which are known to contain large amounts of melanin (eye, skin). The distribution of activity of the radioiodinated analog of chloroquine was similar to that seen with chloroquine in rats (8) and chloroquine-^{14}C in mice (9). Moreover, the low thyroid activity observed for the animals receiving the radioiodinated compound *versus* those given radioiodide, indicates that significant deiodination did not occur. Studies using mice with transplanted melanomas are now in progress.

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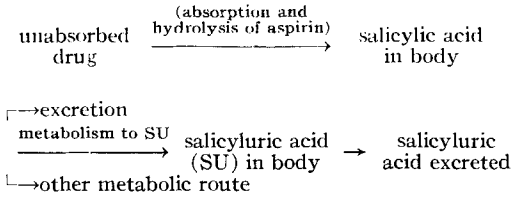
Evidence for Nonfirst-Order Kinetics of Salicylate Elimination—A Rebuttal

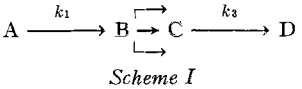
Sir:

Wagner's recent article (1) relating to the pharmacokinetics of salicylate elimination contains unwarranted conclusions and therefore requires an early rebuttal.

He claims that our pharmacokinetic model for salicylate elimination in man, which assumes capacity-limited formation of salicyluric acid at doses of 1 Gm. aspirin and above (2), is unjustified, and that all processes are likely to be apparent first-order. He bases his reasoning on a model involving a catenary chain of the type shown in Scheme I.

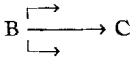


i.e.,



Scheme I

where all processes are first-order and the over-all rate constant for decline of B is defined as k. A direct and unambiguous test of this model is available by using experimental conditions which reduce the model to that shown in Scheme II.



Scheme II

This is accomplished by injecting B intravenously and following its concentration in the plasma as a function of time.[1]

Wagner's model requires that the half-life for the decline of salicylate concentrations in the plasma after intravenous injection of sodium salicylate be independent of dose. In fact, the average half-life [or the apparent half-life, since we do not consider the kinetics at higher doses to be first-order (2)] is 2.4 hr. with 0.25-Gm. doses (4), 6.1 hr. with 1.3-Gm. doses (5), and 19 hr. with 10–20-Gm. doses (6). In all instances, the drug was injected intravenously as salicylate.[2] These data, which were cited in our original paper, provide direct evidence that Wagner's contention is incorrect.

Wagner's pharmacokinetic model consists entirely of first-order rate processes. As a consequence (and in addition to the requirement stated in the preceding paragraph), the time course of urinary excretion of drug in all forms,

[1] Salicylate distribution is so rapid relative to elimination (3) that blood level data are not distorted by the distributive process beyond a very short time following intravenous injection.

[2] Only with the lowest dose was the half-life determined from urinary excretion data (which is acceptable in the context of the present discussion since it yielded the shortest half-life).

the shape of a cumulative plot of salicylurate excretion *versus* time, and the composition of urinary metabolites must be independent of dose (*i.e.*, superimposable) when expressed in per cent (or fraction of dose) terms.[3] Here are the actual facts:

(*a*) *All* published data on the urinary excretion of salicylates of which this author is aware show that the urinary excretion rate of total salicylates (*i.e.*, fraction of dose excreted after t hours, where t is less than the time required for total excretion) decreases with increasing dose. Appropriate data may be found in *References 2, 7, 8,* and *9*.

(*b*) The composition of urinary metabolites of salicylate changes with dose when the doses exceed about 0.5 Gm. in adults. Specifically, the fraction excreted as salicylurate decreases with increasing dose (2,10).

(*c*) Cumulative plots of salicylurate excretion as a function of time after salicylate administration are curved with low doses (10, 11) and linear over an appreciable period of time after higher doses (10, 12). An example of this is shown in Fig. 1. Wagner's kinetic model predicts that the two curves in the figure should be superimposable, *i.e.*, that all data points (regardless of dose) should fall on the same line!

(*d*) Semilogarithmic plots of total drug remaining to be excreted *versus* time after drug administration become linear, independent of dose, when the drug in the body has declined to a certain *amount* (2) rather than to a certain *fraction* of the dose, as would be the case with Wagner's model.

(*e*) Figure 2, based on the work of Salassa *et al.* (13), shows that a semilogarithmic plot of salicylate concentration in the plasma following a 3-Gm. dose of sodium salicylate *curves downward* for almost 30 hr. It is practically a straight line when plotted on linear coordinates, reflecting the constant rate of formation of salicylurate and the fact that this process is still the predominant one in the elimination of salicylate in the range of drug levels encountered in the study. When the salicylurate formation process is effectively blocked by co-administration of *para*-aminobenzoate, the decline of salicylate concentration in the plasma becomes exponential. This evidence is discussed in greater detail in previous publications from this laboratory (2, 14).

