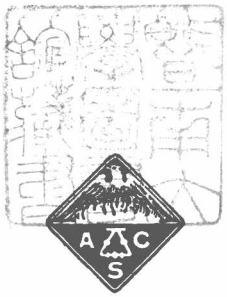
The SULFONAMIDES and ALLIED COMPOUNDS

by
ELMORE H. NORTHEY, Ph.D.
Administrative Director
Stamford Research Laboratories
American Cyanamid Company
Stamford, Connecticut



American Chemical Society
Monograph Series

REINHOLD PUBLISHING CORPORATION
330 West Forty-second Street, New York, U. S. A.
1948

Printed in United States of America
WAVERLY PRESS, INC., BALTIMORE, MD.

GENERAL INTRODUCTION

American Chemical Society Series of Scientific and Technologic Monographs

By arrangement with the Interallied Conference of Pure and Applied Chemistry, which met in London and Brussels in July, 1919, the American Chemical Society was to undertake the production and publication of Scientific and Technologic monographs on chemical subjects. At the same time it was agreed that the National Research Council, in coöperation with the American Chemical Society and the American Physical Society, should undertake the production and publication of Critical Tables of Chemical and Physical Constants. The American Chemical Society and the National Research Council mutually agreed to care for these two fields of chemical development. The American Chemical Society named as Trustees, to make the necessary arrangements for the publication of the monographs, Charles L. Parsons, secretary of the society, Washington, D. C.; the late John E. Teeple, then treasurer of the society, New York; and Professor Gellert Alleman of Swarthmore College. The Trustees arranged for the publication of the A. C. S. series of (a) Scientific and (b) Technologic Monographs by the Chemical Catalog Company, Inc. (Reinhold Publishing Corporation, successors) of New York.

The Council, acting through the Committee on National Policy of the American Chemical Society, appointed editors (the present list of whom appears at the close of this introduction) to have charge of securing authors, and of considering critically the manuscripts submitted. The editors endeavor to select topics of current interest, and authors recognized as authorities in their respective fields.

The development of knowledge in all branches of science, especially in chemistry, has been so rapid during the last fifty years, and the fields covered by this development so varied that it is difficult for any individual to keep in touch with progress in branches of science outside his own speciality. In spite of the facilities for the examination of the literature given by Chemical Abstracts and by such compendia as Beilstein's Handbuch der Organischen Chemie, Richter's Lexikon, Ostwald's Lehrbuch der Allgemeinen Chemie, Abegg's and Gmelin-Kraut's Handbuch der Anorganischen Chemie, Moissan's Traité de Chimie Minérale Générale, Friend's and Mellor's Textbooks of Inorganic Chemistry and Heilbron's Dictionary of Organic Compounds, it often takes a great deal of time to coördinate the knowledge on a given topic. Consequently when men who have spent years in the study of important subjects are willing to coördinate their knowledge and present it in concise, readable form, they perform a service of the highest value. It was with a clear recognition of the usefulness of such work that the American Chemical Society undertook to sponsor the publication of the two series of monographs.

Two distinct purposes are served by these monographs: the first, whose fulfillment probably renders to chemists in general the most important service, is to present the knowledge available upon the chosen topic in a form intelligible to those whose activities may be along a wholly different line. Many chemists fail to realize how closely their investigations may be connected with other work which on the surface appears far afield from their own. These monographs enable such men to form closer contact with work in other lines of research. The second purpose is to promote research in the branch of

science covered by the monographs, by furnishing a well-digested survey of the progress already made, and by pointing out directions in which investigation needs to be extended. To facilitate the attainment of this purpose, extended references to the literature enable anyone interested to follow up the subject in more detail. If the literature is so voluminous that a complete bibliography is impracticable, a critical selection is made of those papers which are most important.

Preface

This monograph attempts to cover the chemical side of the new chemotherapy which has revolutionized medicine in recent years. Progress has been so rapid and the number of new compounds synthesized (now over 5000) so great, that it has been all but impossible for chemists active in the field to keep up with developments. Duplication of effort has been enormous. It is hoped that by listing most of the compounds that have been made as the result of the discovery of antibacterial properties of sulfonamides and related compounds, some of the waste of duplication can be avoided and the assembled information can be used as background for further conquest of disease. It is also an aim of this monograph to provide pharmacologists and clinicians with data on activities and sources of information on other important properties of the drugs. It is anticipated that further study will be stimulated because, unquestionably, there are valuable compounds passed over in the first cursory tests which may prove to be the answer to some specific need. A further aim is to provide all research workers in the field with a brief summary on medical uses and abuses of these drugs. Such information is not intended as a therapeutic guide but as a research tool, since final proof of usefulness is obtained only by widespread employment of the drugs in human and veterinary medicine. Success or failure in medical practice is the criterion by which experimental results are finally judged.

