symposium chaired by Queirido on protein metabolism. This includes consideration of the influence of the growth hormone, anabolic steroids, and nutrition in general in health and disease.

An important review on the current status of anabolic steroids was offered by Fruehan & Frawley (35). After review of some 26 reports on newer anabolic agents, it is concluded that none appear to offer any advantages over the proper use of testosterone alone or in combination with estrogens. The use of anabolic agents is contraindicated in hormone-sensitive malignancies, or in the presence of severe cardiac, renal, or liver disease.

DRUGS USED IN DIAGNOSIS AND PREVENTION OF DISEASE

Wagner (112) prepared a useful review on radioactive pharmaceuticals for diagnostic problems. This refers to some 58 reports, and includes considerations of the carrier state, and rates of decomposition. Radioactive agents are surveyed in reference to their use as diagnostic aids in renal disease, in cardiovascular disease, in estimating cardiac output and regional blood flow, in thyroid disease, in hematologic disorders, in gastroenteric disease, in malabsorption of fat, and in neurological disease.

An interesting suggestion has been made by Ferebu and colleagues (29) in reviewing the action of isoniazid, that it be used prophylactically to prevent tuberculosis where contact with a tuberculous patient is inevitable.

CHEMOTHERAPY

There is revival of interest and activity in chemotherapy. This is reflected by many reviews covering various aspects of this always important matter. While much of this material relates to antibiotics, it is surprising

that many other types of chemicals are being reviewed again with reference to their chemotherapeutic use.

For antibiotics related to penicillin, Abraham (2) offers a comprehensive survey of cephalosporins with reference to 110 reports. Pisano (81) summarizes the activities of the cephalosporia, giving 104 references. Hewitt (46) offers an analysis of strategy and tactics in the use of penicillins. Berté & Vandoni (11) review the intestinal absorption and organotropism of tetracyclines, in a general symposium on this type of compound. The use and abuse of broad spectrum antibiotics are reviewed by Org & Yow (77).

A Ciba Foundation study group, under the direction of Sir Charles Harrington (44), has surveyed the various aspects of the resistance of bacteria to the penicillins. This survey includes considerations of the mode of the penicillins as well as a discussion on penicillinase. In it, Barber offers a particularly helpful review of coagulase-positive staphylococci resistant to benzyl penicillin and other related compounds.

New types of penicillins are reviewed by Neumann (73). An interesting tableau review of penicillin chemistry, pharmacy, and pharmacology is offered by Schumacher (101). A general formal survey of bacterial chemotherapy with 137 references is given by Robson & Stacey (95).

In regard to specific chemotherapy, a symposium on fungus infections was opened by Baker (7). Lindemeyer, Turck & Petersdorf (58) review factors determining the outcome of chemotherapy in infections of the urinary tract. Montale & Peris (69), with 692 references, review the clinical applications of nitrofurans. A full analysis of antimalarial and anthelmintic drugs is given by Robson & Stacey (91), with 72 references. Clark (18) and his colleagues offer a comparative study of drugs used for vaginal trichomoniasis.

Appropriate to his long experience, Shimkin (103) introduces what is to be a continuing review on chemical carcinogenesis. This is to be expected to have significant relationship to the chemotherapy of cancer. Allison and his associates (3) survey electron transfer by carcinogens. Wheeler (115) carefully reviews the mechanisms of action of cytotoxic alkylating agents.

Tuberculosis chemotherapy was well reviewed in a symposium held under the auspices of the New York Academy of Sciences. In this symposium, D'Esopo (24), in surveying the treatment of pulmonary tuberculosis, concludes that streptomycin, *p*-aminosalicylic acid, and isoniazid remain the best drugs available after the experience of a decade of use. Fust (36) considers the requirements of new antitubercular drugs. Grünberg & Price (40) review experimental approaches to tuberculosis chemotherapy. Lepper & Spies (57) conclude that isoniazid has greatly improved the therapy and prognosis of central nervous tuberculosis. McLean (63) finds ACTH and corticosteroids impair host defense and promote dissemination of tuberculosis but not when used with effective antitubercular drugs. Under the cover of chemotherapy, ACTH and corticosteroids may help to control tubercular allergy and bronchospasm, and aid in clearing lungs.

