described with several exceptions. The compounds were solubilized or suspended in acetone (0.1%). Paper disks were dipped into the acetone solution or suspensions, allowed to dry, and then placed on the agar. Disks were removed after 1, 5, and 30 min and 1, 3, and 6 hr, and zone sizes were measured after incubation for 96 hr. As in the previous experiment, tolnaftate gave larger zones of inhibition than undecylenic acid and zinc undecylenate, even after only 1 min of contact (Table II). These differences again were highly significant, with the greatest differences occurring at the early time points.

The minimum inhibitory concentration was obtained in the conventional manner (2) using Sabouraud dextrose broth (Table III). Tolnaftate again was far more active than the two undecylenates in this second model of *in vitro* testing. The minimum inhibitory concentration values for tolnaftate all were <1.0 μg/ml, while the values for the undecylenates ranged from 7.5 to >10 μg/ml after 72 hr of incubation. These differences again were highly significant.

Since our data indicated *in vitro* superiority for tolnaftate over undecylenates and since efficacy *in vivo* certainly is more meaningful, it was of interest to determine if this superiority would be seen with formulated material. Results of a double-blind study comparing commercial powder A (Lot 7A503), commercial powder C[6] (Lot 14765), and commercial talc (USP M.I. No. N-03294) against a topical *T. mentagrophytes* infection in guinea pigs are shown in Table IV. Treatment was topical (powder liberally sprinkled on infected area) twice daily for 10 days. Hair and scales were removed from the infection site and plated onto Mycosel agar every other day. In addition, animals were scored for lesion appearance every day.

Procedures for establishing, culturing, and scoring the infection were described previously (4). All animals treated with commercial powder A were negative (as measured by lack of growth of the infecting organisms) throughout the treatment period (first culture taken after 2 days of treatment), and all remained negative up to 7 days posttreatment, at which time the experiment was terminated. These results were highly significant when compared with commercial powder C. Culture results seen with commercial powder C were similar to those seen with the talc controls. During treatment, all animals treated with commercial powder C remained positive; after treatment, 33% of the cultures obtained from animals treated with commercial powder C and 29% from animals treated with talc were negative. In both groups, no negative cultures were obtained until 15 days after treatment began. In addition, the average lesion scores both during and after treatment were lower with commercial powder A than with commercial powder C, and there was no statistical difference between commercial powder C and untreated controls.

Our results with this guinea pig model are similar to those reported by other investigators using similar procedures (5). In those experiments, 1% tolnaftate powder was compared to commercial powder D to determine the activity of both substances as prophylactic agents. The results showed that 1% tolnaftate powder was far more effective than commercial powder D.

[6] Cruex (contains 10% calcium undecylenate), Pharmacraft, Pennwalt Corp., Rochester, N.Y.

In the 15 years since the guinea pig model was described, the relationship between this model and clinical effectiveness has been demonstrated for many antifungal agents. Tolnaftate (4), clotrimazole (6), and miconazole (7) all were very active in the guinea pig model, and all are presently recommended for clinical use against dermatophytes (8).

Our *in vitro* and *in vivo* data obtained following conventional testing methodology clearly indicate that tolnaftate, commercial solution T, and commercial powder A are far more active than undecylenic acid, zinc undecylenate, commercial powder C, and commercial solution D.

(1) L. P. Amsel, L. Cravitz, R. VanderWyk, and S. Zahry, *J. Pharm. Sci.*, **68**, 384 (1979).

(2) B. J. Winer, "Statistical Principles in Experimental Design," McGraw-Hill, New York, N.Y., 1962.

(3) A. I. Barry, in "Infectious Diseases," 2nd ed., P. D. Hoeprich, Ed., Harper & Row, New York, N.Y., 1977.

(4) M. J. Weinstein, E. M. Oden, and E. L. Moss, Jr., *Antimicrob. Agents Chemother.*, **1964**, 595 (1965).

(5) J. A. Waitz and E. L. Moss, Jr., *Chemotherapy*, **14**, 170 (1969).

(6) J. A. Waitz, E. L. Moss, Jr., and M. J. Weinstein, *Appl. Microbiol.*, **22**, 891 (1971).

(7) J. M. VanCutsem and D. Thienpoint, *Chemotherapy*, **17**, 392 (1972).

(8) *Med. Lett.*, **18**, 101 (1976).

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Comparative *In Vitro* and *In Vivo* Antifungal Activity of Tolnaftate and Various Undecylenates: A Rebuttal

Keyphrases □ Antifungal activity—tolnaftate and various undecylenates, comparison *in vitro* and *in vivo* □ Tolnaftate—antifungal activity *in vitro* and *in vivo*, comparison with various undecylenates □ Undecylenates—antifungal activity *in vitro* and *in vivo*, comparison with tolnaftate

To the Editor:

When different groups of scientists perform studies using differing techniques, one may expect somewhat different results, as evidenced by the work of Amsel *et al.* (1) and Loebenberg *et al.* (2). A rebuttal to the Loebenberg *et al.* communication (2) is clearly in order. The stress of Loebenberg *et al.* on our "unusual" methodology seems to hint that the use of a new or nonstandard method may be unacceptable. Our method (1) was reproducible by different investigators, rapid, and equivalent to older "standard" methods.

The following comments are presented in reply to the criticisms of Loebenberg *et al.* (2).

