amount/cm^2 sec, where $V = 2.0$ cm^3 and $A = 1.54$ cm^2. Because the full thick skin used also contained some subcutaneous tissue and dermis, there appeared to be a lag time of about 5 min (Fig. 1).

Using the value for F_A, we can compute that $C_A(h)/-F_A = 2.03 \times 10^4$ sec/cm, where $V = 2.0$ cm^3 and $A = 1.54$ cm^2. A reasonable upper limit for P_{aqA} might be estimated as $P_{aqA} \doteq 5 \times 10^{-4}$ cm/sec, which corresponds to a 200-μm aqueous diffusion layer with a diffusion coefficient for III of 10^{-5} cm^2/sec. When assuming a III epidermal diffusivity of 10^{-6} cm^2/sec, $C_1 \doteq 1.8 \times 10^{-2}$ cm.

Finally, plotting each side of Eq. 3 *versus* κ for an epidermis of 300 μm, we find that $\kappa = 82$ or $k_m \doteq 6.7 \times 10^{-3}$ sec^{-1} from the intersection of the two curves. This calculation for the linear enzyme parameter, k_m, assumed some typical values for the diffusion coefficient of III in the epidermis and aqueous diffusion layer and the thicknesses of these layers. Experiments are planned to determine these parameters directly. In addition, the validity of assuming a first-order enzyme reaction must be investigated.

The determination of the metabolic parameter, κ, can be used to predict to what degree metabolism affects the bioavailability of the drug when it is administered topically. Figure 5 shows an *in vitro* situation relevant to the clinical application of a topical dosage form. The drug passes from the topical vehicle through the stratum corneum, S, into the metabolizing epidermis, M, and then through the aqueous diffusion layer into the receptor compartment. Suppose that there is a virus lesion halfway through the epidermal layer of 100 μm. How might drug bioavailability be affected by the fact that the epidermis metabolizes the drug?

For the application of a topical drug, the relevant equations (11) are:

$$C_{AM}(x) = -\frac{P_{SA}(P_{aqA}\sinh\kappa S - D_A\kappa\cosh\kappa X)C_A(-s)}{D_A\kappa(P_{SA}+P_{aqA})\cosh\kappa M + [P_{SA}P_{aqA}+(D_A\kappa)^2]\sinh\kappa M} \quad \text{(Eq. 7)}$$

and:

$$C_{A0}(x) = -\frac{\left(\frac{1}{D_A/X}-\frac{1}{P_{aqA}}\right)C(-s)}{\frac{1}{P_{aqA}}+\frac{1}{P_{SA}}+\frac{1}{D_A/m}} \quad \text{(Eq. 8)}$$

where $C_A(-s)$ is the concentration of III in the vehicle at the stratum corneum boundary; $C_{AM}(x)$ and $C_{A0}(x)$ are the concentrations of III at the distance X for a metabolizing and a nonmetabolizing epidermis, respectively; and P_{SA} is the III permeability of the stratum corneum. For P_{SA} values of 10^{-6} and 10^{-7} cm/sec and for the computed κ:

$$\frac{C_{AM}(-m/2)}{C_{A0}(-m/2)} = 0.181 \quad \text{(Eq. 9)}$$

$$\frac{C_{AM}(-m/2)}{C_{A0}(-m/2)} = 0.183 \quad \text{(Eq. 10)}$$

These results show that, for a metabolizing membrane, the bioavailability of III due to metabolism does not depend strongly on the stratum corneum permeability and that the concentration of the active drug, III, is only 18% of the level that would have existed at the site of the lesion (halfway through the epidermis) had there been no metabolism.

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H. Y. Ando
Philadelphia College of Pharmacy and Science
Philadelphia, PA 19104

N. F. H. Ho
W. I. Higuchi ˣ
College of Pharmacy
University of Michigan
Ann Arbor, MI 48109

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ˣ To whom inquiries should be directed.

Antineoplastic Agents L: Isolation and Characterization of Sphyrnastatins 1 and 2 from the Hammerhead Shark *Sphyrna lewini*

Keyphrases □ *Sphyrna lewini*—hammerhead shark, potential antineoplastic constituents isolated from body fluids, muscle tissue, and liver, identified □ Sphyrnastatins—isolated from hammerhead shark, preliminary evaluation of antineoplastic activity □ Antineoplastic activity—preliminary evaluation of sphyrnastatins isolated from hammerhead shark □ Marine antineoplastic agents, potential—sphyrnastatins isolated from hammerhead shark

To the Editor:

Hammerhead sharks of the Sphyrnidae family (cartilaginous fishes of the class Chondrichthyes) have inhabited the oceans for 181–350 million years (1) and represent a most successful evolutionary achievement. Sharks are rarely affected by diseases (2) and, to our knowledge, hammerhead sharks have not been found with cancer. In 1966, we began a long-term study (3) of marine animals for the purpose of developing cancer chemotherapeutic drugs (4). Early in this investigation, it was found that extracts of certain marine vertebrates exhibited a confirmed level of activity against the National Cancer Institute's PS (murine lymphocytic leukemia) screening system.

