Table III—Effect of Sunlight on Chloroform Solutions with and without Added Stabilizers

Parameter	Total Exposure Time, min	Ratio of Δ^9-Tetrahydrocannabinol to Methadone Peak Areas	Ratio of Cannabidiol to Methadone Peak Areas
With stabilizers	30	1.1	0.32
Control	—	1.1	0.31
Without stabilizers	30	0.63	0.20
Control	—	1.0	0.27

roform extraction solutions (100-μl portions) were exposed to these conditions for controlled periods. Stability was tested by comparison of ratios from the exposed solutions to daily ratios from the standard solutions (Table II).

Thirty minutes of exposure to sunlight caused rapid decomposition and decolorization in the chloroform solution and a significant, although lesser, amount of decomposition in the ethanol solution. Overnight exposure to a combination of fluorescent light and room temperature, an approximation of normal ambient laboratory conditions, caused a marked decomposition in the chloroform solution; the ethanol solution remained stable within experimental error after more than 18 hr of exposure to these conditions.

Decomposition in chloroform solution is not significant for our current method, which limits solution exposure to ambient laboratory conditions to 30–45 min. For other laboratories, handling and sampling procedures may make lengthy exposure to normal ambient laboratory conditions unavoidable. In such cases, the demonstrated cannabinoid stability in ethanol suggests that the most reliable procedure for analysis would be extraction with chloroform, flash evaporation of the solvent, and redissolution in ethanol. This procedure is still inconvenient, however, for any analyst who does not do such work on a routine basis or who has a large number of samples to analyze. The convenience of maintaining the cannabinoids in the extracting solvent is often desirable, so a means of stabilizing the chloroform solution would be useful.

Since cannabinoid degradation by chloroform is thought to be a free radical reaction (4), a combination of free radical inhibitors was added to portions of the chloroform solutions immediately subsequent to the extraction procedure. To each 5-ml aliquot, 2.6 μl of mercaptoethanol and enough sodium diethyldithiocarbamate to saturate the solution were added. Portions of this solution (100 μl) were removed for timed exposures to sunlight or normal laboratory conditions. Control solutions were refrigerated routinely, and stability was measured by comparison of peak area ratios from these 100-μl portions with those from the control solutions.

After 30 min of exposure to sunlight, there was no evidence of decomposition in the stabilized solution, as compared to 25–35% decreases in the cannabinoid–methadone ratios for the solution without added stabilizers (Table III). In addition, the solution containing the stabilizers remained stable for up to 10 hr of exposure to normal ambient laboratory conditions. Therefore, we suggest that chloroform solutions of naturally occurring cannabinoids either be refrigerated at all times or, if substantial exposure to fluorescent or natural light cannot be avoided, that the combination of stabilizers, sodium diethyldithiocarbamate and mercaptoethanol, be added as a protective measure.

(1) M. J. Parker, M. L. Borke, L. M. Block, and T. G. Cochran, *J. Pharm. Sci.*, **63**, 970 (1974).
(2) C. E. Turner and J. T. Henry, *ibid.*, **64**, 357 (1975).
(3) P. Lerner, *Bull. Narcotics*, **21**, 39 (1969).
(4) E. R. Garrett, A. J. Gouyette, and H. Roseboom, *J. Pharm. Sci.*, **67**, 27 (1978).

Catherine M. Bonuccelli
U.S. Customs Service
Washington, DC 20229

Received June 28, 1978.
Accepted for publication December 1, 1978.
The author thanks Dr. Carlton E. Turner for providing the column-purified cannabidiol, which Dr. Turner assayed at 95.47% pure.

Selectivity of Silicone Rubber toward Prostaglandin Permeability

Keyphrases □ Silicone rubber membranes—selectivity toward transport of E and F prostaglandins □ Prostaglandins, E and F—transport selectivity of silicone rubber membranes □ Delivery systems, potential—silicone rubber membranes, selectivity toward transport of E and F prostaglandins

To the Editor:

Considerable interest is being focused on the design of controlled-release drug delivery systems (1, 2). Their rational development requires a basic understanding of the physical–chemical parameters that control drug transport through the delivery module. The type of polymer matrix and the chemical form of the drug must provide a delivery rate in phase with the pharmacological potency of the therapeutic agent.

