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FUNGOUS AND BACTERIAL SKIN INFECTIONS IN THE TROPICS.(U)
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FUNGOUS AND BACTERIAL SKIN INFECTIONS IN THE TROPICS (U)

LEVEL III

ANNUAL PROGRESS REPORT
1 Jun 73 - 31 May 74

by

David Taplin

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WORK IN PROGRESS

1) At the end of this contract year, plans were well advanced to conduct a large scale survey of skin diseases among Colombian Army units, in collaboration with the Dermatological Research Unit LAIR. The principle investigator (D. T.) made two liason visits to Bogota to coordinate the programme with the U.S. Embassy, the Central Military Hospital at Bogota, and the Colombian Ministry of Defense, and permissions were obtained to conduct the study.

The team will consist of LTC Alfred M. Allen M.C., Captain Robert King, and Ms. Judy Richie, from the Letterman Army Institute of Research, David Taplin and Ms. Patricia M. Mertz from the University of Miami. Logistical and laboratory support for mycology in the field will be provided by the Miami team. Most of the bacteriology and the data processing will be conducted by the LAIR team. Colonel Allen will be team chief and will be responsible for the planning and statistical design of the population sampling.

2) The original plan to deploy the mobile field laboratory in Nigeria have been abandoned, primarily due to the prohibitively expensive costs of shipping the unit, and because we expect to be able to accomplish the same objectives in Latin America at much less expense.

Meanwhile, the trailer is being modifies to provide additional security screens on the windows, greater storage capacity for the internal 12 volt electrical supply, and additional internal circuits to operate laboratory equiptment.

SUMMARY

Work is in progress to establish the importance of natural wet environments and wet sources in hospitals as the breeding grounds for multiply drug resistant gram-negative bacteria. First data suggests that these reservoirs constitute a potential threat to patients or those injured in wet terrain, and that transfer of antibiotic resistance may occur between gram-negative bacteria in these reservoirs.

A cream containing Nystatin and Tolnaftate was effective in the treatment of Tinea Cruris and Candidiasis, but the Thimerosol preservative in the cream was responsible for several allergic skin reactions.

A new topical antifungal agent, Clotrimazole, was shown to be effective against Tinea Corporis, Tinea Cruris and Tinea Pedis.

Control of environmental reservoirs of opportunistic pathogens continues to play a major role in the prevention of infections within a Burn Unit.

A large study on the value of an antibacterial soap in the prevention of common skin infections has been conducted. Results will be reported after evaluation by the United States Food and Drug Administration.

6) Plans are well advanced to conduct a large scale survey of skin diseases among Colombian Army Units. The study will combine personnel from the Letterman Army Institute of Research and the University of Miami.

Transfer of Antibiotic Resistance Among Gram-negative Bacteria Found in Wet Hospital Environments

During our work on gram-negative bacteria found in hospital flower vases, (Lancet, December 8, 1973, pp. 1279-1281.) we were impressed by the frequency of isolation of gram-negative bacteria resistant to several useful antibiotics, including gentamicin. In some vases, almost half of the total flora consisted of organisms which could grow on media containing 50 μg/ml gentamicin. Most of these organisms were aquatic bacteria belonging to the genera Pseudomonas and Flavobacteria, often found in natural waters.

We considered the possibility that these highly resistant bacteria, which are only rarely involved in human infections, could transfer their resistance to more virulent pathogens such as Pseudomonas aeruginosa. We therefore began a series of experiments to test this hypothesis.

Antibiotic resistant bacteria from flower vases were mixed in broth and autoclaved water from flower vases with clinical strains of P. aeruginosa sensitive to gentamicin. After incubation at room temperature for periods of two to twenty four hours, it was clear that we could now recover substantial numbers of P. aeruginosa which were resistant to 25 μg/ml gentamicin.

It seemed likely that the flower bacteria had transferred this resistance to the P. aeruginosa. However, we could also recover resistant P. aeruginosa from control broth and autoclaved flower water which had been innoculated only with the recipient strain (P. aeruginosa). Thus it appeared that placing a sensitive strain of P. aeruginosa in water overnight enabled it to express resistance previously not detectable by routine isolation and transfer on more nutritious culture media.

We have since examined several freshly isolated strains of P. aeruginosa from human infections of burn wounds. The work is by no means complete, and many questions remain unanswered, but the phenomenon appears to be as follows:

Most clinical isolates contain a proportion of organisms with the potential to develop or express resistance to aminoglycoside antibiotics. This is not detectable on routine laboratory medium because the more sensitive strains, being in the majority, overgrow the resistant cells, or, that resistance is not expressed on complex media.

When the two bacterial populations in a clinical isolate were seperated by careful replicate plating techniques, an interesting observation was made. When highly sensitive cells were placed in broth or water, they were still sensitive when recovered twenty four hours later. When cells which showed some resistance to gentamicin were placed in water, they were always more resistant when recovered, e.g. a population with an MIC of 6 μg/ml gentamicin grew luxuriously on 50 μg/ml gentamicin after being in water overnight. This suggests that wet hospital reservoirs, including nembulizers, flower vases etc., may be a potential breeding ground for antibiotic resistant gram-negative bacteria.

At the recent meeting of the American Society for Microbiology (April - May 1975) during a symposium on Environmental Sources of Pseudomonas, other workers expresses the view that organisms from wet sources were usually more tolerant to high temperatures and more resistant to chemical disinfectants than those passed through routine laboratory culture media. There seem to be little doubt that hospital infections due to multiply drug resistant gram-negative bacteria are on the increase. It would seem prudent to investigate the role of environmental sources in this problem, since many of the sources can be eliminated or modified to reduce hazards.

Favero et al, (Science, 173:836 - 838, 1971.) have shown that P. aeruginosa can increase from 100, to 1 $\overline{\text{x } 10^7}$ cells, in distilled water, and be viable for forty two days.

We plan to continue our studies to determine the factors responsible for the expression of resistance in aqueous fluids, and to further explore the possibility of resistance transfer in environmental reservoirs.

This report includes data from clinical trials on new topical antifungal agents for the treatment of dermatophytosis and candidasis.

These studies are reported completely because we believe the results will be of value to in-service investigators interested in new topical agents of potential military value, and to enable them to more effectively plan future comparative trials of the newer agents.

These findings should not be considered an endorsement of any product or manufacturer by the investigators, nor by the University of Miami.

Nystatin/Tolnaftate Cream for the Treatment of Groin Dermatitis

Tucupita, Venezuela 1974

Department of Dermatology & Epidemiology & Public Health
University of Miami, School of Medicine

Investigational Team

David Taplin: Project Chief and Photography

William Eaglstein, M.D.: Clinical Director

Julia Ellis, M.D.: Research Fellow

Patricia M. Mertz: Laboratory Studies

Greg Crawford: Medical Student monitor

Bruce Murray: Medical Student monitor

During this contract year we conducted another clinical trial in collaboration with the pharmaceutical industry, the Food and Drug Administration and the School of Agronomy, Tucupita, Venezuela.

Tolnaftate and nystatin have been the most common forms of topical therapy in the military for dermatophytosis and candidiasis respectively. Unfortunately, the physician is not always able to make an accurate diagnosis, resulting in failure to respond to therapy, with the subsequent waste of money and manpower, to say nothing of the disgruntled patient.

In addition, the two diseases may co-exist, and require two forms of therapy. We, therefore, enlisted the aid of a major pharmaceutical company in formulating a cream containing nystatin and tolnaftate, and initiated a study in a boys school of Agronomy in Venezuela, where we had previously noted a high prevalence of groin dermatoses. In this study, the boys were required to report to the dispensary twice per day, where our own monitors issued numbered tubes of cream and observed the use of the medication.

Because the F.D.A. did not require further proof of efficacy of either tolnaftate or nystatin, but only that we prove the two agents to be compatible and as effective as the single agents alone when used for the appropriate disease, no placebo vehicle was included.

Eleven individuals received no therapy at all, and therefore, served as something of a control in respect to longevity of the disease in relation to climate, etc.

Criteria for entry into this study were positive KOH and/or gram stain for fungi and/or yeasts with clear cut evidence of clinical infection in the groin. Medication was applied twice per day for two weeks under close supervision. Eighty-three cases were found who fulfilled the criteria for entry into the study.

There were three drop outs for reasons not related to the study, leaving eighty subjects for final evaluation.

After the study was completed and the code broken, the distribution of the creams were as follows:

Tolnaftate cream	26 boys
Nystatin cream	27 boys
Tolnaftate/nystatin cream	27 boys

Table 1 shows the analysis of variables to determine baseline comparability between the groups.

Table II shows the results of clinical responses and laboratory data in 66 cases of dermatophytosis. Essentially all three creams worked as well in this study.

After two weeks of treatment, 80% or more of the cases were either cleared or markedly improved. Other scoring systems were used, including numerical assessments of scaling, erythema, vesicles, denudation, fissures, pustules, etc., and matched clinical photographs were evaluated and scored. Regardless of the system, all creams appeared to work equally well.

What was of even greater interest to us was the fact that six of the eighty cases suffered adverse reactions to the creams and described in Table III.

When the adverse reactions occurred after one week of treatment, we immediately sent a telegram to the manufacturers for relay to the F.D.A. The company prepared a set of patch testing agents for all ingredients in the creams, and on return to Miami, Taplin and Dr. Julia Ellis returned to Venezuela to perform patch tests. Forty-eight hours later it was clear to us that the offending agents were the preservatives in the creams, with thimerosal being the most common and severe.

The second point of scientific interest from this study suggested that nystatin in this particular cream formulation was effective against dermatophytosis. This is perhaps not surprising in view of the in vitro activity. Nystatin, like other polyene antibiotics is fungicidal to the dermatophytes in the test tube, in addition to its activity against Candida albicans. The historical development of nystatin has led to its use exclusively for candidiasis, but we could find in the literature no double blind trials of nystatin topical preparations used for dermatophytosis.

Another explanation is that some other ingredient in the cream was responsible for the clinical cures, perhaps the thimerosal itself, which also has good antifungal activity in the test tube. This could not be determined under the conditions of this trial because no placebo vehicle group was included, since none was required by the F.D.A. We do not intend to miss this opportunity to study vehicle effects in future trials; another obvious lesson re-affirmed.