1. Their comment that minimum fungicidal concen-

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trations as well as minimum inhibitory concentrations for products used were not presented is irrelevant. Our purpose was not to compare the potency of undecylenic acid and tolnaftate (studied at 20–21°) but rather to show differences in their activity (*i.e.*, killing time).

2. Loebenberg *et al.* (2) questioned the use of suspensions *versus* solutions. Suspensions of active ingredients as well as finished products were used to eliminate, as much as possible, problems that frequently occur in *in vitro* testing (*e.g.*, differences in diffusion due to different vehicles). Thus, the use of polyethylene glycol 400 as a solvent for tolnaftate and of ethanol for undecylenic acid (both would be in solution) was, in our opinion, less justified and might have introduced more error into the results than the use of an aqueous suspension for both. Diffusional differences due to the solvent could well overshadow any antifungal action. Also, an "in-use" condition would be mimicked most closely by having the products in aqueous suspension (as might be expected in the humid cutaneous environment).

3. Certainly no claim for "more bioavailability" of undecylenic acid over tolnaftate was made based on an *in vitro* study (1), as suggested by Loebenberg *et al.* (2). We are unaware of any selectivity of polysorbate in aiding dispersion or wetting of any particular product.

4. Preliminary experimentation indicated that rinsing in simple peptone solution did not remove all active drug from the cultures. To ensure complete removal of the active ingredients, the rinsing solutions and procedures described (1) were utilized.

5. It appears to us that if the contact time between the drug and organism were increased, any benefit would be reaped by both compounds and not by one exclusively. The longest contact time was 240 min.

6. Loebenberg *et al.* (2) noted wide variation in our results (1). Although the differences in Table IV are less often significant, the trend is in the same direction as in Table II. Statistical procedures were employed and presented to substantiate the conclusions.

While Loebenberg *et al.* (2) criticized our use of suspensions of commercial powders[1,2], they did not present data on these commercial powders to refute our *in vitro* results. Instead, they compared solutions[1,3] *in vitro*. The vehicles of these products differ markedly (propanol and polyethylene glycol 400, respectively). Therefore, we used an aqueous powder suspension to eliminate vehicle differences and, hence, possible differences in diffusion. Even though lower minimum inhibitory concentrations were noted for tolnaftate, concentration obviously is not the sole criterion of an effective drug.

The introduction by Loebenberg *et al.* (2) of a guinea pig study into a discussion of *in vitro* results is perplexing; here, also, different commercial products were compared[2,4]. Loebenberg *et al.* (2) noted that the average lesion score for one product[2] (16.4) was lower than that for the other[4] (18.2). Whether a difference in scores of 1.8 is significant or of clinical importance is doubtful. Moreover, the guinea pig test system referred to (3) is of limited use. Weinstein *et al.* (3) noted that the system "can have suggestive value only" and that: "The absolute relationship between guinea pig efficacy and clinical utility in acute and particularly chronic human infections has not been established." These investigators (3) also noted that the *in vivo* test can act only as a guide to suggest possible clinical usefulness.

[1] Desenex.
[2] Aftate.
[3] Tinactin.
[4] Cruex.

(1) L. P. Amsel, L. Cravitz, R. VanderWyk, and S. Zahry, *J. Pharm. Sci.*, **68**, 384 (1979).
(2) D. Loebenberg, R. Parmegiani, M. Hanks, and J. A. Waitz, *ibid.*, **69**, 739 (1980).
(3) M. J. Weinstein, E. M. Oden, and E. L. Moss, *Antimicrob. Agents Chemother.*, **1964**, 595 (1965).

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Hygroscopicity of Poorly Soluble Porous Substances

Keyphrases □ Hygroscopicity—poorly soluble and insoluble substances, correlation between pore structure and equilibrium moisture content □ Pore-size distribution—overall porosity of poorly soluble substances, effect on hygroscopicity, equilibrium moisture content □ Equilibrium moisture content—poorly soluble substances, effect of overall porosity on hygroscopicity

To the Editor:

The general problem of hygroscopicity of soluble compounds has been defined (1, 2) and was reviewed recently (3). However, the hygroscopicity of poorly soluble compounds has attracted little attention. El-Sabaawi and Pei (4) showed that a correlation exists between pore structure and equilibrium moisture content for insoluble substances. This report extends this principle to insoluble substances with log-normally distributed pore spaces and shows that the equilibrium moisture curves obtained are of a traditional contour. It is presumed that this principle also extends to poorly soluble substances, as defined in the USP.

A liquid with zero contact angle exerts a vapor pressure when confined in a capillary pore of diameter d which is given by the modified Kelvin equation (5):

$$\ln(P/P^*) = -4\gamma V/[RT(d-t)] \qquad \text{(Eq. 1)}$$

where P is the vapor pressure over the liquid in the pore, P^* is the vapor pressure of pure water at the given temperature T, γ is the interfacial tension between the solid and liquid (water), V is the molar volume of the liquid (water), R is the gas constant, and t is the correction factor for the sorbed layer *in* the pore.

For the purpose of the example and for simplicity, t is neglected in the following equation, so Eq. 1 becomes:

$$\ln(P/P^*) = -4\gamma V/RTd \qquad \text{(Eq. 2)}$$

The hygroscopicity of a compound or powder mixture often is studied by means of equilibrium moisture curves. To obtain these curves, a given amount (W_0, expressed in

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