The chemotherapy of tuberculosis has further been reviewed by Robson & Sullivan (96). They analyze screening tests, tissue persistence of myco-

bacteria, and various types of drugs that have been recommended for the treatment of tuberculosis. Included are 361 references.

A welcome review of the chemotherapy of viral diseases is offered by Sadler (97). He analyzes the quantitative formulation of methods involving enzyme inhibitors, as well as metabolic analogues. He considers structure-action relations, and discusses tissue culture specificity. The review gives special attention to xenamine and the thiosemicarbazones. There are 200 references.

Much interest has recently been aroused in the problem of homografts. This problem is becoming increasingly significant as a result of technical advances in organ transplantation. An interesting aspect of chemotherapy is the possible development of compounds which will suppress immune responses, and thus make organ transplantation and skin grafting increasingly successful. The chemical suppression of immune responses is reviewed by Hitchings & Elion (47). Surveying 382 references, they show that many different kinds of drugs may modify tolerance to homografts.

DRUGS USED FOR THE ALLEVIATION OF SYMPTOMS

As judged by reviews, interest in the pharmacology of the autonomic nervous system seems to be decreasing while there is increasing attention to the pharmacology of the central nervous system and to endocrines. There is evidence also of greater attention to biologically active polypeptides.

Autonomic nervous system.—A comprehensive review on supersensitivity and subsensitivity to sympathomimetic amines has been made by Trendelenberg (108). He classifies these agents, considers mechanisms of supersensitivity, and the deformation of receptors. He offers 164 references. Shore (104) surveys the release of serotonin and catecholamines by drugs, citing 111 references. Vane (109) offers a general review of catecholamines, listing 249 references. Robson & Stacey (94) review 5-hydroxytryptamine, listing 171 references. Barker (8) edits a broad symposium on muscle receptors, and Guyonneau (41) reviews the biochemorphology of spasmolytics and curaroids.

Central nervous system.—Robson & Stacey (92) review pharmacologically active substances in the central nervous system with an important table giving the brain distribution of many important compounds and enzymes. They also discuss gamma-aminobutyric acid and substance P, a polypeptide, as a transmitting agent. Reed & Woodbury (86) review the effects of hypertonic urea on cerebral-spinal fluid pressure and vein volume. Hornykiewicz (49) reviews the appearance of dopamine (3-hydroxytyramine) in the central nervous system and its relation to parkinsonism, and Onuaguluchi (75) appraises drug therapy in Parkinson's disease.

Anesthesia.—Artusio (6) edits the first volume of *Clinical Anesthesia* dealing with halogenated anesthetic agents. Featherstone & Muehlbacher (28) offer an important survey of the role of inert gases in the search for anesthesia mechanisms. Foldes & McNall (32) review anesthesia in myasthenia gravis, listing 299 references. Lurie (60) surveys anesthesia and the

systemic venous circulation, giving 300 references. Van Poznak (110) offers a review of electrical anesthesia.

Central nervous system depressants.—Berger (10) analyzes similarities and differences between the meprobamates and barbiturates, listing 98 references. Domino (25) offers a depth study of the actions and effects of tranquilizers in humans. Robson & Stacey (90) give a brief review of the current status of hypnotics, anticonvulsants, analgesics, and antitussives. They also give a review of psychotropic drugs (89), quoting 275 references. Jacobsen (51), listing 177 references, surveys the clinical pharmacology of hallucinogens.

Cardiovascular respiratory.—Erdös (26) edits a symposium on the structure and function of biologically active peptides, with reference to bradykinin, kallidin, and congeners. Euler (27) opens a symposium on bradykinin and vasodilating polypeptides. Cater (17) reviews changes in oxygen tension induced by vasoconstricting and vasodilating drugs in tumors. Simson (105) helps in reviewing the current status of digitalis assay. Trautwein (107) surveys the action of drugs on the generation and conduction of cardiac impulses, with reference to 352 reports. Page & Bumpus (79) review pertinent data on angiotensin. The depressant effects on respiration of tris (hydroxymethyl) amino methane are reviewed by Nahas (70), and he also offers a full analysis of this interesting compound with reference to 166 reports (71). David (23) well reviews information on new antihypertensive drugs, citing 101 references, and Robson & Stacey (93) give a brief review of hypotensive drugs.