There was no question in our minds that this product resulted in rapid and dramatic cures of most cases of dermatophytosis, but a 5% reaction rate is far too high to be considered an acceptable agent for the treatment of dermatophytosis or candidiasis.

The study again demonstrated the value of conducting trials in a closed population with a high prevalence of disease. We were able to find 150 cases of moderate to severe groin dermatitis in a school of 380 boys, and 83 fulfilled the F.D.A.'s requirements for laboratory diagnosis. Moreover, within two weeks we had established that adverse reactions could be expected in at least 5% of the subjects. Subsequent trials in other institutions required a year to complete, and confirmed that reactions occurred in 5-8% of subjects.

The excellent cooperation we receive from the health authorities in Venezuela, and the enthusiasm with which the boys took part in the studies is also an important aspect. In addition to curing many of the cases of troublesome groin dermatitis in the school, we were able to identify individuals who were previously sensitized to thimerosal, probably as a result of the merthiolate solution used on all cuts and abrasion at the dispensary.

Professor David Taplin, Dr. William Eaglstein, Patricia Mertz, Bruce Murray, and Greg Crawford conducted this study in a young man's school in South America. Nearly all patients were empaneled and treated during the same two-week period in July 1974. From this study 83 case reports were completed, of these, three were excluded from the analysis because of protocol deviations as follows (Table 1):

Table 1

Tinactin/nystatin cream study in groin dermatosis
Analysis of variables to determine baseline comparability

	Tolnaftate/ Nystatin (N=27)		Tolnaftate (n=26)		Nystatin (n=27)		Significance
	Freq	%	Freq	%	Freq	%	P-Value
Primary Dx							
Dermatophytosis	21	77.7	23	88.5	24	88.9	
Candidiasis	0	0	1	3.8	0	0.0	
Mixed	6	22.4	2	7.7	3	11.1	P > 0.10
Total Duration							
1/2 - 1 month	9	33.3	5	19.2	2	7.4	
1-2 months	2	7.4	5	19.2	6	22.2	
2-6 months	11	40.7	10	38.5	14	51.9	
6-12 months	1	3.7	1	3.8	3	11.1	
1-5 years	4	14.8	5	19.2	2	7.4	P > 0.10
Disease Status[1]							
Worsening	18	66.7	19	73.1	16	61.5	
Stable	9	33.3	7	26.9	10	38.5	
Improving	0	0.0	0	0.0	0	0.0	P > 0.10
Duration of Disease Status							
1 week	2	7.4	2	7.7	3	11.1	
2 weeks	2	7.4	1	3.8	0	0.0	
3-4 weeks	6	22.2	3	11.5	1	3.7	
1-2 months	5	18.5	8	30.8	10	37.0	
2 plus months	12	44.4	12	46.2	13	48.1	P > 0.10
Anti-fungal Rx Used							
No	27	100.0	26	100.0	27	100.0	
Yes	0	0.0	0	0.0	0	0.0	P = 1.00
Concomitant Medication							
No	27	100.0	26	100.0	27	100.0	
Yes	0	0.0	0	0.0	0	0.0	P = 1.00

1. The disease status of one Tolnaftate patient was not rated.

Table II

Tolnaftate/nystatin Cream Study in Groin Dermatosis
Primary Diagnosis = Dermatophytosis
Analysis of Clinical Efficacy and Mycological Response

	No.	%	No.	%	No.	%
Clinical Efficacy (Final Visit)						
Cleared	14	70	19	86	17	71
Marked Improvement	2	10	0	0	3	13
Improved	2	10	3	14	1	4
No Change	0	0	0	0	1	4
Worse	2	10	0	0	2	8
TOTAL[1]	20	100	22	100	24	100
		Not Significant: P 0.10				
Mycological Response[2] (Final Visit)						
Neg. Lab. & no Symptoms	14	70	18	82	17	71
Neg. Lab. & Symp.	5	25	3	14	4	17
Pos. Lab. & No. Symp.	0	0	1	4	1	4
Pos. Lab. & Symp.	1	5	0	0	2	8
TOTAL[1]	20	100	22	100	24	100
		Not Significant: P 0.10				

1. One Tolnaftate/nystatin patient and one Tolnaftate patient were dropouts at visit 3 and thus are not included in total patient counts for this table.
2. Neg. lab. includes neg. KOH, gram stain, and culture; if any one of these three is pos., then the lab result is positive.

Table III

Adverse Effects

Patient number and treatment	Nature of Effect	Skin Patch Test Result*
24 (tolnaftate)	Inguinal fissure and tenderness	Positive for parabens**
37 (nystatin)	Site redness and burning	Negative
67 (tolnaftate/ nystatin)	Site redness, vesicles, burning, weeping, and pustules	Positive for thimerosal
70 (nystatin)	Site redness, vesicles, and weeping	Positive for thimerosal
73 (tolnaftate/ nystatin)	Site redness and vesicles called allergic contact dermatitis	Positive for thimerosal
81 (nystatin)	Inguinal fissure and pain	Negative

*Standard patch test technique was used. Each formulation and each individual ingredient in petroleum was used in each patient. Petroleum was used as a negative control and the parabens were the only ingredients tested at a concentration (15%) higher than that in the formulation. These tests were done about one month after treatment (study) was completed.

**This patch test was negative at the concentration used in the formulation, but was positive with the 15% concentration.

[redacted] CLOTRIMAZOLE STUDY

Treatment of Tinea Corporis/Cruris with
Clotrimazole (Bay 5097) 1% Solution

Report on a study done by Taplin, Eaglstein,
Mertz, Bamford, Radimer, and Walther

DETAILED DESIGN OF THE STUDY

The investigators who participated in the multicentric study project agreed on the design prior to institution of the trials. The same protocol was used and the results were recorded on identical case report forms.

The study was of the double-blind, noncrossover type with test preparations assigned to patients at random. Patients of either sex, any race, and within an age range of 3 to 70 years, who had mycologically proven tinea corporis/cruris, were to be included in the study. A fungal infection was considered proven if scrapings from skin lesions were found positive in KOH mount and/or culture.

The patients were to apply the assigned test solution twice a day for 28 days. No other topical or systemic anti-infectious or anti-inflammatory therapy was to be used during this study. All previous anti-infectious therapy was to be discontinued at least two weeks prior to the institution of the test therapy.

At intervals of no more than two weeks during the study, patients were to be examined and evaluated clinically, and scrapings from lesions were to be taken for KOH mount and for culture. It was stipulated that specimens for dermatophytes would be plated on Mycosel Agar (BBL), Taplin's Dermatophyte Test Medium (Schering Diagnostics), or comparable media. The findings were recorded on the case report forms supplied to the investigators.

The data accrued from the study were tabulated and analyzed statistically.

CONTROL AGENT

Vehicle (polyehtylene glycol 400).

DRUG CODES [redacted]

The two test preparations were:

1) a 1% solution of clotrimazole, and

2) its vehicle, polyethylene glycol 400.

DESIGN FOR SELECTION OF CONTROL AND DRUG GROUPS

The test preparations were assigned at random according to a predetermined code, which was unknown to the patient and the investigator. The randomization schedule was generated in blocks of size 6 utilizing random numbers obtained from the Rand Corporation Tables entitled "A Million Random Digits with 100,000 Normal Deviates", The Free Press, 1966.

It was hoped that by entry of the patients at random into the study, the distribution in the drug-treated and the vehicle-treated groups would be comparable. To ascertain this, the following epidemiological parameters were analyzed: sex and age, duration of disease, stage of disease, and severity of clinical signs and symptoms.

PRIMARY AND SECONDARY DIAGNOSES, INCLUDING SEVERITY AND STAGE OF DISEASE, OF PATIENTS IN DRUG AND CONTROL GROUPS WITH NUMBERS, SEX AND AGE DISTRIBUTION

A total of 41 case reports were received from these investigators. They were all reviewed for evidence of adverse effects; however, 11 were excluded from the evaluation of efficacy because the patients had received treatment for a longer period of time than stipulated in the protocol or because they had been lost to follow-up.

The remaining 30 patients (15 treated with the drug and 15 treated with the vehicle), all being mycologically proven cases of tinea corporis/cruris, are enumerated. Noted for each patient are his or her number, test preparation and frequency of application, age, sex, weight and height, diagnosis, duration of the disease, length of treatment, overall results with mycological findings at each visit, and side effects.

All patients listed received treatment for no less than three and no more than four weeks, unless they were declared treatment failures by the investigators and, for that reason, treatment was discontinued earlier, as provided for by the protocol.

Comparability of Treatment Groups

The epidemiological parameters listed previously were tabulated by treatment group, as shown in Tables 1-3:

Table 1

Distribution of Patients Between Treatment Groups by Age and Sex

	BAY 5097	Vehicle	
Range of age (yr)	8-70	15-92	p = 0.435*
Median age (yr)	25.0	27.0	
Number males	12	8	p = 0.246
Number females	3	7	

*Unless otherwise specified, the p-values noted in the tables were derived from a comparison of the drug-treated group with the vehicle-treated group.

Table 2

Distribution of Patients by Treatment Groups vs. Duration of Disease

	0 - 1 mo.	>1 - <2 mo.	>2 - <6 mo.	>6 mo. - <1 yr.	>1 yr. - <5 yr.	over 5 yr.	
BAY 5097	7	3	1	2	2	0	p > 0.20
Vehicle	7	1	1	1	3	2	
TOTAL	14	4	2	3	5	2	

Table 3

Distribution of Patients by Treatment Group vs. Stage of Disease and Initial Severity of Clinical Signs and Symptoms

	Stage of Disease						Init. Severity of Clin. Signs & Symptoms				
	Exacerbating			Improving							
	RAPIDLY	SLOWLY	STABLE	SLOWLY	RAPIDLY	NOT SPEC	NONE	MILD	MODERATE	SEVERE	NOT SPEC
BAY 5097	5	6	3	1	0	0	0	0	5	9	1
Vehicle	4	6	1	3	1	0	0	2	7	6	0
TOTAL	9	12	4	4	1	0	0	2	12	15	1
	$p > 0.20$						$p > 0.20$				

The analysis showed that there were no significant differences between the groups in any of these parameters at the type 1 error significance level, $p = 0.10$; thus, the patients group treated with 1% clotrimazole in poluethylene glycol and the patient group treated with polyethylene glycol, 30 subjects in all, were considered comparable for the key variables at entry into the study, and with regard to adherence to the protocol, comparable throughout the study. The fact that one patient who received clotrimazole, reported at visit five to have applied the preparation three times a day, was considered to have interfered with the comparability of the treatments groups.