The importance of these drugs to modern medicine may be gauged from the fact that the United States produced 10,005,307 pounds of the sulfonamide drugs in 1943. If we assume that an average course of treatment requires 35 grams of drug, this would mean that an incredible number of patients (129,000,000) could have been treated with the drugs produced in 1943! Undoubtedly much of this huge production was used in stocking the needs of our armed forces and those of our allies all over the world, and may represent a peak production which will not be duplicated now that penicillin and other antibiotics are replacing the sulfonamides for certain uses and supplementing them in many other uses.

The author shares with many others active in the field the inner satisfaction of having contributed in some measure to the accomplishments which are reflected in otherwise cold life insurance statistics. Death rates are now the lowest in history for many infectious diseases. The lives of at least twenty-five thousand wage earners are being saved yearly in the United States through the use of sulfa drugs in the treatment of pneumonia. Spectacular accomplishment credited wholly to the new chemotherapy is shown by reduction in mortality from meningitis in United States Army camps from 39 per cent in the World War I to 3.5 per cent in World War II.

This monograph is an outgrowth of a review prepared and presented before Section C of the American Association for the Advancement of Science at the Research Conference in Chemistry held at Gibson Island, Maryland, July, 1939. The original review was revised and enlarged under sponsorship of the Division of Medicinal Chemistry of the American Chemical Society and was published in *Chemical Reviews*, *27*, 85–196 (1940). Since then the literature has expanded so enormously that a real need for revision and amplification was felt. Press of war work delayed completion of these efforts, but delay brought the benefits of broader scope and better evaluation of data.

The present monograph owes much to the cooperative spirit demonstrated by the drug industry and various medical research institutions of the country who supplied much unpublished data on new compounds and the chemotherapeutic evaluation of both old and new compounds. Exceptionally large contributions were made by Eli Lilly and Co. (activities on about 600 old and new compounds), The American Cyanamid Co. (data on 600 old and new compounds), The Upjohn Co., Sharpe and Dohme, Inc., and Abbott Laboratories.

Clinical applications have not been reviewed with thoroughness but it is hoped that the most important papers on recent developments have been surveyed. The literature on these applications is huge and much of it is now merely of historical interest, so rapid has been the obsolescence of compounds in the field. A number of reviews have been written which cover special fields of medical literature up to the date of their publication. The literature up to 1940 is adequately covered by several of these.

Some of the more important reviews are:

Buttle, G. A. H., *Trans. Roy. Soc. Trop. Med. Hyg.*, **33,** 141–168 (1939).
[Particularly good on applications to tropical medicine.]

Marshall, E. K., Jr., *Ann. Rev. Physiol.*, **3,** 643–670 (1941).
[Review of experimental chemotherapy from 1938 to Sept., 1940.]

Findlay, G. M., "Recent Advances in Chemotherapy", Philadelphia, Blakiston, 1939.

Long, P. H., and Bliss, E. A., "Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds, New York, The Macmillan Co., 1939.
[Very complete literature on pharmacological and clinical findings to 1939.]

Mellon, R. R., Gross, P., and Cooper, F. B., "Sulfanilamide Therapy of Bacterial Infections", Springfield, Ill., Charles C. Thomas, 1939.

Spink, W. W., "Sulfanilamide and Related Compounds in General Practice", Chicago, Ill., The Yearbook Publishers Inc., 2nd. Ed., Revised reprint (July, 1943).
[An authoritative handbook on clinical applications.]

Goodman, L., and Gilman, A., "The Pharmacological Basis of Therapeutics", Chap. 56 to 60, New York, The Macmillan Co., 1941.

Henry, R. J., "The Mode of Action of Sulfonamides", *Bact. Revs.*, **7,** 175–262 (1943); Enlarged reprint, Josiah Macy Jr. Foundation (1944).
[An excellent critical review stressing the bacteriological side of the subject.]

Rune Frisk, A., "Sulfanilamide Derivatives", English translation by Helen Frey, Stockholm, Sweden, P. A. Norstedt & Söner, 1943.
[A very complete description of the pharmacology of 29 N^1-substituted sulfanilamides including literature and the author's own extensive studies.]

Special Chemotherapy Number, *Schweiz. med. Wochschr.*, **73,** 549–684 (1943).
[An excellent presentation by Swiss medical authorities of the clinical use of sulfonamides, including a bibliography of 958 references. Mode of action, nomenclature and structure are also discussed.]

Medical Research Council, War Memorandum No. 10, "The Medical Use of Sulphonamides", London, His Majesty's Stationery Office, 1943.
[An excellent short guide in use of the sulfa drugs, but colored by the supply situation in England at time of issuance.]

Kolmer, J. A., "Chemotherapy of Bacterial Diseases", *Arch. Internal Med.*, **65,** 671–743 (1940).
[A review of the medical literature on the Prontosils, sulfanilamide and sulfapyridine; about 400 references.]

