surements are made on compounds that are relatively insoluble in water, the results have little meaning unless the particle size of the administered powder is taken into account.

(1) Dittert, L. W., Adams, H. J., Alexander, F., Chong, C. W., Ellison, T., and Swintosky, J. V., *J. Pharm. Sci.*, **57**, 1146 (1968).
(2) Swintosky, J. V., Adams, H. J., Caldwell, H. C., Dittert, L. W., Ellison, T., and Rivard, D. E., *ibid.*, **55**, 992 (1966).
(3) Caldwell, H. C., Adams, H. J., Rivard, D. E., and Swintosky, J. V., *ibid.*, **56**, 920(1967).
(4) Berkson, J., *J. Am. Statistical Assoc.*, **48**, 565(1953).

L. W. Dittert*
H. J. Adams†

C. W. Chong
J. V. Swintosky*

Received July 24, 1967.
Accepted for publication March 31, 1968.
Smith Kline & French Laboratories, Philadelphia, PA 19101 and *College of Pharmacy, University of Kentucky, Lexington, KY 40506
†Present address: Astra Pharmaceutical Products, Inc., Worcester, Mass.

Keyphrases

Trichloroethyl carbonate—toxicity
Particle size—trichloroethyl carbonate toxicity
LD_{50} value—particle size effect

Books

REVIEWS

Potential Carcinogenic Hazards from Drugs. Evaluation of Risks. UICC Monograph Series, vol. 7. Edited by Rene Truhaut. Springer-Verlag, 1 Berlin 31 (Wilmsdorf), Heidelberger Platz 3, Germany, 1967. vii + 249 pp. 16.5 × 25 cm. Price DM 68,–; U.S. $17.00.

This is the seventh volume of the monograph series sponsored by the International Union Against Cancer. It consists of a series of 24 papers presented at a symposium of the Cancer Control Commission held in Paris, November 1965.

It is quite apparent from both the formal papers and the abbreviated versions of the discussions which follow that emphasis was placed on chemical contact or ingestion as the principal etiological factor in carcinogenesis. While this orientation may be justified in a symposium dealing with drugs, it must be recognized that there are many oncologists who subscribe to the view that chemical carcinogenesis is of only minor significance in relation to the incidence of human cancer.

The initial papers in the symposium deal with the present state of methodology for evaluating the potential carcinogenicity of drugs. The statistical assessment of data from the point of view of predictability is then discussed. In view of the law prohibiting the use of carcinogenic substances as food additives, it is interesting to note the view expressed by one of the participants, Prof. I. Berenblum, that "for all practical purposes, a carcinogen is, like any other noxious substance, only harmful above a certain critical dose level." In this connection, the opinion of Prof. H. Druckrey based on his analysis of the dose–time relationships of chemical carcinogenesis, is especially pertinent. He distinguishes between the primary effect of a carcinogen at the cellular or molecular level, and the subsequent multiplication of cancer cells to the point of tumor induction. As far as the primary effect is concerned he holds to the view that "there is no indication for the existence of a subthreshold dose." Nevertheless, he recognizes that a zero tolerance for carcinogens is "not always practicable and is scientifically objectionable" and proposes as a basis for future discussion that "1% of the lowest dosage which, given daily over the whole life span to susceptible experimental animals, produces cancer only at the end of the life span, can be considered as the maximum tolerable dose for human beings."

A number of papers in this volume deal more specifically with the potential carcinogenicity of specific classes of substances such as metal-containing drugs, petroleum hydrocarbons, lactones, and hormones including progesterone. In the two reports dealing with plastics used in orthopedic or surgical practice, as well as in the discussions of these papers, the weight of evidence is in support of a physical rather than chemical explanation of the carcinogenic effect of experimental implants.

In his remarks reflecting the point of view of the pharmacologist, Professor Alastair C. Frazer emphasizes the need for discrimination and judgment in deciding when a drug should be subjected to life-span study for potential carcinogenesis, and questioned the need for identifying "extremely feeble" carcinogenic drugs intended for use over short periods in people whose life expectancy is unlikely to provide time for any effect to be induced.

This monograph is required reading for those who wish to keep up with current thought among the experts in drug safety evaluation. Although the discussions following each presentation reveal the lack of unanimity on many aspects, there is agreement that much remains to be done to get at the root of these problems from both the methodological and interpretative standpoints.

Reviewed by Bernard L. Oser
Food and Drug Research Laboratories
Maspeth, N. Y.

Advances in Pharmaceutical Sciences. Vol. 2. Edited by H. S. Bean, A. H. Beckett, and J. E.

CARLESS. Academic Press Inc., 111 Fifth Avenue, New York, NY 10016, 1967. x + 329 pp. 15.5 × 23 cm. Price $14.00.

In the preface to this series the editors state that their task "is to present topics of current and growing interest, written by experts, so that the development of the subject is portrayed in depth rather than providing a condensed review article." The contributors to this volume have successfully fulfilled the editors' objectives. Besides being an invaluable reference to the topics covered through 1965, *Advances in Pharmaceutical Sciences* can serve as a primary text in pharmaceutics courses at the graduate level.