Additional diagnoses were reported for four of the 30 patients, none of them, however, having any probable bearing on the treatment under investigation. The same was true of therapy given concurrently with the investigational treatment to six of the patients.

DETAILED CRITERIA OF EFFECTIVENESS, OBJECTIVE AND SUBJECTIVE

Therapeutic effectiveness was determined on the basis of:

1) mycological findings (KOH mount and culture)
2) clinical findings (severity of clinical signs and symptoms before and after treatment)
3) investigator's assessment of treatment (taking into account mycological and clinical results).

ADVERSE EXPERIENCE LOOKED FOR BY THE PATIENT AND BY THE INVESTIGATOR

All 41 case reports from this study, including the 11 that had been nonevaluable for the assessment of efficacy, were examined for adverse reactions, particularly of the kind occurring with topical administration of a test preparation. When side effects occurred they were recorded as described by the physician and as described by the patients, separately, for each visit. A final statement made by the physician at the last visit determined the occurrence of adverse effects in the patient.

CONTROL AND DRUG PERIODS AND KIND AND NUMBER OF OBSERVATIONS MADE IN EACH

At an initial visit, prior to treatment, patients were examined and given a two-week supply of the test preparation. Follow-up visits were scheduled for two weeks, with new supply of the preparation, and for four weeks after initiation of therapy. Patients were instructed to apply the test preparation, i.e., drug solution or vehicle, twice a day for 28 days. The final examination was scheduled for two days after the end of therapy.

Clinical: Signs and symptoms were assessed before, during and after the trial by recording the degree of scaling, vesiculation, inflammation, maceration, and pruritis. Entries in the case reports were graded and formed the basis of the investigator's judgment of the overall severity of clinical signs and symptoms.

Mycological: Skin lesions were scraped for a wet mount and culture, and the causative organism was identified where possible.

ADVERSE REACTIONS AND ALL ADVERSE EXPERIENCE BY SYSTEM AND ORGAN, GENERAL AND LOCAL

In four patients, one treated with drug and three treated with vehicle, adverse reactions were reported. After two weeks of treatment, patients #24 who received the drug, and patients #39, who received the vehicle, reported a warm sensation on application of the test preparation; for the latter patient this was also mentioned by the investigator in his final evaluation. Patient #16, who received the vehicle, complained after two weeks of treatment of mild burning on application, and this was also listed by the investigator in his final evaluation. Patient #34, after four weeks of treatment with the vehicle, mentioned odor on application as a side effect.

Treatment did not have to be discontinued in any of the patients.

In no case did the sealed envelope which was provided with each medication box for the physician's convenience have to be opened. The envelopes contained, as mentioned earlier, a listing of ingredients of the accompanying medication in case a drug reaction required urgent medical attention. All envelopes were returned to the sponsor and were inventoried.

ALL RESULTS, POSITIVE, NEGATIVE, OR INCONCLUSIVE

Mycological and clinical parameters were used to determine and to compare the drug's and the vehicle's theraeputic effectiveness.

1) Myclolgical findings: The distribution of patients by treatment group vs. KOH test and culture results before treatment is shown in Table 4. All patients had mycological confirmation of the clinical diagnosis by either culture or KOH mount, and all but two had positive results in both tests.

Table 4

Distribution of patients by treatment group vs. results of mycological tests before treatment

KOH → / Culture →	Positive	
	P O S	N E G
Bay 5097	14	1
Vehicle	14	1
Total	28	2

The distribution of patients by treatment group vs. KOH test and culture results after treatment is shown in Table 5. Both KOH test and culture were done for all patients.

Table 5

Distribution of patients by treatment group vs.
results of mycological tests after treatment

	KOH Positive		KOH Negative	
	Cult. Pos.	Cult. Neg.	Cult. Pos.	Cult. Neg.
Bay 5097	0	1	1	13
Vehicle	7	0	5	3
TOTAL	7	1	6	16

Table 6 summarizes mycology results before and after treatment. Results are defined as positive when KOH test and/or culture indicated the presence of fungus, and are defined as negative when both KOH test and culture showed absence of fungus.

Table 6

Distribution of patients by mycology
results before and after treatment

	Pre-RX		Post-RX	
	Pos.	Neg.	Pos.	Neg.
Bay 5097	15	0	2	13
Vehicle	15	0	12	3
TOTAL	30	0	14	16
	$p = 1.00$		$p < 0.001$	

Statistical analysis indicated no significant differences before treatment between the drug-treated and the vehicle-treated groups. However, after treatment, highly significant differences in favor of the drug-treated groups were detected (P 0.001).

The rate of mycological conversion to negative of both KOH mount and culture was 87% for the drug-treated group, and 20% for the vehicle-treated group.

Positive cultures were identified as to type of fungus. For specific organisms isolated, the response to treatment is shown in Table 7.

Table 7

Distribution of Patients by Specific Organism Isolated vs. Mycological Response to Treatment

	Post-Rx Mycology	
	Pos.	Neg.
Bay 5097		
Negative*	1	0
T. rubrum	0	7
T. menta.	0	3
E. Floc.	0	0
Candida	0	2
M. Canis	1	0
M. Gyseium	0	1
Sub total	2	13
Vehicle		
Negative*	0	1
T. rubrum	5	1
T. menta.	0	0
E. Floc.	0	0
Candida	0	0
M. Canis	4	0
M. Gypseum	0	0
T. rubrum & Candida	0	1
T. Rub. & T. Ton.	1	0
T. menta. & E. floc.	0	0
T. menta. & M. Gyp.	1	0
T. menta. & M. canis	1	0
Sub total	12	3
TOTAL	14	16

For Trichophyton rubrum, which was the fungus detected in the largest number of patients, the rate of mycological conversion from positive to negative was 100% (all of seven patients) in the drug-treated group and 25% (two of eight patients) in the vehicle-treated group. The difference is highly significant in favor of the drug-treated group (P = 0.006).

2) Clinical Findings: The severity of clinical signs and symptoms at weekly visits throughlut the trial was one indicator of the patient's response to treatment.

Table 8

Distribution of Patients by Severity of Clinical Signs and Symptoms Before and After Treatment

Pre-Rx Severity	None	Mild	Moder-ate	Severe	Not Spec.
Bay 5097					
None	0	0	0	0	0
Mild	0	0	0	0	0
Moderate	5	0	0	0	0
Severe	5	2	1	0	1
Not Spec.	1	0	0	0	0
Sub total	11	2	1	0	1
Vehicle					
None	0	0	0	0	0
Mild	0	2	0	0	0
Moderate	1	4	2	0	0
Severe	0	2	1	3	0
Not Spec.	0	0	0	0	0
Sub total	1	8	3	3	0
TOTAL	12	10	4	3	1

P < 0.001

From the data in this table, the difference in the distribution of patients response was found to be highly significant (P 0.001) in favor of the drug-treated group.

Despite the random allocation of therapy to the patients, there was a predominance of clinically more severe cases in the drug-treated group before treatment. The difference was not statistically significant.

In the drug-treated group five of nine patients who had entered the study with severe clinical signs and symptoms were clinically cured as compared with none of six in the vehicle-treated group. For one of the patients treated with the drug, the severity after treatment was not specified. The difference between these proportions was statistically significant in favor of the drug-treated group (P = 0.042).

Also in the group with initially severe disease, three of six patients remained unchanged with vehicle-treatment, whereas none of the nine patients (one of them was not specified) remained unchanged with clotrimazole treatment. Again, there was a significant difference (P = 0.444) in favor of the drug-treated group.

Numerical values between 1 = none and 4 = severe were assigned to ratins recorded every two weeks for the severity of clinical signs and symptoms; the averages were as follows:

