Alich *et al.*[1] claimed that many possible variables introduced by others had been eliminated from their studies, but failed to recognize that they had introduced new variables that others had not introduced and that their results are subject to an alternative interpretation. As it turns out, this is the second paper coauthored by Alich and Wittmers on the subject of $Cu(II)_2(aspirinate)_4$ wherein conclusions were not supported by the evidence provided. In an earlier paper[14] these authors contended that salicylic acid was a contaminant of $Cu(II)_2(aspirinate)_4$, but failed to provide evidence in support of this contention[15]. The present contention by Alich *et al.* that $Cu(II)_2(aspirinate)_4$ causes erosions and vascular leakage at a dose of 100 mg/kg is not supported by evidence and it is also clearly inconsistent with results reported by ourselves and others they cited. Results obtained by Alich *et al.*[1] may be better interpreted in terms of absorption of copper compounds.

John R. J. Sorenson
University of Arkansas
College of Pharmacy
Little Rock, AR 72205

[1] A. A. Alich, V. J. Welch, and L. E. Wittmers, Jr., *J. Pharm. Sci.*, **72**, 1457 (1983).
[2] D. A. Williams, D. T. Waltz, and W. O. Foye, *J. Pharm. Sci.*, **65**, 126 (1976).
[3] J. R. J. Sorenson, T. M. Rolniak, and L. W. Chang, *Inorg. Chim. Acta*, **91**, L31 (1984).
[4] J. R. J. Sorenson, *J. Med. Chem.*, **19**, 135 (1976).
[5] F. Marletta, E. Rizzarelli, A. Mangiameli, M. Alberghina, A. Brogna, S. Sammartano, and A. Blasi, *Rend. Gastroenterol.* **9** Suppl. 1, 35 (1977).
[6] F. Marletta, E. Rizzarelli, A. Mangiameli, M. Alberghina, A. Brogna, S. Monaco, S. Sammartano, and A. Blasi, "The XIVth International Congress on Internal Medicine," October 1978, pp. 132 and 133.
[7] R. Goburdhun, K. Gulrez, H. Haruna, and G. B. West, *J. Pharmacol. Meth.*, **1**, 109 (1978).
[8] G. B. West, *J. Pharmacol. Meth.*, **8**, 33 (1982).
[9] L. J. Hayden, G. Thomas, and G. B. West, *J. Pharm. Pharmacol.* **30**, 244 (1978).
[10] K. D. Rainsford and M. W. Whitehouse, *J. Pharm. Pharmacol.*, **28**, 83 (1976).
[11] J. R. J. Sorenson, *J. Pharm. Pharmacol.*, **29**, 450 (1977).
[12] E. Boyle, P. C. Freeman, A. C. Goudie, F. R. Mangan, and M. Thompson, *J. Pharm. Pharmacol.*, **28**, 865 (1976).
[13] S. F. Townsend and J. R. J. Sorenson, in "Trace Elements in the Pathogenesis and Treatment of Inflammatory Conditions," Agents and Actions Suppl. 8, K. D. Rainsford, K. Brune, and M. W. Whitehouse, Eds., Birkhauser, Basel, 1981, pp. 389–398.
[14] A. A. Alich and L. E. Wittmers, Jr., *J. Pharm. Sci.*, **69**, 725 (1980).
[15] J. R. J. Sorenson, *J. Pharm. Sci.*, **70(3)**, IV (1981).

Response to: "The Ulcerogenic Potential of Copper Aspirinate Seems to be More Imaginary than Real"

Dr. John Sorenson has responded to a paper in which we showed that when intact rat stomachs were subjected to aspirin or copper aspirinate under normal conditions of absorption, and when mucosal damage was highlighted with a protein-binding dye, observations differed from those made on Shay-prepared rats by Sorenson[1]. Our data indicated that copper aspirinate gave much larger superficial lesion indices and slightly smaller deep lesion indices than aspirin alone[2]. Dr. Sorenson's article contains several comments deserving of our response.

1. Dr. Sorenson, in taking exception to our results, makes frequent reference to studies which employed the Shay rat as a model. As we indicated in our paper, the Shay rat is quite a different model from ours. We attempted to approximate normal conditions under which drugs are presented to and absorbed from the stomach. We wish to reiterate that our model is different from the Shay model, and appears to produce different results. Since the Shay rat has frequently been used by other laboratories, an effort was made to refer to such data where appropriate.