Blood.—Arna & Mathur (5) analyze the structure and anti-coagulant action of coumarins. Kappert (55) surveys experimental and chemical studies on thrombogenesis and fibrinolysis. With reference to 138 reports, Pranker (83) reviews the hemolytic effects of drugs and chemicals. Jacobson & Doyle (52) edit an extensive monograph on erythropoiesis, dealing mostly with erythropoietin. Sherry (102) introduces a general symposium on thrombosis and anticoagulants.

Endocrines.—Collip, Best & Fletcher (19) well retell the insulin story. Butterfield & Mahler (15) review hypoglycemic agents in relation to diabetes mellitus, listing 113 references. The steroids are extensively reviewed, from the standpoint of chemical and biological factors in their activity, by Bush (14), who lists 825 references. Green (37), in analyzing new concepts of fever, describes etiocholanolone fever, which is related to defects in steroid metabolism. Kappas & Palmer (54) survey selected aspects of steroid pharmacology. Robson & Stacey (87) give quick reviews of cholesterol and new steroids (88). Barker (9) surveys new ideas on thyroid function with reference to the involvement of sympathetic nerves in thyroxine action. Michael (64) discusses uses and abuses of adrenocorticosteroids.

MISCELLANEOUS

In a review of the pharmacology of central and peripheral inhibition, Curtis (21) considers the problem of transmitter substances, and analyzes the action of tetanus toxin, strychnine, and picrotoxin. There are 385 refer-

ences. Milne (65) reviews diuretics and electrolyte balance. Schachter (98) offers a general survey of pharmacologically active polypeptides, with reference to 130 reports. Bowman & Sanghvi (13) analyze the pharmacological actions of hemlock alkaloids from *conium maculatum*. Hueper (50) reviews environmental and occupational cancer hazards.

In spite of much publicity, the White House Conference on Narcotic and Drug Abuse (116) indicates a continuance of a prejudiced approach and of unwise judgment on the basis of demonstrable scientific evidence. The Committee on Public Health of the New York Academy of Medicine (74), in its report on drug addiction, gives an indication of a wise approach to this long-baffling social problem. This report cites 129 references.

A helpful clinical survey of drugs useful in geriatric practice is edited by Freeman (34). While this contains little that is not already well known, it is nonetheless an interesting example of how pharmacological knowledge may be well applied to a particular type of patient. All important types of drugs are well discussed in this neatly organized volume.

Poser & Osbourn (82) classify some 375 drugs recommended in neurology and psychiatry into 28 groups on the basis of uses. This gives public, chemical and trade names, but arbitrarily omits such familiar compounds as ether, chloroform and paraldehyde.

IN PROSPECT

The shifts and changes in interest in pharmacological affairs are well represented by the varying emphases in review articles dealing with drugs. It is significant that the extensive excitement over psychotropic drugs seems to be subsiding. On the other hand, there seems to be increasing interest in some of the classical problems of pharmacology such as chemotherapy. Reviews in pharmacology will continue to offer a satisfactory way to keep abreast of current progress in this ever-increasingly important science.