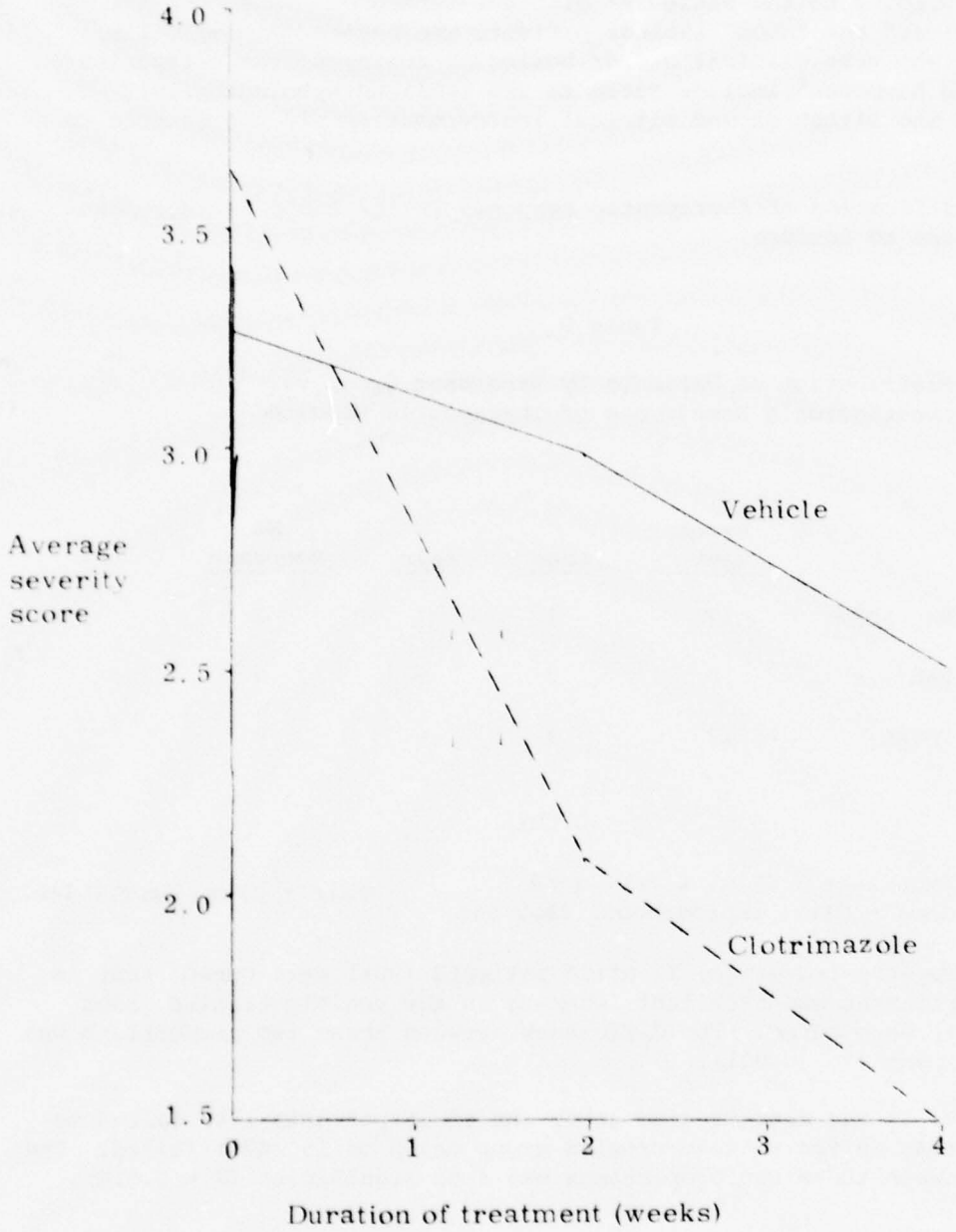
	Week		
	0	2	4
Clotrimazole	3.64	2.09	1.50
Vehicle	3.27	3.00	2.53

These values were plotted on the following graph. The two curves thus formed indicated the rate and the degree of decrease for the total severity score in each treatment group. For the purpose of this graph the treatment failures were given the severity score of their last visit for all subsequest visits which they did not attend. Visits missed for reasons other than treatment failures were not counted in the calculation of the weekly average score.

From the graph it can be seen that the drug-treated group initially had a somewhat higher average score for severity and that this group responded more rapidly and to a greater degree, compared with the vehicle-treated group.

3) Investigator's Assessment of Treatment: At the end of treatment with the test preparation, samples from all patients were examined by KOH wet mount and culture for the presence of fungus. To be considered negative,

AVERAGE SEVERITY OF CLINICAL SIGNS
AND SYMPTOMS DURING TREATMENT



scrapings from lesions had to be negative under the microscope as well as in culture.

In Table 9, drug- and vehicle-treated patients are separated into those who converted to negative and those who did not. Both groups are further subdivided according to the patients' clinical repsonse. Thus, the categories "Excellent" and "Good" include patients who became mycologically negative, and who were clinical either healed or improved; the categories "Fair" and "No Response" include patients who remained mycologically positive, and who either showed clinical improvement or did not respond to treatment.

The classification of therapeutic response in the table is therefore graded from cure to failure.

Table 9

Distribution of Patients by Treatment Group vs.
Investigator's Assessment of Therapeutic Results

	Excellent	Good	Fair	No Response
Bay 5097	12	1	1	1
Vehicle	0	3	5	7
TOTAL	12	4	6	8

$P < 0.001$

Excellent - Clin. & lab. cure
Good - Clin. improvement, lab. neg.
Fair - Clin. impr., lab. pos.

In the drug-treated grcup, 12 of 15 patients (80%) were cured, that is, response to treatment was excellent, whereas in the vehicle-treated group none of 15 (0%) were cured. The difference between these two proportions was highly significant (° 0.001).

Similarly, in the drug-treated group one of 15 patients (7%) failed to responde, whereas in the vehicle-treated group seven of 15 (47%) failed. The difference between these two proportions was also significant ($P = 0.018$).

In Tables 10-12, treatment results were plotted against the duration and the stage of the disease and against the severity of clinical signs and symptoms prior to treatment. This was in order to determine whether or not cures after clotrimazole treatment, as compared with cures after vehicle treatment, were more prevalent among patients with either less chronic or less severe infections.

Table 10

Distribution of Patients by Investigator's Assessment of Therapeutic Results vs. Duration of Disease Prior to Treatment

	Duration of Disease	
Invest. Eval.	<1 Mo.	>1 Mo.
Bay 5097		
Excellent	5	7
Good	0	1
Fair	1	0
No. Resp.	1	0
Sub total	7	8
Vehicle		
Excellent	0	0
Good	0	3
Fair	3	2
No. Resp	4	3
Sub total	7	8

In recent infections, i.e., of up to one month duration, five of seven (71%) drug-treated and none of seven (0%) vehicle-treated patients were cured. In inrfctions of more than one month duration, seven of eight (88%) drug-treated and none of eight (0%) vehicle-treated patients were cured. Clotrimazole is, compared with the vehicle, apparently of superior benefit in acute as well as in chronic cases (P = 0.01 and P 0.001, respectively).

Table 11

Distribution of Patients by Investigator's Assessment of Therapeutic Results vs. Stage of Disease Before Treatment

		Pre-Rx Stage of Disease	
	Invest. Eval.	Exacer-bating	Stable or Improving
Bay 5097	Excellent	12	0
	Good	1	0
	Fair	1	0
	No. resp.	1	0
Sub total		15	0
Vehicle	Excellent	0	0
	Good	3	0
	Fair	5	0
	No. resp.	7	0
Sub total		15	0

In all 30 evaluable patients (15 treated with drug and 15 treated with vehicle) the disease has exacerbated prior to treatment. Twelve (80%) of the drug-treated patients responded with clinical and mycological cure, whereas none (0%) of the vehicle-treated patients did. The difference in the number of patients with exacerbating disease who were cured was highly significant (P 0.001) in favor of the drug-treated group.

Table 12

Distribution of Patients by Investigator's Assessment of Therapeutic Results vs. Initial Severity of Clinical Signs and Symptoms

	Pre-Rx Severity				
Invest. Eval.	None	Mild	Moder-ate	Severe	Not Specified
Bay 5097					
Excellent	0	0	5	6	1
Good	0	0	0	1	0
Fair	0	0	0	1	0
No. resp.	0	0	0	1	0
Sub total	0	0	5	9	1
Vehicle					
Excellent	0	0	0	0	0
Good	0	0	1	2	0
Fair	0	0	4	1	0
No. resp.	0	2	2	3	0
Sub total	0	2	7	6	0

In the drug-treated group six of 11 cures (in one patients, severity was not specified) occurred in patients that had severe clinical signs and symptoms initially, as compared with no cures in the vehicle-treated group.

Expressed differently, six of nine drug-treated patients with severe clinical signs and symptoms were cured, but none of six behicle-treated patients were.

Comparison of these two proportions showed a significant difference ($P = 0.017$) in favor of the drug-treated group.

STATISTICAL ANALYSIS

Statistical evaluation of the data was carried out via a series of

noneparametric Wilcoxon Tests or Fischer's Exact Probability Tests.* The advantage of the nonparametric approach is that the assumption regarding the underlying requirements of parametric tests need not be met. The probability values tend to be more conservative, and one can be more confident about the individual probability values which are calculated.

Data from the trial conducted by Dr. Eaglstein were analyzed separately in this part of the report, but data for key parameters are also combined with results of other trials in a summary evaluation of the multicentric study project.

CONCLUSIONS

A total of 41 patients entered the trial and were evaluated for tolerance. Adverse reactions were reported for four patients, three on vehicle and one on drug. Only in two of them, both treated with the vehicle, did the investigators mention an adverse effect in their overall assessment of treatment; in none of them did the treatment have to be discontinued.

Results from 30 patients were evaluated for efficacy; 15 had been treated with drug, and 15 with vehicle.

By both clinical and mycological criteria, it is clear that 1% clotrimazole solution in polyethylene glycol is very effective as a therpeutic agent in tinea corporis/cruris and more effective than the vehicle alone. Incidence and kind of adverse reactions appear to be quite acceptable.

*Nonparametric Statistics, John E. Walsh, D. Van Nostrand & Co., 1962, Vol. 1-3.

Treatment of Tinea Versicolor with Clotrimazole (Bay 5097) 1% Solution

Report on a study by Taplin, Eaglstein, Mertz, Bamford, Radimer, and Walther

DETAILED DESIGN OF THE STUDY

The study was of the double-blind, noncrossover type with test preparations assigned to patients at random. Patients of either sex, any race, and within an age range of 3 to 70 years, who had mycologically proven tinea versicolor, were to be included in the study. A fungal infection was considered proven if scrapings from skin lesions were found positive in KOH mount and/or any other accepted microscopic procedure.

The patients were to apply the assigned test solution twice a day for 14 days. No other topical or systemic anti-infectious therapy was to be used during the study. All previous anti-infectious therapy was to be discontinued at least two weeks prior to the institution of the test therapy.

Once each week during the treatment and two weeks after the termination of treatment patients were to be examined and evaluated clinically, and scrapings from lesions were to be examined microscopically. Also at the week 4 visit, an examination under Wood's light was to be carried out. The findings were recorded on the case report forms supplied to the investigator.

The data from the study were tabulated and analyzed statistically.

CONTROL AGENT

Vehicle (polyethylene glycol 400).

DRUG CODES

The two test preparations were: 1) a 1% solution of clotrimazole and 2) its vehicle, polyethylene glycol 400.

DESIGN FOR SELECTION OF CONTROL AND DRUG GROUPS

The test preparations were assigned at random according to a predetermined code, which was unknown to the patient and the investigator. The randomization schedule was generated in blocks of size 6 utilizing random numbers obtained from the Rand Corporation Rables entitled "A Million Ransom Digits with 100,000 Normal Deviates," The Free Press, 1966.