2. Dr. Sorenson interprets the lesion index graphs incorrectly. The lesion index does not measure depth of color, but sums over the number of lesions of each diameter within one of the two color groups. Therefore, the index gives a number related to total area of mucosa damaged for each kind of lesion. Our paper indicates that the two color groups were independently verified by microscopic examination to be deep and superficial erosions, the deep erosions being a very dark blue, the superficial a royal blue. Dr. Sorenson hypothesizes that the color in the mucosa is caused by a dye-protein-copper complex formed when the copper is absorbed into the mucosa and the dye-protein complex leaves the vascular system. While this is an interesting hypothesis, it does not account for all of our results portrayed in Fig. 1A and B of our paper[2]. Dr. Sorenson's hypothesis may be possible or appropriate in A, for the sets of data containing Cu(II), but does not account for the lesion index in the controls or in those rats treated with aspirin. Likewise, in B of Fig. 1, the hypothesis may fit the last two sets of bars, but not the copper sulfate control or the rats treated with aspirin. Our observations from past work indicate that Cu(II) is absorbed into the mucosa whether complexed or not. In 1- or 2-h experimental periods similar to those described in our paper, but in which no dye was used, mucosal tissue exposed to copper-containing compounds, became a uniform grey-blue color and yielded extremely high values for copper analysis indicating that copper was absorbed into the tissue[3].

In any case, the amounts of copper present in our experiments would be too small to account for the extent of the coloration of the lesions. Likewise the hypothesis does not explain why there are two distinct shades of blue. Finally, the hypothesis cannot be applied to all the data presented in the paper.

3. Sorenson states that appearance of the protein-dye complex in the mucosa under the conditions of our experiment "does not provide evidence of either erosions or vascular damage." He attributes the leakage to absorption-induced hyperemia. Under normal physiological conditions, Pontamine Sky Blue 6BX, and other protein-binding dyes, do not leak from the vascular system in any significant amount[4]. The protein movement from the vascular volume into the interstitial space is very slow, as indicated by the small permeability coefficients for molecules of this size range. All animals in our experiments were sacrificed 10 min post dye injection. The discussion in our paper details the damage to blood vessels which allows leakage of the protein–dye complex into the tissue. Use of a protein-bound dye to aid assessment of mucosal damage is not unique with us. Dr. Sorenson is aware of the papers of West and co-workers[5,6] who also used this method.

4. Dr. Sorenson, commenting on our observations of hemorrhage in the absence of visible erosions, claims we ". . . offered no rationale as to how this hemorrhage which occurred in the absence of erosions was relevant to their gastric study or in any way supported their interpretation of their results." Sorenson appears not to have understood the description of Robins' work[7]. Robins observed (electron microscope) that prior to the appearance of visible mucosal erosions, and within minutes of being placed in the stomach, aspirin caused small blood vessels to develop fenestrations and later to break down completely[7]. These observations lend support to our suggestion that bleeding occurs prior to the appearance of visible lesions. Our paper describes samples which were found, on microscopic examination, to have no lesions, but by the dye method to present superficial erosions. The extravascular accumulation of the protein-dye complex in these cases indicated that the capillary endothelium was damaged prior to the development of the lesions. We also observed complete ischemia in the centers of a number of erosions, suggesting that the circulation was severely disrupted in these areas within the 2-h exposure to the drug.

5. Dr. Sorenson refers to a reduction in gastric acid secretion in response to the treatment of the Shay rat with copper complexes. The Sorenson reference given[8] contains no mention of the measurement of acid secretion. Further, other references described inhibition of acid secretion in Shay rats by copper–amino acid complexes[9,10]. Since controls were also Shay rats, it is not possible to determine whether the acid secretion was more or less than that in a non-Shay rat. It does not appear legitimate to extrapolate such results, in Shay rats, treated with copper–amino acid complexes, to non-Shay rats treated with copper aspirinate. West and co-workers (whose work Sorenson uses to buttress his arguments in this discussion) did not find the Shay-prepared rat to be the perfect model for testing activities of drugs[6].

6. Dr. Sorenson proposes that the complex of copper aspirinate is formed by the 10-min sonication of the Cu^{2+} and aspirin mixture to be placed in the stomach. He also proposes that $CuCO_3$ or "some other nonabsorbable form of copper" is formed from copper aspirinate during the sonication in the buffered system. This is an interesting proposal, the decomposition appearing more plausible than the formation of the complex (although in our thermal analysis experiments decomposition is not observed below 265°C). In any case, it does not seem to be legitimate to propose two opposite effects by the same sonication.

7. Dr. Sorenson states that we "incorrectly indicated" that he had reported that aspirin was an active antiulcer agent in the Shay rat. Our reference is to a specific paper[1], in which the statement is made (on p. 139): "Aspirin and anthranilic acid were active at 225 mg/kg ig. Again, if this is real activity in this model then these two compounds lack potency. The question as to whether or not these are irritant-induced or false positive results remains to be answered."