In the field of fertility regulation, several prostaglandins in various vaginal dosage forms have been studied to optimize bioavailability, reduce side effects, eliminate mul-

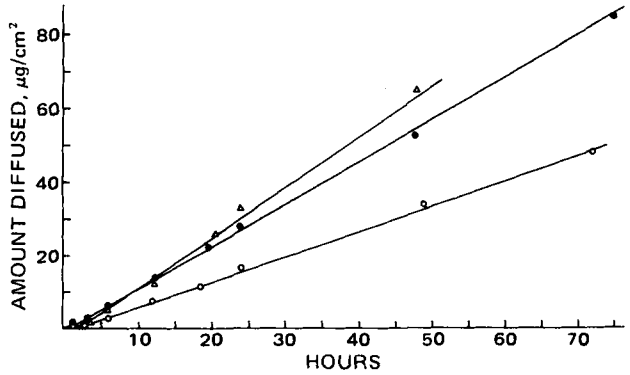

Figure 1—*Amount of prostaglandin transported across a silicone rubber membrane as a function of time. The donor compartment was maintained saturated with drug, and the membrane thickness was 0.05 cm. Key:* △, *dinoprost isopropyl ester;* ●, *dinoprost ethyl ester; and* ○, *dinoprost methyl ester.*

0022-3549/79/0200-0263$01.00/0

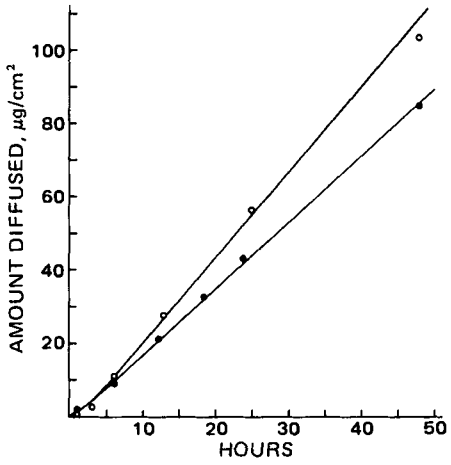

Figure 2—*Amount of prostaglandin transported across a silicone rubber membrane as a function of time. The donor compartment was maintained saturated with drug, and the membrane thickness was 0.05 cm. Key:* ○, *(15S)-15-methylprostaglandin $F_{2\alpha}$ ethyl ester; and* ●, *(15S)-15-methylprostaglandin $F_{2\alpha}$ methyl ester.*

tiple dosing regimens, and allow for self-administration (3, 4). This communication reports on the selectivity of silicone rubber toward the transport of E and F prostaglandins and its potential as a controlled-release delivery system.

Figures 1–3 show the diffusion profiles[1] of certain prostaglandins[2] across fillerless silicone rubber[3] membranes mounted in a diffusion cell (5). The free acid forms of dinoprost (prostaglandin $F_{2\alpha}$) and (15*S*)-15-methylprostaglandin $F_{2\alpha}$ did not permeate the membrane and are not presented on the graphs.

The presence of an ester linkage at the C-1 position markedly enhanced the permeation of dinoprostone (prostaglandin E_2) and the two F prostaglandins. Substitution of the C-9 hydroxyl group in dinoprost with a ketone moiety (*i.e.*, forming dinoprostone) also substantially increased the transport rate. Under saturation conditions

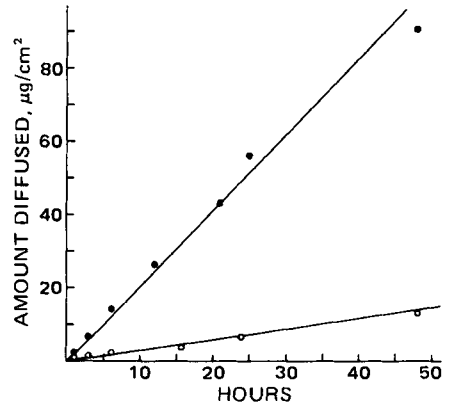

Figure 3—*Amount of prostaglandin transported across a silicone rubber membrane as a function of time. The donor compartment was maintained saturated with drug, and the membrane thickness was 0.05 cm. Key:* ●, *dinoprostone methyl ester; and* ○, *dinoprostone.*

[1] A GLC assay was used for prostaglandins of the F series while a UV assay was employed for the E series. Stability of E prostaglandins was verified by TLC, and stability of F prostaglandins was confirmed by GLC or TLC.

[2] The Upjohn Co., Kalamazoo, MI 49001.

[3] Dimethylpolysiloxane, Dow Corning Medical Products Division, Midland, Mich.