It was hoped that by entry of the patients at random into the study, the distribution of the drug-treated and the vehicle-treated groups would be comparable. To ascertain this the following epidemiological parameters were analyzed: sex and age, duration of disease, and size of skin area involved.

PRIMARY AND SECONDARY DIAGNOSES, INCLUDING SEVERITY AND STAGE OF DISEASE, OR PATIENTS IN DRUG AND CONTROL GROUPS WITH NUMBERS, SEX, AND AGE DISTRIBUTION

A total of 36 case reports were recieved from these investigators. They were all reviewed for evidence of adverse effects; however, nine patients were excluded from the evaluation of efficacy.

The remaining 27 patients (13 treated with the drug and 14 treated with the vehicle), all being mycologically proven cases of tinea versicolor, are enumerated.

Noted for each patient are his or her number, the test preparation and frequency of application, length of treatment, age, sex, height and weight, diagnosis, duration of the disease, site of infection, skin area involved, the result of Wood's light examination, microscopic findings at each visit, side effects, patient's evaluation, physician's evaluation, and overall adverse reactions.

All patients listed recieved treatment for two weeks.

Comparability of Treatment Groups

The epidemiological parameters listed previously were tabulated by treatment group, as shown in Tables 1-3:

Table 1

Distribution of Patients between Treatment Groups by Age and Sex

	Bay 5097	Vehicle	
Range of age (yrs)	12-68	12-62	P = 0.835*
Median Age (yrs)	31	30.5	
Number of males	6	6	P = 1.00
Number of females	7	8	

Table 2

Distribution of Patients by Treatment Group vs. Duration of Disease

	Duration of Disease	
Treatment	≤6 mos.	>6 mos.
Bay 5097	2	11
Vehicle	2	12
TOTAL	4	23

P = 1.00

*Unless otherwise specified, the P-values noted in the tables were derived from a comparison of the drug-treated group with the vehicle-treated group.

Table 3

Distribution of Patients by Treatment Group vs. Size of Skin Area Involved

	Overall size of skin area in sq cm				
	≤ 10	10-50	51-200	> 200	Not Spec.
Bay 5097	1	6	5	1	0
Vehicle	3	3	7	0	1
TOTAL	4	9	12	1	1

P > 0.20

The analysis showed that there were no significant differences between the groups in any of these parameters at the type 1 error significance level, P = 0.10; thus, the patient group treated with 1% clotrimazole in polyethylene glycol and the patient group treated with polyethylene glycol, 27 subjects in all, were considered comparable for the key variables at entry into the study, and with regard to adherence to the protocol, comparable throughout the study.

An additional diagnosis was reported for four patients, with specific therapy being given concurrently with the investigative treatment for these four patients. In no case was this thought to have any probable bearing on the patient's response to antifungal therapy.

DETAILED CRITERIA OF EFFECTIVENESS, OBJECTIVE AND SUBJECTIVE

Therapeutic effectiveness was determined on the basis of:

1) mycological findings (microscopy)
2) clinical findings (presence and nature of clinical signs and symptoms before and after treatment)
3) physician's assessment of treatment (taking into account mycological and clinical results together with the result of Wood's light examination).

ADVERSE EXPERIENCES LOOKED FOR BY THE PATIENT AND BY THE INVESTIGATOR

All 36 case reports from this study, including the nine that had been nonevaluable for the assessment of efficacy, were examined for any adverse experiences, particularly of the kind occurring with topical administration of a test preparation. When side effects occurred they were recorded as described by the physician for visits at weeks 1 and 2. A final statement made by the physician at the week 4 visit determined the occurrence of adverse effects in the patient.

CONTROL AND DRUG PERIODS AND KIND AND NUMBER OF OBSERVATIONS MADE IN EACH

At an initial visit, prior to treatment, patients were examined and given a week's supply of test preparation. Follow-up visits were scheduled for day 7, with a new supply of test preparation, day 14, and day 28 after initiation of therapy. Patients were instructed to apply the test preparation, i.e., drug solution or vehicle, at bedtime for 14 days. The final examination was scheduled for two weeks after the end of therapy, i.e. day 28,

Clinical: Signs and symptoms were assessed before, during and after the trial be recording the degree of pruritus and any other sign or symptom. An examination under Wood's light was mandatory at the week 4 visit.

Mycological: Skin lesions were scraped for a microscopic examination, and the causative organism was identified.

ADVERSE REACTIONS AND ALL ADVERSE EXPERIENCE BY SYSTEM AND ORGAN, GENERAL AND LOCAL

In four patients, two treated with drug and two treated with vehicle, adverse experiences were reported. Patient #22, who received the drug and patient #36, who received the vehicle, experienced some moderate burning.

Patient #17, who received the vehicle, experienced stinging during the first week. Patient #30, who recieved the drug, experienced increased pruritus with treatment and, therefore, discontinued treatment after one week.

In no case did the sealed envelope which was provided with each medication box for the physician's convenience have to be opened. The envelopes contained, as mentioned earlier, a listing ofingredients of the accompanying medication in case a drug reaction required urgent medical attention. All envelopes were returned to the sponsor and were inventoried.

ALL RESULTS, POSITIVE, NEGATIVE, OR INCONCLUSIVE

Mycological and clinical parameters were used to determine and to compare the drug's and the vehicle's therapeutic effectiveness.

1) Mycological Findings: A KOH mount or alternative accepted microscopic examination was carried out at each visit throughout the trial.

Table 4 summarizes mycology results before and after treatment. Results are defined as positive when any microscopic test indicated the presence of fungus and are defined as negative wehn all microscopic tests showed absence of fungus.

Table 4

Distribution of Patients by Mycology
Results Before and After Treatment

	Pre-Rx		Week 4	
Treatment	Pos.	Neg.	Pos.	Neg.
Bay 5097	13	0	2	11
Vehicle	14	0	4	10
TOTAL	27	0	6	21
	P = 1.00		P = 0.362	

Statistical analysis indicated no significant differences before or after treatment between the drug-treated and the vehicle-treated groups.

The rate of mycological conversion to negative of all tests was 85% for the drug-treated group and 71% for the vehicle-treated group.

2) Clinical Findings: The nature of clinical signs and symptoms (recorded at weekly visits throughout the trial) was one indicator of the patient's response to treatment. Before treatment, 17 patients complained of pruritus, and for all of them the symptoms disappeared with treatment. Table 6 shows the response of these patients.

Table 5

Distribution of Patients by Treatment Group vs. Incidence of Pruritus

	Incidence of Pruritus			
Treatment	Pre	Week 1	Week 2	Week 4
Bay 5097	9	3	0	0
Vehicle	8	1	1	0
TOTAL	17	4	1	0

In addition, each patient assessed the overall response of the disease to treatment as shown in Table 6.

Table 6

Distribution of Patients by Treatment Group vs. Patient Evaluation

	Patient evaluation			
Treatment	Improved	Same	Worse	
Bay 5097	11	1	1	
Vehicle	12	2	0	$P > 0.10$
TOTAL	23	3	1	

In the drug-treated group, 85% of the patients considered that they were clinically improved as compared with 86% of the patients in the vehicle-treated group. The difference between these proportions was not statistically significant (P = 0.673).

3) Physician's Overall Evaluation: The overall therapeutic response, as judged by the investigator, was graded from "success" to "failure" according to the following scheme:

success: Mycologically negative and no fluorescence under Wood's light

improvement: mycologically negative, but some fluorescence

failure: mycologically still positive.

Table 7

Distribution of Patients by Treatment Group vs. Physician's Evaluation of Response to Treatment

Treatment	Success	Improved	Failure	No. Eval.
Bay 5097	11	0	2	0
Vehicle	9	1	4	0
TOTAL	20	1	6	0

P > 0.10

In the drug-treated group, 11 of 13 patients (85%) were successfully cured, whereas in the vehicle-treated group, nine of 14 (64%) were cured. The difference between these two proportions was not significant (P = 0.224).

Similarly, in the drug-treated group, two of 13 patients (15%) failed to respond, whereas in the vehicle-treated group four of 12 (29%) failed. Again, the difference between these two proportions was not significant (P = 0.155).

STATISTICAL ANALYSIS

Statistical evaluation of the data was carried our via a series of nonparametric Wilcoxon Tests or Fischer's Exact Probability Tests.* The advantage of the nonparametric approach is that the assumption regarding the underlying requirements of parametric tetst need not be met. The probability values tend to be more conservative, and one can be more confident about theindividual probability values which are calculated.

CONCLUSIONS

A total of 36 patients entered the trial and were evaluated for tolerance. Adverse reactions were reported for four patients, two treated with vehicle and two treated with drug. Only in one of them, treated with clotrimazole, was the treatment discontinued.

Results from 27 patients were evaluated for efficacy; 13 had been treated with drug, and 14 with vehicle.

By both clinical and mycological criteria, it is clear that 1% clotrimazole solution in polyethylene glycol is very effective as a therapeutic agent in tinea versicolor, and that it is numerically more effective than the polyethylene glycol vehicle, although the sample size in this study was such that this difference was not statistically significant. The mycological cure rate after treatment with clotrimzaole 1% solution was 85%, and the incidence and kind of adverse reactions appears to be quite acceptable.

*Nonparametric Statistics, John E. Walsh, D. Van Nostrand & Co., 1962, Vol. 1-3.

TREATMENT OF TINEA PEDIS, INTERDIGITAL AND INSTEP VESICULAR TYPE, WITH CLOTRIMAZOLE (BAY 5097) 1% SOLUTION

Report on a multicentric stucy by Taplin,
Eaglstein, Mertz, Bamford, Radimer, and Walther

DETAILED DESIGN OF THE STUDY

The investigators who participated in the multicentric study project agreed on the design prior to institution of the trials. The same protocol was used and the results were recorded on identical case report forms.

The study was of the double-blind, noncrossover type with test preparations assigned to patients at random. Patients of either sex, any race, and within an age range of 3 to 70 hears, who had mycologically proven tinea pedis of the interdigital and/or instep vesicular type, were to be included in the study. A fungal infection was considered proven if scrapings from skin lesions were found positive in KOH mount and/or culture.