0022-3549/84/1200-1876$01.00/0

These are the major points relevant to this study on which we would differ from Dr. Sorenson's interpretation of our work. It is somewhat difficult to respond to some of his statements because no data is given to support the claims made. For example, Dr. Sorenson challenges the widely accepted use of a protein-binding dye and proposes in its place an "absorption-induced" hyperemia; no substantiating evidence is presented. He proposes a difference in the rate of absorption of the different copper-containing species, giving as evidence only an oleyl alcohol/water partition coefficient for copper aspirinate/aspirin[11]. He proposes both formation and decomposition of copper complexes by sonication, again with no evidence given. Dr. Sorenson states that we neglected to report, in our survey of experiments, that he had pointed out in print[12] that a Rainsford and Whitehouse paper was flawed by the use of an inappropriate suspending agent[13]. No supporting evidence was given.

In conclusion, this challenge of our results is not a legitimate one. We believe that under the experimental conditions employed, copper aspirinate does not appear to be less damaging than aspirin. Further work is in process on the mechanism and characteristics of the gastric mucosal damage inflicted by the copper complex of aspirin as well as that of aspirin in combination with copper.

After consideration of Dr. Sorenson's concerns, as well as a review of the literature, we believe that a more thorough comparison of models is warranted. West and co-workers[5,6] have compared mucosal damage from aspirin and copper aspirinate in the stress-induced, Shay, and drug-induced ulcer models. A study is planned to compare these with the unstressed model in which the ulcers or erosions are caused by the presentation of the drug under study.

A. A. Alich[x]
College of St. Scholastica
Department of Chemistry
Duluth, MN 55811

L. E. Wittmers, Jr.
School of Medicine
University of Minnesota-Duluth
Department of Physiology
Duluth, MN 55812

[1] J. R. J. Sorenson, *J. Med. Chem.*, **19**, 135 (1976).
[2] A. A. Alich, V. J. Welsh, and L. E. Wittmers, Jr., *J. Pharm. Sci.*, **72**, 1457 (1983).
[3] Unpublished results.
[4] E. M. Renkin, *Acta Physiol. Scand.*, **463 Suppl.**, 81 (1979).
[5] G. B. West, *J. Pharmacol. Meth.*, **8**, 33 (1982).
[6] L. H. Hayden, G. Thomas, and G. B. West, *J. Pharm. Pharmacol.*, **30**, 244 (1978).
[7] P. G. Robins, *Br. J. Exp. Pathol.*, **61**, 497 (1980).
[8] J. R. Sorenson, T. M. Rolniak, and L. W. Chang, *Inorg. Chim. Acta (Lett.)*, **91**, L31 (1984).
[9] F. Marletta, F. Rizzarelli, A. Mangiameli, M. Alberghina, A. Brogna, S. Sammartano, S. Monaco, and A. Blasi, "XIVth International Congress on Internal Medicine," Rome, 1978, Abstr. p. 132.
[10] M. Alberghina, A. Brogna, A. Mangiameli, F. Marletta, F. Rizzarelli and S. Sammartano, *Il. Farmaco—Ed. Sci.*, **37**, 805 (1982).
[11] D. A. Williams, D. T. Walz, and W. O. Foye, *J. Pharm. Sci.*, **65**, 126 (1976).
[12] J. R. J. Sorenson, *J. Pharm. Pharmacol.*, **29**, 450 (1977).
[13] K. D. Rainsford and M. W. Whitehouse, *J. Pharm. Pharmacol.*, **28**, 83 (1976).

Pharmaceutical Company Data on Drugs in Breast Milk

The World Health Organization Regional Office for Europe has recently established a Working Group to produce a monograph describing the present state of information about drug excretion in breast milk and the hazards, if any, to the suckling infant. The Group is currently reviewing published literature but is aware that other data may be maintained by drug companies in internal files. The Group would welcome the opportunity to evaluate such information with a view to including it in the monograph. Drug companies which have in their possession unpublished data on excretion of drugs in breast milk are asked to contact:

P.N. Bennett, MD FRCP
School of Pharmacy and Pharmacology
University of Bath
Claverton Down
Bath
Avon BA2 7AY
England

ERRATA

In the article "Determination of Pantothenic Acid in Multivitamin Pharmaceutical Preparations by Reverse-Phase High-Performance Liquid Chromatography" (1), the following should be noted:

On page 114, Figures 1 and 2 were transposed.

(1) T. J. Hudson and R. J. Allen, *J. Pharm. Sci.*, **73**, 113 (1984).

In the article "Diaspirins of Methylenecitric Acid" (1), the following correction should be made:

On page 419, in the last line in Table I the compound name should read [Bis(3,5-dibromo-2-carboxyphenyl)fumarate].

(1) S. E. Massil, G.-Y. Shi, and I. M. Klotz, *J. Pharm. Sci.*, **73**, 418 (1984).

In the article "Physicochemical Model for Dose-Dependent Drug Absorption" (1), the following correction should be made:

On page 1278, in the *Appendix*, the last line should read $R_i = k_{ai} f_{ui} \times C_i V_i$.

(1) J. B. Dressman, D. Fleisher, and G. L. Amidon, *J. Pharm. Sci.*, **73**, 1274 (1984).

0022-3549/84/1200-1877$01.00/0