All of the evidence cited so far (except for the specific data in Fig. 1) is taken from papers which

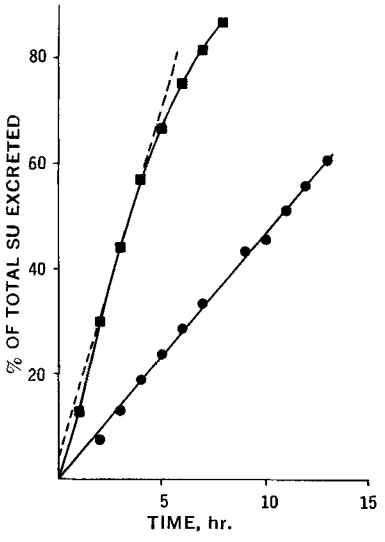


Fig 1—Cumulative excretion of salicyluric acid after 300 mg. (■) and 2 Gm. sodium salicylate (●) given orally in solution to a healthy adult. More than 98% of the dose was recovered in each case. Seventy-five per cent of the low dose and 62% of the high dose were transformed to salicyluric acid. The stippled line is straight and shows that the experimental points for the low dose do not fit a straight line. First-order kinetic models predict that the two curves would be superimposable.

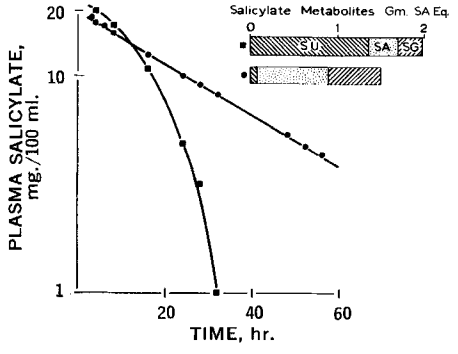


Fig. 2—Plasma concentration of salicylate following a 3-Gm. oral dose of sodium salicylate alone (■) and with para*-aminobenzoate (●) which blocks the salicylurate formation process. Bar graph shows output of salicylate (SA), salicylic glucuronides (SG), and salicyluric acid (SU) in the urine during the time when plasma concentrations were measured. Data from* Reference 13. *The curvature of the plot for salicylate alone reflects the capacity-limited formation of salicylurate and the nonfirst-order elimination of salicylate.*

appeared in the literature prior to the submission of Wagner's article but none of it was mentioned in that article. The impression was given (1) that our own conclusions concerning the elimination kinetics of salicylate in man (2) were based entirely on the time course of urinary excretion data. A review of our paper will show that our

[3] This is shown readily by dividing Wagner's Eq. 8 by X_A°, thus yielding X_D/X_A° (*i.e.*, fraction of dose) on one side and only k's and t on the other.

conclusions were based on much more extensive evidence. While additional reports from our laboratory concerning the elimination kinetics of salicylate as a function of age, dose, route of administration, co-administration of other drugs, *etc.*, will be forthcoming, this rebuttal is limited intentionally to presently published data to show that Wagner's "fallacy" is the result of his disregard for the totality of the evidence available and of his sole reliance on hypothetical models.

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Books

REVIEWS

Organisch-Chemische Arzneimittel und Ihre Synonyma (Organic Chemical Medicaments and Their Synonyms). By MARTIN NEGWER. Published by the Akademie-Verlag, Berlin, Germany. Distributed by Pergamon Press, Inc. 44–01 21st Street, Long Island City, New York, N. Y. 11101, 1966. vii + 1224 pp. 17.5 × 24 cm. Price $35.00.

In tabular fashion, this book lists approximately 3,500 compounds with more than 26,000 synonyms. The book is written in German, but because of the organization, it can be used by those not able to read German. Compounds are presented by their molecular formulas in order of the number of carbon atoms and are numbered individually. For example compound No. *1* is CCl_4, No. *2* is $CHBr_3$, No. *3* is $CHCl_3$, *etc.*, through No. *3567* which is $C_{254}H_{377}N_{65}O_{75}S_6$ (insulin). The information given for each compound includes its structural formula, chemical name, salt form, its synonyms including trade names from many countries, and therapeutic use or pharmacologic category. All of the synonyms and names appearing throughout the book are listed in the index, with cross-references to the compound number. Completeness of coverage and accuracy can be judged only upon continued use.

Staff review

A Systematic Approach to the Interpretation of Infrared Spectra. By HERMAN A. SZYMANSKI. Hertillon Press, Box 1677, Buffalo, NY 14216, 1967. vi + 150 pp. 22 × 28 cm. Price $2.00. Paperbound.

The major purpose of this text is to acquaint the reader with the methods used in correlating the observed infrared absorption bands with the structure of the compound being examined. Each absorption band, appearing at a fixed position, can be related to a specific structural group in a molecule. The position, shape, and intensity of the bands are three parameters that are associated with the structure of the compound.

The subject matter is arranged according to the general types of groupings that occur in organic molecules and the important group frequencies that appear as infrared bands. Spectra of several representative compounds are included to illustrate each grouping and to note shifts from the expected frequencies due to the influence of adjacent groups. Over 100 interpreted spectra are included to encompass the groups usually associated with organic compounds.

The book is intended as an introductory text but a working knowledge of infrared fundamentals is necessary to utilize this volume to the fullest advantage.

Staff review