Circular Lettter No. 17 (Feb. 23, 1942) Office of the Surgeon General United States Army, Washington, D. C., *War Med.*, **2,** 466–481 (1943).
[An excellent guide to military uses of the sulfonamides.]

Bickel, G., "*La Sulfanilamide et ses Dérivés en Thérapeutique*", 687 references, Lausanne, Switzerland, Librairie Payot, 1940.

[Covers the therapeutic uses of sulfanilamide, Prontosil, Septazine, Uleron, sulfapyridine, sulfathiazole, Rodilone and sulfacetamide.]

Schnitker, M. A., "Sulfanilamide, Sulfapyridine and Allied Compounds in Infections", 202 references, New York, Oxford University Press, Inc., 1940.

"The Prevention of Respiratory Tract Bacterial Infections by Sulfadiazine Prophylaxis in the United States Navy, *NavMed* 284, Bureau of Medicine and Surgery, Navy Department, Wash., D. C., U. S. Govt. Printing Office (1944)-599351.

[This is a full report covering the mass prophylactic use of sulfadiazine on 600,000 naval trainees.]

Harold J. White, author of Chapter VIII dealing with measurement of chemotherapeutic activities of sulfonamide drugs, has charge of *in vitro* and *in vivo* antibacterial testing of new drugs at the Stamford Research Laboratories of the American Cyanamid Company. He has described methods of testing new chemotherapeutic agents which should be of value to those engaged in, or wishing to undertake, such studies. In addition to pointing out many of the pitfalls which abound in this work, he has prepared a key to the literature so that the published data on studies of the action of sulfa drugs against particular bacteria may be readily found.

Chapter X, which covers the pharmacology of the more important sulfonamide and sulfone drugs, was written by J. T. Litchfield, Jr., pharmacologist at the Stamford Research Laboratories of the American Cyanamid Company. In addition to his experience at these laboratories, he has conducted pharmacological researches on the sulfonamide drugs at Johns Hopkins University and the University of Minnesota.

Benjamin W. Carey has reviewed and edited the clinical material assembled by the author and is responsible for any unsupported medical opinion expressed in Chapter XII. Dr. Carey is in an excellent position to evaluate such work because he is Director of Lederle Laboratories Division of American Cyanamid Co., in charge of clinical investigations carried out by that company. A major portion of his efforts is directed to evaluation of new chemotherapeutic drugs and to widening the field of usefulness of the existing sulfonamide drugs through sponsoring further clinical research.

The author wishes to thank R. O. Roblin, Jr., Jackson P. English, and Paul H. Bell for constructive criticism of much of the manuscript and particularly the section dealing with mechanism of action.

In addition to the above, the author has been very considerably aided by Doris R. Seeger who arranged the compounds within tables in Beilstein order and who helped in proofreading. The author's wife, Alberta V. Northey, assisted materially in compilation of references and in the difficult task of typing the manuscript.

Stamford, Conn.
March, 1947

ELMORE H. NORTHEY

List of Abbreviations

ASC	acetylsulfanilyl chloride
cc.	cubic centimeters
CSF	cerebrospinal fluid
Gm.	gram(s)
M.	molar
mg.	milligram(s)
mg.%	milligram per cent (usually mg per 100 cc)
ml.	milliliters
mM	millimoles
PABA	*p*-aminobenzoic acid
pH	logarithm of the reciprocal of the hydrogen ion concentration
pKa	logarithm of the reciprocal of the acid dissociation constant

Abbreviations of names of scientific journals correspond to those used in *Chemical Abstracts*.

Abbreviations for organisms or diseases are given in Appendix A.

CONTENTS

Where boldface and lightface numbers occur together within parentheses, the boldface numbers are table numbers and the lightface numbers following the colon give the page location for these tables.

[Where boldface and lightface numbers occur together within parentheses, the boldface numbers are table numbers and the lightface numbers following the colon give the page location for these tables.]

* Not discussed specifically in text.

[Where boldface and lightface numbers occur together within parentheses, the boldface numbers are table numbers and the lightface numbers following the colon give the page location for these tables.]

* Not discussed specifically in text.

[Where boldface and lightface numbers occur together within parentheses, the boldface numbers are table numbers and the lightface numbers following the colon give the page location for these tables.]

* Not discussed specifically in text.

[Where boldface and lightface numbers occur together within parentheses, the boldface numbers are table numbers and the lightface numbers following the colon give the page location for these tables.]

* Not discussed specifically in text.

[Where boldface and lightface numbers occur together within parentheses, the boldface numbers are table numbers and the lightface numbers following the colon give the page location for these tables.]

* Not discussed specifically in text.

Where boldface and lightface numbers occur together within parentheses, the boldface numbers are table numbers and the lightface numbers following the colon give the page location for these tables.

* Not discussed specifically in text.