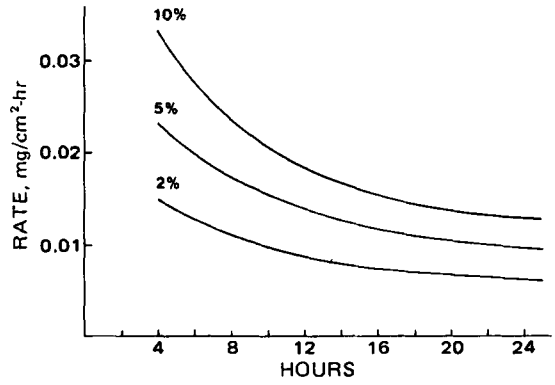

Figure 4—*Theoretical release rate profiles of (15S)-15-methylprostaglandin $F_{2\alpha}$ methyl ester from monolithic devices as a function of concentration.*

in the donor compartment, the steady-state flux, F, is given by (6):

$$F = \frac{C_s D_s}{h} \qquad \text{(Eq. 1)}$$

where C_s and D_s are the solubility and diffusivity in the membrane, respectively, and h is the membrane thickness. The dependence of flux on the chain length of alkyl esters of *p*-aminobenzoic acid was reported previously (7). For short chain lengths, $d \log F_n/dn = 0.19$, where F_n is the flux for a homolog with n carbons in the alkyl chain. Although sufficient data are not available to derive rigorously a dependence of F_n on n for prostaglandins, the flux of prostaglandins apparently is less sensitive to changes in ester chain length.

Release rate profiles of drugs from planar monolithic devices are given by the following time- (t) dependent equation when the total drug concentration, A, is much greater than C_s (8):

$$\text{rate} = \left(\frac{AC_s D_s}{2t}\right)^{1/2} \qquad \text{(Eq. 2)}$$

Normalizing the flux times distance given by Eq. 1 to unit thickness (*i.e.*, F_h) and substitution into Eq. 2 give:

$$\text{rate} = \left(\frac{AF_h}{2t}\right)^{1/2} \qquad \text{(Eq. 3)}$$

where F_h has the units of milligrams per centimeter-hour.

Equation 3 states that the drug release rate from polymer matrixes can be predicted once the steady-state flux across a membrane is determined (9). Theoretical release rate curves are shown in Fig. 4 for (15*S*)-15-methylprostaglandin $F_{2\alpha}$ methyl ester. A forthcoming publication will consider, in further detail, the applicability of Eq. 3 and the influence of membrane diffusivity and solubility on prostaglandin transport.

(1) "Controlled Release of Biologically Active Agents," Advances in Experimental Medicine and Biology, vol. 47, A. C. Tanquary and R. E. Lacey, Eds., Plenum, New York, N.Y., 1974.

(2) "Controlled Release Polymeric Formulations," ACS Symposium Series 33, D. R. Paul and F. W. Harris, Eds., American Chemical Society, Washington, D.C., 1976.

(3) "Prostaglandins and Reproduction," S. M. M. Karim, Ed., MPT Press, St. Leonard's House, Great Britain, 1975.

(4) C. H. Spilman, D. C. Beuving, A. D. Forbes, T. J. Roseman, and L. J. Larion, *Prostaglandins, Suppl.*, **12**, 1 (1976).

(5) G. L. Flynn and E. W. Smith, *J. Pharm. Sci.*, **60**, 1713 (1971).

(6) W. Jost, "Diffusion in Solids, Liquids, Gases," Academic, New York, N.Y., 1960.

(7) G. L. Flynn and S. H. Yalkowsky, *J. Pharm. Sci.*, **61**, 838 (1972).
(8) T. Higuchi, *ibid.*, **52**, 1145 (1963).
(9) D. R. Paul and S. K. McSpadden, *J. Membrane Sci.*, **1**, 33 (1976).

Theodore J. Roseman
The Upjohn Company
Kalamazoo, MI 49001

Received August 28, 1978.
Accepted for publication October 4, 1978.

BOOKS

REVIEWS

Psychopharmacology: From Theory To Practice. Edited by JACK D. BARCHAS, PHILIP A. BERGER, ROLAND D. CIARANELLO, and GLEN R. ELLIOTT. Oxford University Press, 200 Madison Ave., New York, NY 10016. 1977. xxiii + 557 pp. 15 × 23 cm. Price $17.95 cloth, $10.95 paper.