LITERATURE CITED

1. Abelson, P., *Science*, **135**, (1963)
2. Abraham, E. P., *Pharmacol. Rev.*, **14**, 473-500 (1962)
3. Allison, A. C., Peover, M. E., and Gough, T. A., *Nature*, **197**, 758, 764 (1963)
4. Anonymous, *J. Am. Med. Assoc.*, **185**, 304-5 (1963)
5. Arna, R. B., and Mathur, C. N., *Brit. J. Pharmacol. Chemotherap.*, **20**, 29 (1963)
6. Artusio, J. F., *Clinical Anesthesia*, **1** (F. A. Davis, Philadelphia, Penn., 144 pp., 1963)
7. Baker, R. D., *Lab. Invest.*, **11**, 1017-242 (1962)
8. Barker, D., Ed., *Symp. Muscle Receptors* (Hong Kong Univ. Press, Hong Kong, 304 pp., 1962)
9. Barker, S. B., *Physiologist*, **6**, 94-104 (1963)
10. Berger, F. M., *Clin. Pharmacol. Therap.*, **4**, 209-31 (1963)
11. Berté, F., and Vandoni, G., *Chemotherapy*, **5**, 219 (1962)
12. Bothwell, T. H., and Finch, C. A., *Iron Metabolism* (Little, Brown, Boston, Mass., 440 pp., 1962)
13. Bowman, W. C., and Sanghvi, I. S., *J. Pharm. Pharmacol.*, **15**, 1-25 (1963)
14. Bush, I. E., *Pharmacol. Rev.*, **14**, 317-446 (1962)
15. Butterfield, W. J. H., and Mahler, R. F., *Recent Advanc. Pharmacol.*, **3**, 179-213 (1962)
16. Cass, J. S., & Co., *Federation Proc.*, **22**, Pt. 2, Suppl. 3, 250 pp. (1963)
17. Cater, D. B., & Co., *Acta Radiol.*, **58**, 401-34 (1962)
18. Clark, D. H., Solomons, E., and Siegal,

