hypothesis (6) and the lack of correspondence of absolute stereochemistry at the α-carbon of the tyramine unit, the importance of which is reinforced by the virtual lack of activity (mouse vas deferens) of the D-tyr[1] derivative of I[2] (27, 31). The structure–activity relationship between I and II is thus marked by a reversal in stereospecificity. An analogous reversal (by enantiomorphism at the α-carbon stereocenter of a β-phenethylamine unit) occurs in the analgesics (−)-*N,N*-dimethyl-1,2-diphenylethylamine[3] (*R*-configuration) (32) and (+)-1-cyclohexyl-4-(1,2-diphenylethyl)piperazine[4] (*S*-configuration) (33).

Stereochemical inversions in structure–activity relationships are also exhibited in diphenylpropylamine (methadone-type) and certain anilide analgesics and may generally be interpreted in terms of differing substrate–receptor interactions (11, 34) and/or induced-fit theories (35). Recent suggestions (36) of opiate receptor heterogeneity (κ, μ, δ) are especially apropos to this latter stereochemical discussion and have relevance to a comparison of II and the enkephalins, given their stereochemical noncorrespondence.

Any model proposing to rationalize the structure–activity relationships of opiates must consider stereochemical inversion phenomena[5]. If the "tyramine" relationship mentioned is valid, then difficulties arise in defining a structure–activity relationship for II (and its analogs) and, *e.g.*, I.

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[2] Also, D-tyr[1]-β_c-endorphin has minimal opiate activity (ileum assay) and analgesic potency compared to natural β_c-endorphin [see D. Yamashiro, L.-F. Tseng, B. A. Doneen, H. A. Loh, and C. H. Li, *Int. J. Peptide Protein Res.*, **10**, 159 (1977)].

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[5] A recent, simplistic model to explain structure–activity relationships of opiate agents unfortunately ignored absolute stereochemical factors [see A. P. Feinberg, I. Creese, and S. H. Snyder, *Proc. Natl. Acad. Sci. USA*, **73**, 4215 (1976)].

Absolute Drug Bioavailability II: Evaluation of Renal Clearance Perturbation Method Using Literature Data Assuring a Fraction Absorbed of Unity

Keyphrases □ Bioavailability, absolute—evaluation of renal clearance perturbation method using literature data assuring a fraction absorbed of unity □ Renal clearance—perturbation method evaluated using literature data assuring a fraction absorbed of unity

To the Editor:

Three years ago, a technique allowing an estimation of the absolute bioavailability of a drug without reference to a parenteral dose was reported (1). Since that time, two other reports (2, 3) suggested that this method is useful and reasonably accurate. However, the procedure has not been tested using data where the fraction absorbed is known. This communication reports the results of the application of the previously described technique to recently reported furosemide pharmacokinetic data obtained following intravenous administration.

Pharmacokinetic theory predicts that:

$$F = \frac{\Delta Cl_R}{\text{dose}}\left[\frac{(AUC)(AUC')}{AUC' - AUC}\right] \qquad \text{(Eq. 1)}$$

where F is the fraction of the dose absorbed, AUC is the area under the plasma concentration–time curve, the prime notation indicates the AUC in the perturbed renal clearance state, and ΔCl_R is the difference in mean renal clearance between the two experiments (see Ref. 1 for details). Data from a furosemide–probenecid interaction study (4) were used exactly as reported in Table I of that article, and AUC and AUC' values for each individual were determined using the relationship AUC = dose/plasma clearance.

The fundamental mechanism used to perturb the renal clearance of furosemide in this interaction study with probenecid seems to be competition for the renal transport system, which actively secretes organic acids (4). In previous studies, it was observed that the improved reabsorption of weak bases from an alkaline tubular fluid was an appropriate perturbation technique (2) and that the reduction in lithium renal clearance caused by chlorothiazide yielded data (3) supporting the validity of Eq. 1. The principal virtues of the data from Ref. 4 are that the two doses were given parenterally (*i.e.*, F is known to be unity), the physiological status of the volunteers was well controlled, and the plasma and urine concentrations were confirmed by two independent analytical procedures, thus circumventing the assay difficulties that have hampered some furosemide disposition studies.

When Eq. 1 and the values of ΔCl_R, AUC, AUC', and the intravenous dose from Table I of Ref. 4 are used to estimate F, a value of 1.05 ± 0.11 (mean ± SEM) is obtained. This result appears to provide further support for the validity of Eq. 1.

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BOOKS

REVIEWS

Microbiology—1977. Edited by DAVID SCHLESSINGER. American Society for Microbiology, 1913 I St., N.W., Washington, DC 20006. 1977. 593 pp. 17 × 26 cm. Price $22.00.

The book is divided into seven major and numerous minor sections, covering some of the more important and recent findings in microbiology.

Cell envelope and cell division in bacilli are represented by partial proceedings of the conference on bacilli (other material from the conference appeared in "Microbiology—1976"). Various topics concerning *Pseudomonas aeruginosa* and related components and their recognition by specific lymphocytes or other cell types are discussed. Modes of resistance to various antibiotics by the pseudomonads are covered. Endotoxins, cell wall antigens, and modulation of the immune response are presented in various manuscripts.

A historical review of pyrogen research by Otto Westphal *et al.*, and related articles on endotoxins and other cell wall components of Gram-negative bacteria and their biological activities proved to be very interesting and rewarding.

Viral infections are covered, including mechanisms involved in persistent viral infections, and the possible roles of defective virus in these infections. The roles of DNA in RNA viruses are also discussed. Animal and human models of persistent viral infections and live virus vaccines used in humans are topics also covered. Viruses and plasmids in fungi and protozoa are presented as an enlightening view of this little-known subject. Also in the field of virology is a series of studies of endogenous tumor viruses, including propagation, analysis, and regulation of various tumor viruses.

However, to me the most informative section dealt with novel aspects of penicillin action, including a short history written by Jack L. Strominger of the Department of Biochemistry and Molecular Biology, Harvard University, "How Penicillins Kill Bacteria."

"Microbiology—1977" continues the well-thought out series started in 1974 by David Schlessinger and fulfills the original aim of the series: to remedy part of the problem of keeping up with new developments in the field of microbiology.

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Fluorescence and Phosphorescence Spectroscopy: Physiochemical Principles and Practice. By STEPHEN G. SCHULMAN. Pergamon Press, Maxwell House, Fairview Park, Elmsford, NY 10523. 1977. 288 pp. 17 × 14.8 cm. Price $20.00.

The author states in his preface that this book "is written with the analytical chemist and biological scientist in mind and represents an attempt to make the instrumental, and especially the structural and environmental aspects of luminescence spectra intelligible to the reader with a general college background in chemistry and physics."

Chapter I, entitled "Photophysical Processes in Isolated Molecules," deals with a nonmathematic descriptive treatment of the subject. It serves to describe ideal systems and to define basic terms. Chapter II, "Photophysical Process in Molecules in Solution," surveys the effects of solvent–solute and solute–solute interactions on both the ground and excited states in electronic spectra. Chapter III is a brief description of the practical aspects of the instrumentation employed in the measurement