Although the treatment of mental and emotional diseases still leaves much to be desired, some of the most dramatic accomplishments have occurred in the area of pharmacotherapy. A quarter of a century has elapsed since the introduction of the new psychotropic drugs. During this generation of progress, the number of patients in mental hospitals has steadily decreased by about 360,000 from 559,000 in 1955 to the current estimate of less than 200,000. Attitudes have also changed toward mental and emotional disorders, with the recognition that these disorders are treatable and affect people of all ages. The economic cost of mental illness to this nation is estimated at more than $50 billion annually.

This book discusses recent developments in the study of neurotransmitters and neuromodulators (neuroregulators) and evidence indicating that behavioral events alter neurochemical function and that altered neurochemical function also can change behavior. Its central theme is the importance of neuroregulators and how they are affected by drugs. Thus, the interrelationships of drugs, neuroregulators, and behavior become the essence of psychopharmacology.

The text is fundamentally concerned with "the major psychiatric disorders and the manner in which the science of pharmacology may be applied, either immediately or ultimately, to their amelioration." The authors attempt to integrate the basic science and clinical aspects of psychopharmacology for those who will be responsible for the treatment of psychiatric patients. The scientific principles behind psychopharmacology are explained first, and then their relevance to the use of psychotropic drugs in good patient care is demonstrated. The text does not delve deeply into patient management, provide detailed descriptions of drug classes, summarize drug efficacy studies, or review classifications of psychiatric illnesses. Its coverage of pharmacotherapy is not very detailed.

"Psychopharmacology" is divided into five parts. Part I reviews, very nicely, the basic fields of study in psychopharmacology dealing with biochemical information on neuroregulators and the presumed mechanism of action of psychotropic drugs. Part I also includes chapters on the psychological and sociological aspects of psychopharmacology. Part II describes disorders that affect most patients who require psychiatric care, while Part III deals with drug abuse. Part IV discusses the pharmacotherapy of the young and the elderly, and Part V discusses specific topics important to psychopharmacology such as the use of placebos, the psychiatric effects of nonpsychiatric drugs, and the relationship of psychotherapy and pharmacotherapy.

The authors tried to make the treatment sections as practical as possible, providing information on normal dose ranges and side effects. They caution physicians that "the act of prescribing requires knowledge, care and clinical judgment," but omit a warning about individual human variability.

This book was written by 27 contributors, mostly physicians from Stanford University and the Palo Alto Veterans Administration Hospital, who have drawn upon their cumulative research and clinical experience to provide a useful guide, from theory to practice, of the major psychiatric disorders in the "new territory of psychopharmacology." It provides a knowledge base in psychopharmacology that will permit its readers to be informed practitioners and enable them to evaluate new information as it becomes available. Although "Psychopharmacology" is not a comprehensive survey of the generation of progress in this field, it is a good book and should be useful to clinicians, pharmacists, researchers, teachers, and students alike. Those interested in neuroregulators and their relation to behavioral disorders should buy a copy.

Reviewed by George J. Cosmides
National Institutes of Health
Bethesda, MD 20014

Drugs. How They Act and Why. By ALEX GRINGAUZ. C. V. Mosby, 11830 Westline Industrial Drive, St. Louis, MO 63141. 1978. 344 pp. 18 × 26 cm. Price $14.95.

This book is intended to serve as an aid to continuing education of pharmacists and other health professionals, particularly those who completed their formal academic training several years ago, before the advent of modern medicinal chemistry and molecular pharmacology. Accordingly, the level of presentation is elementary, and the discussions should be easily understood by the reader who has only minimal recollection of undergraduate biochemistry and medicinal chemistry.

The first chapter is a general introduction of some fundamentals of biochemistry. Chapters 2–4 consist of a review of some important characteristics of drug action, with emphasis on physicochemical principles, *e.g.*, factors affecting bioactivity, theories of drug action, selective toxicity, drug–receptor interactions, some stereochemistry and topography, some enzymology, antimetabolites, and chelation.

Thereafter, the book discusses some major classes of medicinal agents from the standpoint of biochemical mechanisms of action and clinical pharmacology. As the author emphasizes in the preface, not all categories of drugs are included because the book is not intended to be encyclopedic. Thus, the author selected the following topics: anticancer agents, antibiotics, adrenergic drugs, cholinergic drugs, analgesics, psychotherapeutics, and cardiovascular agents. Considering the objective of the book, most discussions seem to be adequate; however, in some cases extreme brevity leads to incomplete characterizations of important structure–activity relationships and mechanisms of action.