- S. A., *Obstat. Gynecol.*, **20**, 615-21 (1962)
19. Collip, J. B., Best, C. H., and Fletcher, A. A., *Can. Med. Assoc. J.*, **87**, 1045-68 (1962)
20. A.M.A. Council on Drugs, *New and Nonofficial Drugs* (Lippincott, Philadelphia, Penn., 929 pp., 1962)
21. Curtis, D. R., *Pharmacol. Rev.*, **15**, 333-64 (1963)
22. Cutting, W., *Handbook of Pharmacology: The Actions and Uses of Drugs* (Appleton-Century-Crofts, New York, 643 pp., 1962)
23. David, N. A., *Current Therap. Res.*, **5**, Suppl. 2, 93-126 (1963)
24. D'Esopo, N. D., *Ann. N. Y. Acad. Sci.*, **106**, 85-95 (1963)
25. Domino, E. F., *Clin. Pharmacol. Therap.*, **3**, 599-664 (1962)
26. Erdös, E. G., Ed., *Ann. N. Y. Acad. Sci.*, **104**, 1-464 (1963)
27. Euler, U. S. von, *Biochem. Pharmacol.*, **10**, 193 (1962)
28. Featherstone, R. M., and Muehlbacher, C. A., *Pharmacol. Rev.*, **15**, 97-122 (1963)
29. Ferebu, S. H., Mount, F. W., and Comstock, G. W., *Ann. N. Y. Acad. Sci.*, **106**, 151-56 (1963)
30. Fishman, A. P., *Circulation*, **26**, 983-1230 (1962)
31. Fleischer, G. A., and Wakim, K. G., *J. Lab. Clin. Med.*, **61**, 76, 86, 98, 107-19 (1963)
32. Foldes, F. F., and McNall, P. G., *Anesthesia*, **23**, 837-72 (1962)
33. Folsom, J. P., Ed., *Physicians' Desk Reference to Pharmaceutical Specialties and Biologicals*, 16th ed. (Medical Economics, Oradell, N. J., 961 pp., 1962)
34. Freeman, J. T., Ed., *Clinical Principles and Drugs in the Aging* (Thomas, Springfield, Ill., 485 pp., 1963)
35. Fruehan, A. C., and Frawley, T. F., *J. Am. Med. Assoc.*, **184**, 527-32 (1963)
36. Fust, B., *Ann. N. Y. Acad. Sci.*, **106**, 78-84 (1963)
37. Green, L. J., *J.-Lancet*, **82**, 392-401 (1962)
38. Greiner, T., *J. New Drugs*, **2**, 7-22 (1962)
39. Gross, F., Ed., *Protein Metabolism: Influence of Growth Hormone, Anabolic Steroids, and Nutrition in Health and Disease* (Springer, Berlin, 521 pp., 1962)
40. Grünberg, E., and Price, H. N., *Ann. N. Y. Acad. Sci.*, **106**, 72-77 (1963)
41. Guyonneau, M., *J. Physiol. (Paris)*, **54**, Suppl. 4, 88 pp. (1963)
42. Hansen, A. E., Stewart, R. A., Hughes, G., and Soderhjelm, L., *Acta Paediat., Suppl.* **137**, 41 pp. (1962)
43. Hansen, A. E., *Pediat. Clin. N. Am.*, **9**, 877-1046 (1962)
44. Harrington, C., *Ciba Found. Study Group*, **13**, *Resistance of Bacteria to the Penicillins* (Little, Brown, Boston, Mass., 125 pp., 1962)
45. Hayaishi, O., Ed., *Oxygenases* (Academic, New York, 588 pp., 1962)
46. Hewitt, W. L., *J. Am. Med. Assoc.*, **185**, 264-72 (1963)
47. Hitchings, G. H., and Elion, G. B., *Pharmacol. Rev.*, **15**, 365-405 (1963)
48. Holden, J. T., Ed., *Amino-Acid Pools* (Elsevier, Amsterdam, 815 pp., 1962)
49. Hornykiewicz, O., *German Med. Monthly*, **7**, 344 (1962)
50. Hueper, W. C., *Clin. Pharmacol. Therap.*, **3**, 776-814 (1962)
51. Jacobsen, E., *Clin. Pharmacol. Therap.*, **4**, 480-503 (1963)
52. Jacobson, L. O., and Doyle, M., *Erythropoiesis* (Grune & Stratton, New York, 410 pp., 1962)
53. Jerome, J. B., *J. Am. Med. Assoc.*, **185**, 294-97 (1963)
54. Kappas, A., and Palmer, R. H., *Pharmacol. Rev.*, **15**, 123-67 (1963)
55. Kappert, A., *Helv. Med. Acta*, **29**, Suppl. 41, 147 pp. (1962)
56. Laurence, D. R., *Clin. Pharmacol. Therap.*, **4**, 381-89 (1963)
57. Lepper, M. H., and Spies, H. W., *Ann. N. Y. Acad. Sci.*, **106**, 106-23 (1963)
58. Lindemeyer, R. I., Turck, M., and Petersdorf, R. G., *Ann. Internal Med.*, **58**, 201-16 (1963)
59. Lowry, O. H., *Biochem. Pharmacol.*, **9**, 1-253 (1962)
60. Lurie, A. A., *Anesthesia*, **24**, 368-95 (1963)
61. Maloof, F., and Soodak, M., *Pharmacol. Rev.*, **15**, 43-96 (1963)
62. Mark, L. C., *Clin. Pharmacol. Therap.*, **4**, 504-30 (1963)
63. McLean, R. L., *Ann. N. Y. Acad. Sci.*, **106**, 130-47 (1963)
64. Michael, M., *J. Am. Med. Assoc.*, **185**, 280-85 (1963)
65. Milne, M. D., *Recent Advan. Pharmacol.*, **3**, 214-60 (1962)
66. Modell, W., *Clin. Pharmacol. Therap.*, **4**, 371-80 (1963)
67. Modell, W., *Science* **139**, 1180-85 (1963)
68. Mommaerts, W. F. H. M., *Federation Proc.*, **22**, 1 (1963)
69. Montale, P., and Peris, G., *Giorn. Ital. Chemiotherap.*, **5**, 75-205 (1962)
70. Nahas, G. G., Fink, B. R., Ploski,