Now we wish to report the first[1] isolation and characterization of a shark anticancer constituent. The hammerhead shark, *Sphyrna lewini*[2], was found to produce two new antineoplastic agents designated sphyrnastatin 1 and sphyrnastatin 2. These anticancer components were isolated from the blood (and other body fluids), the fins (and other muscle tissue), and the liver.

In a typical isolation sequence, the water extract of blood and body fluids was first chromatographed on macroreticular resin[3]. The aqueous fraction (20 → 13.5 g) was next subjected to gel[4] permeation chromatography (10 × 100-cm column). Following elution with 3.25 liters of water, the PS inhibitory fraction (0.6 g from 5.0 g) was finally purified by chromatographic separation[5] (5 × 69-cm column and elution with a mixture of 0.05 *M* tromethamine and 0.1 *M* potassium chloride). The two highest molecular weight fractions (0.076 and 0.34 g) represented the antineoplastic components.

Sphyrnastatins 1 and 2, isolated by this procedure, were glycoproteins [~22 and 26% carbohydrate, respectively (6)] with apparent molecular weights (7) of at least 40×10^6. Amino acid analyses indicated a minimum protein segment of 274 amino acid units for sphyrnastatin 1 and 380 amino acid units for sphyrnastatin 2. Upon preliminary biological evaluation, the sphyrnastatins produced a 30–40% (at 11–13 mg/kg) life extension in mice inoculated with the PS leukemia. More extensive antineoplastic evaluation of sphyrnastatins 1 and 2 in the National Cancer Institute's exploratory screening systems is in progress. Presently, we are attempting to isolate other shark and marine vertebrate anticancer constituents.

Perhaps the sphyrnastatins and other high molecular weight antineoplastic substances (4) act by stimulating the immune system to more effective action against invading neoplastic disease. If this hypothesis is valid, then immunotherapy approaches to cancer treatment with, for example, BCG might better be considered as just another facet of cancer chemotherapy.

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George R. Pettit [x]
Richard H. Ode

Cancer Research Institute and
Department of Chemistry
Arizona State University
Tempe, AZ 85281

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[x] To whom inquiries should be directed.

[1] More broadly, this report represents the first isolation and characterization of a marine vertebrate antineoplastic agent.
[2] Specimens of *S. lewini* were collected off the coast of Florida from 1971 to 1974, and we thank Dr. C. Swift for the taxonomic identification. Except for inclusion in a recent study of elasmobranch hemoglobins, no prior assessment of *S. lewini* constituents has been made. See Ref. 5.
[3] XAD-2.
[4] G-50 Sephadex.
[5] Sepharose 2B.

BOOKS

REVIEWS

Drug Metabolism: Chemical and Biochemical Aspects. By BERNARD TESTA and PETER JENNER. Dekker, 270 Madison Ave., New York, NY 10016, 1976. xii + 500 pp. 18.5 × 26 cm. Price $47.50.

This is the fourth volume in the new "Drug and Pharmaceutical Sciences" series of textbooks and monographs edited by James Swarbrick. As stated by the editor, the purpose of the series is "to enable the pharmacist, and others in the health sciences field, to stay abreast of the changing trends, advances and innovations associated with drugs and the body of knowledge that has come to be known as the pharmaceutical sciences." According to the authors, the purpose of this volume is "to create a fundamental awareness of the basis of drug metabolic processes to those entering the subject or to those who have worked at higher levels of *in vivo* organization." Both purposes have been admirably met with this volume.

As promised in the title, the authors treat both the chemical and biochemical aspects of drug metabolism. The book is divided into these two major sections, with 60% of the text devoted to chemical considerations.

The five chapters devoted to chemical aspects include the major chapter of the book, phase I (biotransformation of chemical groupings) reactions, and a somewhat shorter chapter, phase II (conjugation) reactions. Together, these two chapters account for nearly one-half the total text. Having detailed the specific chemical reactions of drug metabolism, these chapters are brought together and placed in perspective in the third chapter of this section by presenting schematic views of the metabolism of 15 selected drugs. This is followed by a chapter concerning the stereochemical aspects of drug metabolism, a topic recently reviewed in some depth by the authors. The final chapter of this section deals with the influence of physiochemical factors on drug metabolism. This very short chapter (five pages) perhaps should have been expanded or eliminated.

The biochemical aspects of drug metabolism, primarily at the enzymatic level, are presented in four chapters of approximately equal length. The first describes the basic biochemical nature of the drug-metabolizing enzyme systems responsible for phase I and phase II reactions. The effects