The patients were to apply the assigned test preparation twice a day for 28 days. No other topical or systemic anti-infectious or anti-inflammatory therapy was to be used during this study. All previous anti-infectious therapy was to be discontinued at least two weeks prior to the institution of the test therapy.

At intervals of no more than two weeks during the study, patients were to be examined and evaluated clinically, and scrapings from lesions were to be taken for KOH mount and for culture. It was stipulated that psecimens for dermatophytes would be plated on Mycosel Agar (BBL), Taplin's Dermatophyte Test Medium (Schering Diagnostics), or comparable media. The findings were recorded on the case report forms supplied to the investigators. The data accrued from the study were tabulated and analyzed statistically.

CONTROL AGENT

Vehicle (polyethylene glycol 400)

DRUG CODES

The two test preparations were:

1) a 1% solution of clotrimazole and
2) its vehicle, polyethylene glycol 400.

DESIGN FOR SELECTION OF CONTROL AND DRUG GROUPS

The test preparations were assigned at random according to a predetermined code, which was unknown to the patient and the investigator. The randomization schedule was generated in blocks of size 6 utilizing random numbers obtained from the Rand Corporation Tables entitled "A Million Ransom Digits with 100,000 Normal Deviates," The Free Press, 1966.

It was hoped that by entry of the patients at random into the study, the distribution in the drug-treated and the vehicle-treated groups would be comparable. To ascertain this the following epidemiological parameters were analyzed: sex and age, duration of disease, stage of disease, and severity of clinical signs and symptoms.

PRIMARY AND SECONDARY DIAGNOSES, INCLUDING SEVERITY AND STAGE OF DISEASE, OF PATIENTS IN DRUG AND CONTROL GROUPS WITH NUMBERS, SEX, AND AGE DISTRIBUTION

A total of 30 case reports were recieved from these investigators. They were all reviewed for evidence of adverse effects; however, seven were excluded from the evaluation of efficacy because thepatients had recieved treatment for periods of time longer than stipulated in the protocol.

The remaining 23 patients (11 treated with the drug and 12 treated with the vehicle), all being mycologically proven cases of the interdigital and/or the instep vesicular type of tinea pedis, are enumerated. Noted for each patient are his or her number, test preparation and freuqency of application, age, sex, weight and height, diagnosis, duration of the disease, length of treatment, overall results with mycological findings at each visit, and side effects.

All patients listed received treatment for no less than three and no more than four weeks, unless they were declared treatment failures by the investigator and, for that reason, treatment was discontinued earlier, as provided for by the protocol.

Comparability of Treatment Groups

The epidemiological parameters listed above were tabulated by treatment group, as shown in Tables 1-3:

Table 1

Distribution of Patients between Treatment Groups by Age and Sex

	Bay 5097	Vehicle	
Range of age (yrs)	21-53	16-73	P = 0.553*
Median age (yrs)	33.0	31.0	
Number of males	6	11	P = 0.069
Number of females	5	1	

Table 2

Distribution of Patients by Treatment Group vs. Duration of Disease

	0 - 1 mo.	>1 - <2 mo.	>2 - <6 mo.	>6 - <1 yr.	>1 - <5 yr.	over 5 yr.	
Bay 5097	3	0	0	0	2	6	
Vehicle	0	0	1	0	2	9	P > 0.20
TOTAL	3	0	1	0	4	15	

*Unless otherwise specified, the P-values noted in the tables were derived from a comparison of the drug-treated group with the vehicle-treated group.

Table 3

Distribution of Patients by Treatment Group vs. Stage of Disease and Initial Severity of Clinical Signs and Symptoms

	Stage of Disease					Initial severity of Clin. Signs & Symptoms			
	Exacerbating			Improving					
	RAPIDLY	SLOWLY	STABLE	SLOWLY	RAPIDLY	NONE	MILD	MODERATE	SEVERE
Bay 5097	2	5	3	1	0	0	1	7	3
Vehicle	2	1	8	1	0	0	4	6	2
TOTAL	4	6	11	2	0	0	5	13	5
	P > 0.20					P > 0.20			

The analysis showed that there were no significant differences between the groups at the type 1 error significance level, P = 0.10, except for the distribution of sex (Table 1); in this parameter, the difference was significant at the 10% level, but not at the 5% level. This was not considered relevant in the assessment of response to therapy. Therefore, the patient group treated with 1% clotrimazole in polyethylene glycol and the patient group treated with polyethylene glycol, 23 patients in all, were considered comparable for the key variables at entry into the study and, with regard to adherence to the protocol, comparable throughout the study.

Additional diagnoses were reported for five of the 23 patients, none of them, however, having any probable bearing on the treatment under investigation. The same was true of therapy given concurrently with the investigational treatment to three of the patients.

DETAILED CRITERIA OF EFFECTIVENESS, OBJECTIVE AND SUBJECTIVE

Therapeutic effectiveness was determined on the basis of:

1) mycological findings (KOH mount and culture)
2) clinical findings (severity of clinical signs and symptoms before and after treatment)
3) investigator's assessment of treatment (taking into account mycological and clinical results)

ADVERSE EXPERIENCES LOOKED FOR BY THE PATIENT AND BY THE INVESTIGATOR

All 30 case report forms from this trial, including the seven that had been nonevaluable for the assessment of efficacy, were examined for adverse reactions, particularly of the kind occurring with topical administration of a test preparation. When side effects occurred they were recorded as described by the patient, separately, for each visit. A final statement made by the physician at the last visit determined the occurrence of adverse effects in the patient.

CONTROL AND DRUG PERIODS AND KIND AND NUMBER OF OBSERVATIONS MADE IN EACH

At an initial visit, prior to treatment, patients were examined and given a two-week supply of the test preparation. Follow-up visits were scheduled for two weeks, with new supply of the test preparation, and four weeks after initiation of therapy. Patients were instructed to apply the test preparation, i.e., drug solution or vehicle, twice a day for 28 days. The final examination was scheduled for two days after the end of therapy.

Clinical and mycological findings at the initial visit and at each subsequent visit were noted.

Clinical: Signs and symptoms were assessed before, during and after the trial by recording the degree of scaling, vesiculation, inflammation, erythema, edema, fissures, exudation, maceration, and pruritus. Entries in the case reports were graded and formed the basis of the investigator's judgment of the overall severity of clinical signs and symptoms.

Mycological: Skin lesions were scraped for a wet mount and culture, and the causative organism was identified where possible.

ADVERSE REACTIONS AND ALL ADVERSE EXPERIENCE BY SYSTEM AND ORGAN, GENERAL AND LOCAL

There were no adverse reactions, except for burning or a warm sensation on application, reported by five patients who received the drug.

Treatment did not have to be discontinued for an adverse reaction in any of the patients.

In no case did the sealed envelope which was provided with each medication box for the physician's convenience have to be opened. The envelopes contained, as mentioned earlier, a listing of ingredients of the accompanying medication in case a drug reaction required urgent medical attention. All envelopes were returned to the sponsor and were inventoried.

ALL RESULTS, POSITIVE, NEGATIVE, OR INCONCLUSIVE

Mycological and clinical parameters were used to determine and to compare the drug's and the vehicle's therapeutic effectiveness.

1) Mycological Findings: The distribution of patients by treatment group vs. KOH test and culture results before treatment is shown in Table 4. All patients had mycological confirmation of the clinical diagnosis by either culture or KOH mount, and all but four had positive results in both tests.

Table 4

Distribution of Patients by Treatment Group vs.
Results of Mycological Tests Before Treatment

Pre-Rx

	KOH Positive	
	Cult. Pos.	Cult. Neg.
Bay 5097	10	1
Vehicle	9	3
TOTAL	19	4

The distribution of patients by treatment group vs. KOH test and culture results after treatment is shown in Table 5. Both KOH test and culture were done for all patients.

Table 5

Distribution of Patients by Treatment Group vs.
Results of Mycological Tests After Treatment

	Post-Rx			
	KOH Positive		KOH Negative	
	Cult. Pos.	Cult. Neg.	Cult. Pos.	Cult. Neg.
Bay 5097	0	2	0	9
Vehicle	4	1	3	4
TOTAL	4	3	3	13

Table 6 summarizes mycology results before and after treatment. Results are defined as positive when KOH test and/or culture indicated the presence of fungus, and are defined as negative when both KOH test and culture showed absence of fungus.

Table 6

Distribution of Patients by Mycology
Results Before and After Treatment

	Pre-Rx		Post-Rx	
	Pos.	Neg.	Pos.	Neg.
Bay 5097	11	0	2	9
Vehicle	12	0	8	4
TOTAL	23	0	10	13
	P = 1.00		P = 0.026	

Statistical analysis indicated no significant difference before treatment between the groups. However, after treatment a significant difference was detected (P = 0.026) in favor of the drug-treated group.

The rate of mycological conversion to negative of both KOH mount and culture was 82% for the drug-treated group, and 33% for the vehicle-treated group.

Positive cultures were identified as to type of fungus. For specific organisms isolated, the response to treatment is shown in Table 7.

Table 7

Distribution of Patients by Specific Organism Isolated vs. Mycological Response to Treatment

	Pos.	Neg.
Bay 5097		
Negative*	0	1
T. rubrum	0	2
T. menta.	1	3
E. floc.	1	1
Candida	0	1
Dermatophyte**	0	1
Sub total	2	9
Vehicle		
Negative*	0	2
T. rubrum	4	0
T. menta.	2	1
Candida	1	1
T. rubrum & T. menta.	1	0
Sub total	8	4
TOTAL	10	13

*These patients had negative cultures throughout, but positive KOH tests before treatment.

**Not further identified.

The overall rate of conversion to negative was 80% in the drug-treated group (eight of ten organisms isolated), and 27% in the vehicle-treated group (three of 11 organisms isolated); instances of negative cultures were not counted in both groups. The difference was significant in favor of the drug-treated group (P = 0.023).

The number of separate species of organisms isolated from the patients was too small to permit infividual evaluation.