- W. S., and Teneick, R. E., *Ann. N. Y. Acad. Sci.*, **109**, 783-803 (1936)
71. Nahas, G. G., *Pharmacol. Rev.*, **14**, 447-72 (1962)
 72. Nelson, G., *Clin. Pharmacol. Therap.*, **4**, 283-92 (1936)
 73. Neumann, P., *Deut. Med. Wochschr.*, **88**, 176-71 (1963)
 74. N. Y. Academy of Medicine Committee on Public Health, *Clin. Pharmacol. Therap.*, **4**, 425-60 (1963)
 75. Onuaguluchi, G. O., *Brit. Med. J.*, **1**, 443 (1963)
 76. Opie, E. L., *J. Exptl. Med.*, **117**, 425 (1963)
 77. Ory, E. M., and Yow, E. M., *J. Am. Med. Assoc.*, **185**, 273-79 (1963)
 78. Ottoson, D., *Pharmacol. Rev.*, **15**, 1-42 (1963)
 79. Page, I. H., and Bumpus, F. M., *Clin. Pharmacol. Therap.*, **3**, 785-73 (1962)
 80. Papper, E. M., and Kitz, R. J., Eds., *Uptake and Distribution of Anesthetic Agents* (McGraw, New York, 321 pp., 1963)
 81. Pisano, M. A., *Trans. N. Y. Acad. Sci.*, **25**, 716-30 (1963)
 82. Poser, C. M., and Osbourn, V., *International Dictionary of Drugs Used In Neurology and Psychiatry* (Thomas, Springfield, Ill., 168 pp., 1962)
 83. Pranker, P. A. J., *Clin. Pharmacol. Therap.*, **4**, 334-50 (1963)
 84. President's Science Advisory Committee, *Science, Government and Information* (U. S. Govt. Printing Office, Washington, D. C., 52 pp., 1963)
 85. Price, D. J., *Little Science, Big Science* (Columbia Univ. Press, New York, 119 pp., 1963)
 86. Reed, D. J., and Woodbury, D. M., *J. Physiol. (London)*, **164**, 252, 265 (1962)
 - 86a. Robson, J. M., and Stacey, R. S., Eds., *Recent Advan. Pharmacol.* **3** (Churchill, London, 406 pp. 1962)
 87. Robson, J. M., and Stacey, R. S., *Recent Advan. Pharmacol.*, **3**, 294-305 (1962)
 88. Robson, J. M., and Stacey, R. S., *Recent Advan. Pharmacol.*, **3**, 261-93 (1962)
 89. Robson, J. M., and Stacey, R. S., *Recent Advan. Pharmacol.*, **3**, 42-94 (1962)
 90. Robson, J. M., and Stacey, R. S., *Recent Advan. Pharmacol.*, **3**, 381-94 (1962)
 91. Robson, J. M., and Stacey, R. S., *Recent Advan. Pharmacol.*, **3**, 355-80 (1962)
 92. Robson, J. M., and Stacey, R. S., *Recent Advan. Pharmacol.*, **3**, 1-41 (1962)
 93. Robson, J. M., and Stacey, R. S., *Recent Advan. Pharmacol.*, **3**, 306-21 (1962)
 94. Robson, J. M., and Stacey, R. S., *Recent Advan. Pharmacol.*, **3**, 122-55 (1962)
 95. Robson, J. M., and Stacey, R. S., *Recent Advan. Pharmacol.*, **3**, 322-54 (1962)
 96. Robson, J. M., and Sullivan, F. M., *Pharmacol. Rev.*, **15**, 169-224 (1963)
 97. Sadler, P. W., *Pharmacol. Rev.*, **15**, 407-47 (1963)
 98. Schachter, M., *Recent Advan. Pharmacol.*, **3**, 156-78 (1962)
 99. Schanker, L. S., *Pharmacol. Rev.*, **14**, 501-30 (1962)
 100. Schreiner, G. E., *J. Am. Med. Assoc.*, **185**, 259-63 (1963)
 101. Schumacher, G. E., *Am. J. Hosp. Pharm.*, **19**, 555-63 (1962)
 102. Sherry, S., *Am. J. Med.*, **33**, 619-753 (1962)
 103. Shimkin, M. B., *Clin. Pharmacol. Therap.*, **3**, 774 (1962)
 104. Shore, P. A., *Pharmacol. Rev.*, **14**, 531-50 (1962)
 105. Simson, G., *Am. Heart J.*, **64**, 401-15 (1962)
 106. *Sollmann Bibliographies* (Dow Chemical Co., Midland, Mich., 1962)
 107. Trautwein, W., *Pharmacol. Rev.*, **15**, 277-332 (1963)
 108. Trendelenberg, U., *Pharmacol. Rev.*, **15**, 225-76 (1963)
 109. Vane, J. R., *Recent Advan. Pharmacol.*, **3**, 95-121 (1962)
 110. Van Poznak, A., *Anesthesia*, **24**, 101 (1963)
 111. Van Rossum, J. M., *J. Pharm. Pharmacol.*, **15**, 285-316 (1963)
 112. Wagner, J. N., *Clin. Pharmacol. Therap.*, **4**, 351-70 (1963)
 113. Way, E. L., and Adler, T. R., *Biological Disposition of Morphine and Some of its Surrogates* (World Health Organ., Geneva, 117 pp., 1962)
 114. Webb, J. L., *Enzyme and Metabolic Inhibitors, 1: General Principles of Inhibition* (Academic, New York, 951 pp., 1963)
 115. Wheeler, G. P., *Cancer Res.*, **22**, 651 (1962)
 116. *Proc. White House Conf. Narcotic Drug Abuse*, (U. S. Govt. Printing Office, Washington, D. C., 330 pp., 1963)
 117. Williams, R. T., *Clin. Pharmacol. Therap.*, **4**, 234-54 (1963)