The two central chapters, "Particle-Size Analysis" by I. C. Edmundson and "Flow Properties of Powders" by Barbara S. Neumann, complement one another. The former chapter reviews the problems encountered in particle-size specification and discusses statistical and graphical representation of particle-size data. Methods of particle-size measurement are described in sufficient detail to enable one to appreciate their limitations. The lengthy analysis of the Coulter counter method, including a review of its application in dissolution studies, is particularly useful. The chapter on powder rheology by Mrs. Neumann, while brief, updates her contribution in "Flow Properties of Disperse Systems," now out of print.

The first chapter in the book, "Kinetics and Mechanisms in Stability of Drugs" by Edward R. Garrett, brings up to date Dr. Garrett's review article in the September 1962 issue of *J. Pharm. Sci.* The current version is improved by discussion of the stability of specific drugs and classes of drugs in separate sections. While this review primarily emphasizes solvolytic degradation, it also discusses drugs which degrade through oxidation. The inclusion of a general description of autoxidative mechanisms would have broadened the usefulness of this chapter.

The last chapter, "Water Determination and its Significance in Pharmaceutical Practice" by C. A. Johnson, complements the first chapter by emphasizing the significance of water in relation to physical and chemical stability. The principle, methodology, limitations, and advantages of each method of water determination is detailed. Methods covered in depth include drying, distillation, the Karl Fischer titration, dielectric measurements, spectroscopy, and gas chromatography. Techniques adaptable to continuous measurement of water in processes are also reviewed.

The index, in conjunction with the outlines included at the head of each chapter, is adequate for one to find most specific topics covered in the book.

Reviewed by Nicholas G. Lordi
Rutgers—The State University
Newark, N.J.

Glass Electrodes for Hydrogen and Other Cations. Edited by GEORGE EISENMAN. Marcel Dekker, Inc., 95 Madison Ave., New York, NY 10016, 1967. xii + 582 pp. 15 × 22.5 cm. Price $24.75.

The twenty-one international contributors to this volume have combined to give a comprehensive treatment of the theory and practice of cation-sensitive glass electrodes. The book covers the advances in knowledge made in the past ten years, and it is to the editor's credit in selecting his authors that these advances have been made largely by the contributors to this volume.

The book is organized so as to present first the principles upon which the functioning of ion-sensitive electrodes is based and then to examine modern practice in making and using such electrodes. The volume is divided into nineteen chapters; however, I believe that the pharmaceutical scientist interested in using cation-sensitive electrodes as an analytical tool will find the following eight sections of primary interest: Interpretation of pH and Cation Measurement, Cation-Sensitive Glass Electrodes in Analytical Chemistry, Ion-Sensitive Electrodes and Individual Ion Activity Coefficients, Hydrogen and Cation Analysis in Biological Fluids *in Vitro*, H^+ and Cation Analysis of Biological Fluids in the Intact Animal, Cation-Selective Microelectrodes for Intracellular Use, Glass Microelectrodes and Their Uses in Biological Systems, and Clinical Application of Cation-Sensitive Glass Electrodes.

The authors have done a good job of defining the present limits of cation-sensitive electrodes, and most have taken the opportunity to outline the problems that still must be solved. The latter facet of the book should catalyze the ingenious investigator to envisage many new uses for cation sensitive electrodes. As one author points out, the advent of glass electrodes which can be made to respond selectively to various cations, has opened a veritable "Pandora's box" for investigators in the biological sciences. With such glass electrodes a non-destructive, continuous, high-sensitivity measurement of ionic activity may be made either *in vitro* or *in vivo*.

Each chapter in the volume is essentially self-contained, with its own table of contents and references, and can usually be read independent of the preceding chapters. The book can, therefore, serve as a valuable reference and should be in the library of anyone planning to use cation-sensitive electrodes (hydrogen or otherwise) as an analytical tool.

Reviewed by Leslie Z. Benet
College of Pharmacy
Washington State University
Pullman, Wash.

Steroid Hormone Analysis. Vol. I. Edited by HANS CARSTENSEN. Marcel Dekker, Inc., 95 Madison Ave., New York, NY 10016, 1967. xiii + 493 pp. 15 + 23 cm. Price $23.50.

A series of reviews in steroid methodology are presented as individual chapters of two types. The majority of chapters are technique oriented and have the following titles and scope: "Isotope Derivative Methods for the Determination of Steroid Hormones with ^{35}S-Sulfonylating Reagents," "Elementary Aspects of Infrared Spectroscopy of Steroids," "Outline of the Application of Nuclear Magnetic Resonance to the Investigation of Steroids," "Chromatography of Steroids on Paper," "Gas Chromatography of Steroids." In addition, there are two chapters that center on compounds rather than technique. These chapters are entitled: "Testosterone" and "Analysis and Identification of Steroid Conjugates."