2) Clinical Findings: The severity of clinical signs and symptoms at weekly visits throughout the trial was one indicator of the patient's response to treatment.

Table 8

Distribution of Patients by Severity of Clinical Signs and Symptoms Before and After Treatment

Pre-Rx Severity	None	Mild	Moderate	Severe	
Bay 5097					
None	0	0	0	0	
Mild	0	1	0	0	
Moderate	0	6	1	0	
Severe	1	2	0	0	
Not Spec.	0	0	0	0	
Sub total	1	9	1	0	P > 0.20
Vehicle					
None	0	9	0	0	
Mild	1	3	0	0	
Moderate	2	2	2	0	
Severe	0	0	1	1	
Not spec.	0	0	0	0	
Sub total	3	5	3	1	
TOTAL	4	14	4	1	

P > 0.10

Distribution of severity scores did not show statistically significant differences between the two treatment groups before treatment (P 0.20). With therapy, nine of 11 drug-treated patients improved clinically, as against six of 12 vehicle-treated patients. However, the patient sample was not large enough to detect a statistically significant difference either in these two proportions or in the total distribution of clinical severity scores in both groups after treatment.

Numerical values between "1 = none" and "4 = severe" were assigned to ratings recorded every two weeks for the severity of clinical signs and symptoms; the averages were as follows:

	Week		
	0	2	4
Clotrimazole	3.18	2.63	1.90
Vehicle	2.83	2.20	2.27

These values were plotted on the following graph. The two curves thus formed indicate the rate and the degree of decrease for the total severity score in each treatment group. For the purpose of this graph, the treatment failures were given the severity score of their last visit for all subsequent visits which they did not attend. Visits missed for reasons other than treatment failures were not counted in the calculation of the weekly average score.

From the graph it can be seen that the drug-treated group initially had a somewhat higher average score for clinical severity but showed a lower average score after treatment.

3) Investigator's Assessment of Treatment: At the end of treatment with the test preparation, samples from all patients were examined by KOH wet mount and culture for the presence of fungus. To be considered negative, scrapings from lesions had to be negative under the microscope as well as in culture.

In Table 9, drug- and vehicle-treated patients are separated into those who converted to negative and those who did not. Both groups are further subdivided according to the patients' clinical response. Thus, the categories "Excellent" and "Good" include patients who became mycologically negative, and who were clinically either healed or improved; the categories "Fair" and "No Response" include patients who remained mycologically positive, and who either showed clinical improvement or did not respond to treatment.

The classification of therapeutic response in the table is therefore graded from cure to failure.

AVERAGE SEVERITY OF CLINICAL SIGNS
AND SYMPTOMS DURING TREATMENT

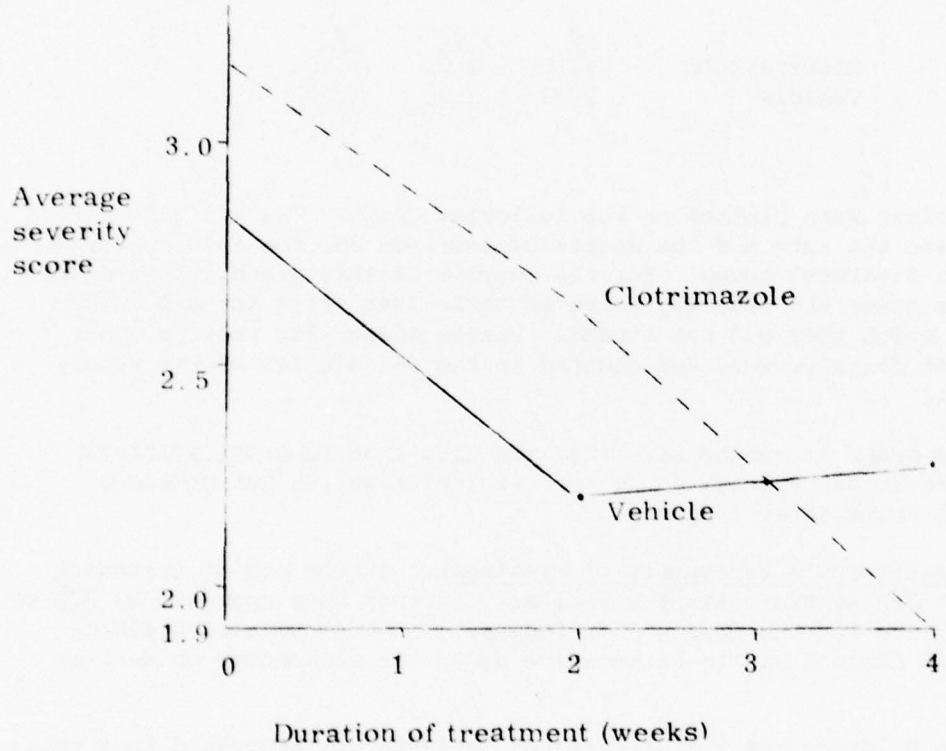


Table 9

Distribution of Patients by Treatment Group vs.
Investigator's Assessment of Therapeutic Reuslts

	Excel-lent	Good	Fair	No Response
Bay 5097	1	8	2	0
Vehicle	2	2	4	4
TOTAL	3	10	6	4

P = 0.045

Excellent = Clin. & lab cure
Good - Clin. impr., lab. neg.
Fair - Clin. impr., lab pos.

A comparison of therapeutic response, as graded in the table, showed a significant difference in favor of the drug-treated group (P = 0.045). In order to determine that the higher success rate following clotrimazole therapy, as compared with vehicle therapy, was not obtained in an inordinately large number of patients with either less chronic or less severe infection. The results of this multicentric study were evaluated collectively.

STATISTICAL ANALYSIS

Statistical evaluation of the data was carried out via a series of nonparametric Wilcoxon Tests or Fischer's Exact Probability Tests.* The advantage of the nonparametric approach is that the assumption regarding the underlying requirements of parametric tests need not be met. The probability values tend to be more conservative, and one can be more confident about the individual probability values which are calculated.

*Nonparametric Statistics, John E. Walsh, D. Van Nostrand & Co., 1962, Vol. 1-3.

CONCLUSIONS

A total of 30 patients entered the trial and were evaluated for tolerance. Adverse reactions, of a minor nature, were reproted for five patients who had all been treated with drug. In none of them did the treatment have to be discontinued.

Reuslts from 23 patients were evaluated for efficacy; 11 had been treated with the active drug, and 12 with the vehicle.

By both clinical and mycological criteria, it is clear that 1% clotrimazole solution in polyethylene glycol is very effective as a therapeutic agent in the interdigital and/or instep vesicular type of tinea pedis, and more effective than the vehicle alone. Incidence and kind of adverse reactions appear to be quite acceptable.

Treatment of Tinea Pedis, Plantar Hyperkeratotic, Nonvesicular Type, with Clotrimazole (Bay 5097) 1% Solution

Report on a multicentric study project by
Taplin, Eaglstein, Mertz, Bamford, Radimer, and Walther

DETAILED DESIGN OF THE STUDY

The investigators who participated in the multicentric study project agreed on the design prior to institution of the trials. The same protocol was used and the reuslts were recorded on identical case report forms.

The study was of the double-blind, noncrossover type with test preparations assigned to patients at random. Patients of either sex, any race, and within an age range of 3 to 70 years, who had mycologically proven tinea pedis of the plantar hyperkeratotic, nonvesicular type, were to be included in the study. A fungal infection was considered proven if scrapings from skin lesions were found positive in KOH mount and/or culture.

The patients were to ayply the assigned test preparation twice a day for 42 days. No other topical or systemic anti-infectious or anti-inflammatory therapy was to be used during the study. All previous anti-infectious therapy was to be discontinued at least two weeks prior to the institution of the test therapy.

At intervals of no more than two weeks during the study, patients were to be examined and evaluated clinically, and scrapings from lesions were to be taken for KOH mount and for culture. It was stipulated that specimens for dermatophytes would be plated on Mycosel Agar (BBL), Taplin's Dermatophyte Medium (Schering Diagnostics), or comparable media. The findings were recorded on the case report forms supplied to the investigators. The data accrued from the study were tabulated and analyzed statistically.

CONTROL AGENT

Vehicle (Polyethylene glycol 400).

DRUG CODES

The two test preparations were:

1) a 1% solution of clotrimazole and
2) its vehicle, polyethylene glycol 400.

DESIGN FOR SELECTION OF CONTROL AND DRUG CODES

The test preparations were assigned at random according to a predetermined code, which was unknown to the patient and the investigator. The randomization schedule was generated in blocks of size 6 utilizing random numbers obtained from the Rand Corporation Tables entitled "A Million Random Digits with 100,000 Normal Deviates," The Free Press, 1966.

It was hoped that by entry of the patients at random into the study, the distribution in the drug-treated and the vehicle-treated groups would be comparable. To ascertain this the following epidemiological parameters were analyzed: sex and age, duration of disease, stage of disease, and severity of clinical signs and symptoms.

PRIMARY AND SECONDARY DIAGNOSES, INCLUDING SEVERITY AND STAGE OF DISEASE, OF PATIENTS IN DRUG AND CONTROL GROUPS WITH NUMBERS, SEX, AND AGE DISTRIBUTION

A total of 30 case reports were received from these investigators. They were all reviewed for evidence of adverse effects; however, four were excluded from the evaluation of efficacy.

The remaining 26 patients (14 treated with the drug and 12 treated with the vehicle), all being mycologically proven cases of the plantar hyperkeratotic type of tinea pedis, are enumerated. Noted for each patient are his or her number, test preparation and frequency of application, age, sex, weight and height, diagnosis, duration of the disease, length of treatment, overall results with mycological findings at each visit, and side effects.

All patients listed recieved treatment generally for six weeks, but for no more than eight weeks, and no less than four weeks, unless they were declared treatment failures by the investigator and, for that reason, treatment was discontinued earlier, as provided for by the protocol.

Comparability of Treatment Groups

The epidemiological parameters listed above were tabulated by treatment group, as shown in Tablew 1-3.