CONTENTS

OUTLINES OF A PHARMACOLOGICAL CAREER, <i>Ernst Rothlin</i>	ix
BIOCHEMICAL MECHANISM OF DRUG ACTION, <i>Jack R. Cooper</i>	1
RECEPTOR MECHANISMS, <i>Robert F. Furchgott</i>	21
MODERN CONCEPTS IN RELATIONSHIP BETWEEN STRUCTURE AND BIO- LOGICAL ACTIVITY, <i>F. N. Fastier</i>	51
MECHANISMS OF DRUG ABSORPTION AND EXCRETION, <i>Ruth R. Levine</i> and <i>Edward W. Pelikan</i>	69
METABOLIC FATE OF DRUGS, <i>R. T. Williams and D. V. Parke</i>	85
ANTIBACTERIAL CHEMOTHERAPY, <i>Mary Barber and E. B. Chain</i>	115
CARDIOVASCULAR PHARMACOLOGY, <i>Domingo M. Aviado</i>	139
EFFECT OF DRUGS ON THE INOTROPIC PROPERTY OF THE HEART, <i>Bernard H. Marks</i>	155
PHARMACOLOGY OF REPRODUCTION AND FERTILITY, <i>Louis Fridhandler</i> and <i>Gregory Pincus</i>	177
EFFECT OF DRUGS ON CONTRACTIONS OF VERTEBRATE SMOOTH MUS- CLE, <i>E. E. Daniel</i>	189
TOXICOLOGY: ORGANIC, <i>Horace W. Gerarde</i>	223
TOXICOLOGY: INORGANIC, <i>George Roush, Jr., and Robert A. Kehoe</i>	247
DRUG ALLERGY, <i>Max Samter and George H. Berryman</i>	265
KININS—A GROUP OF ACTIVE PEPTIDES, <i>M. Schachter</i>	281
COMPOSITION AND MODE OF ACTION OF SOME INVERTEBRATE VENOMS, <i>John H. Welsh</i>	293
NEW SUBSTANCES OF PLANT ORIGIN, <i>T. A. Geissman</i>	305
EXCERPTS FROM THE PHARMACOLOGY OF HORMONES AND RELATED SUBSTANCES, <i>José Ribeiro do Valle</i>	317
EFFECTS OF DRUGS ON THE CENTRAL NERVOUS SYSTEM, <i>Harry Grundfest</i>	341
PHARMACOLOGY OF THE AUTONOMIC NERVOUS SYSTEM, <i>Eleanor Zaimis</i>	365
REVIEW OF REVIEWS, <i>Chauncey D. Leake</i>	401
AUTHOR INDEX	411
SUBJECT INDEX	431
CUMULATIVE INDEXES, VOLUMES 1-4	450