Table 1

Distribution of Patients between Treatment Groups by Age and Sex

	Bay 5097	Vehicle	
Range of Age (yrs)	15 - 66	20 - 62	P = 0.932*
Median Age (yrs)	36.5	33.0	
Number of males	11	7	P = 0.401
Number of females	3	5	

Table 2

Distribution of Patients by Treatment Group vs. Duration of Disease

	0 - 1 mo.	>1 - <2 mo.	>2 - <6 mo.	>6 - <1 yr.	>1 - <5 yr.	over 5 yr.
Bay 5097	1	0	2	1	4	6
Vehicle	1	0	0	3	0	8
TOTAL	2	0	2	4	4	14

P > 0.20

Table 3

Distribution of Patients by Treatment Group vs. Stage of Disease and Initial Severity of Clinical Signs and Symptoms.

	Stage of Disease						Initial severity of Clin. Signs & Symptoms				
	Exacerbating			Improving							
	RAPIDLY	SLOWLY	STABLE	SLOWLY	RAPIDLY	NOTSPEC	NONE	MILD	MODERATE	SEVERE	NOSPEC
Bay 5097	0	5	9	0	0	0	0	4	5	5	0
Vehicle	0	0	10	2	0	0	0	0	7	5	0
TOTAL	0	5	19	2	0	0	0	4	12	10	0
	P = 0.050						P > 0.20				

The analysis showed that, in respect to duration of the disease and in respect to the initial severity of clinical signs and symptoms, there were no significant differences between the groups at the type 1 error significance level, P = 0.10. In respect to the stage of the disease, there was a significant difference (P = 0.050) which indicated that a higher number of drug-treated patients than of vehicle-treated patients had exacerbation of their disease. It was assumed that in plantar hyperkeratotic tinea pedis the stage of the diseast - exacerbating or stable - does not materially influence the response to antimycotic therapy. Therefore, the patient group treated with 1% clotrimazole in polyethylene glycol and the patient group treated with polyethylene glycol, 26 patients in all, were considered comparable for the key variables at entry into the study and with regard to the adherence to the protocol, comparable throughout the study. All patients adhered to the dose regimen (b.i.d.) except for one treated with vehicle, who applied the test preparation once a day during the fourth week.

Additional diagnoses were reported for two drug-treated patients, none of them, however, having any probable bearing on the treatment under investigation. The same was true of therapy given concurrently with the investigational treatment to four of the patients, two in the drug-treated

group and two in the vehicle-treated group.

DETAILED CRITERIA OF EFFECTIVENESS, OBJECTIVE AND SUBJECTIVE

Therapeutic effectiveness was determined on the basis of:

1) mycological findings (KOH mount and culture)
2) clinical findings (severity of clinical signs and symptoms before and after treatment)
3) investigator's assessment of treatment (taking into account mycological and clinical results)

ADVERSE EXPERIENCES LOOKED FOR BY THE PATIENT AND BY THE INVESTIGATOR

All 30 case report forms from this trial, including the four that had been nonevaluable for the assessment of efficacy, were examined for adverse reactions, particularly of the kind occurring eith topical administration of a test praparation. When side effects occurred they were recorded as described by the physician and as described by the patient, separately, for each visit. A final statement made by the physician at the last visit determined the occurrence of adverse effects in the patient.

CONTROL AND DRUG PERIODS AND KIND AND NUMBER OF OBSERVATIONS MADE IN EACH

At an initial visit, prior to treatment, patients were examined and given a two-week supply of the test preparation. Follow-up visits were scheduled for two weeks and four weeks, with new supplies of the test preparation, and for six weeks after initiation of therapy. Patients were instructed to apply the test preparation, i.e., drug solution or vehicle, twice a day for 42 days. The final examination was scheduled for two days after the end of therapy.

Clinical and mycological findings at the initial visit and at each subsequent visit were noted.

Clinical: Signs and symptoms were assessed before, during, and after the trial by recording the degree of scaling, vesiculation, inflammation, erythema, edema, fissures, exudation, maceration, and pruritus. Entries in the case reports were graded and formed the basis of the investigator's judgment of the overall severity of clinical signs and symptoms.

Mycological: Skin lesions were scraped for a wet mount and culture, and the causative organism was identified where possible.

ADVERSE REACTIONS AND ALL ADVERSE EXPERIENCE BY SYSTEM AND ORGAN, GENERAL AND LOCAL

There were no adverse reactions, except for a sensation of mild burning on application which was reported by one drug-treated patient.

Treatment did not have to be discontinued for an adverse reaction in any of the patients.

In no case did the sealed envelope which was provided with each medication box for the physician's convenience have to be opened. The envelopes contained, as mentioned earlier, a listing of ingredients of the accompanying medication in case a drug reaction required urgent medical attention. All envelopes were returned to the sponsor and were inventoried.

ALL RESULTS, POSITIVE, NEGATIVE, OR INCONCLUSIVE

Mycological and clinical parameters were used to determine and to compare the drug's and the vehicle's therapeutic effectiveness.

Mycological Findings

The distribution of patients by treatment group vs. KOH test and culture results before treatment is shown in Table 4, and all but six had positive results in both tests.

Table 4

Distribution of Patients by Treatment Group vs.
Results of Mycological Tests Before Treatment

	PRE-RX	
	KOH Positive	
	Cult. Pos.	Cult. Neg.
Bay 5097	12	2
Vehicle	8	4
TOTAL	20	6

The distribution of patients by treatment group vs. KOH test and culture results after treatment is shown in Table 5. Both KOH and culture were done for all patients.

Table 5

Distribution of Patients by Treatment Group vs.
Results of Mycological Tests After Treatment

	Post-RX			
	KOH Positive		KOH Negative	
	Cult. Pos.	Cult. Neg.	Cult. Pos.	Cult. Neg.
Bay 5097	1	2	2	9
Vehicle	7	0	1	4
TOTAL	8	2	3	13

Table 6 summarizes mycology results before and after treatment. Results are defined as positive when KOH test and/or culture indicated the presence of fungus, and are defined as negative when both KOH test and culture showed absence of fungus.

Table 6

Distribution of Patients by Mycology
Results Before and After Treatment

	PRE-RX		POST-RX	
	Pos.	Neg.	Pos.	Neg.
Bay 5097	14	0	5	9
Vehicle	12	0	8	4
TOTAL	26	0	13	13
	P = 1.00		P = 0.119	

The rate of mycological conversion to negative of both KOH mount and culture was 64% (nine of 14 patients) for the drug-treated group and 33% (four of 12 patients) for the vehicle-treated group. The difference between these two proportions was not statistically significant.

Positive cultures were identified as to type of fungus. For specific organisms isolated, the response to treatment is shown in Table 7.

Table 7

Distribution of Patients by Specific Organism Isolated
vs. Mycological Response to Treatment

		Post-RX Mycology	
		Pos.	Neg.
Bay 5097	Negative*	0	2
	T.rubrum	4	4
	T. menta.	1	2
	T. menta. & E. floc.	0	1
	Sub total	5	9

*These patients had negative cultures throughout, but positive KOH tests before treatment.

		Pos.	Neg.	
Vehicle	Negative*	0	1	
	T. rubrum	7	1	**Not further identified.
	T. menta.	0	1	
	E. floc.	1	0	
	Hyphae**	0	1	
	Sub total	8	4	
	TOTAL	13	13	

The overall rate of conversion to negative was 62% in the drug-treated group (eight of 13 organisms isolated), and 27% in the vehicle-treated group (three of 11 organisms isolated); instances of negative cultures were not counted in both groups. The difference was not statistically significant.

The number of separate species of organisms isolated from the patients was too small to permit individual evaluation.

2) Clinical Findings

The severity of clinical signs and symptoms at biweekly visits throughout the trial was one indicator of the patient's response to treatment.

Table 8

Distribution of Patients by Severity of Clinical Signs and Symptoms Before and After Treatment

	None	Mild	Mod-erate	Se-vere	
Bay 5097					
None	0	0	0	0	
Mild	0	4	0	0	
Moderate	1	2	2	0	
Severe	0	2	2	1	
Sub total	1	8	4	1	
Vehicle					
None	0	0	0	0	
Mild	0	0	0	0	
Moderate	0	1	6	0	
Severe	1	1	2	1	
Sub total	1	2	8	1	
TOTAL	2	10	12	2	P = 0.086

Before treatment the distribution of severity scores did not show a statistically significant difference; after treatment the distribution was significant in favor of the drug-treated group at the 10% level, but not at the 5% level (P = 0.086). With therapy, seven of 14 drug-treated patients improved clinically, as compared with five of 12 vehicle-treated patients.

Numerical values between "1 = none" and "4 = severe" were assigned to ratings recorded every two weeks for the severity of clinical signs and symptoms; the averages were as follows:

Week:	0	2	4	6
Clotrimazole	3.07	2.67	2.75	2.46
Vehicle	3.42	2.67	2.78	2.70

These values were plotted on the following graph. The two curves thus formed indicate the rate and the degree of decrease for the total severity score in each treatment group. For the purpose of this graph the treatment failures were given the severity score of their last visit for all subsequent visits which they did not attend. Visits missed for reasons other than treatment failures were not counted in the calculation of the weekly average score.

In this study of plantar hyperkeratotic tinea pedis, the average clinical severity was distinctly lower after a six-week course of topical therapy with the test preparation. The differenc between the treatment groups was, however, not marked.

Investigator's Assessment of Treatment

At the end of treatment with the test preparation, samples from all patients were examined by KOH wet mount and culture for the presence of fungus. To be considered negative, scrapings from lesions had to be negative under the microscope as well as in culture.

In Table 9, drug- and vehicle-treated patients are separated into those who converted to negative and those who did not. Both groups are further subdivided according to the patients' clinical response. Thus, the categories "Excellent" and "Good" include patients who became mycologically negative, and who were clinically either healed or improved; the categories "Fair" and "No Response" include patients who remained mycologically positive, and who either showed only clinical improvement or did not respond to treatment.

The classification of therapeutic response in the table is therefore graded from cure to failure.

AVERAGE SEVERITY OF CLINICAL SIGNS
AND SYMPTOMS DURING TREATMENT

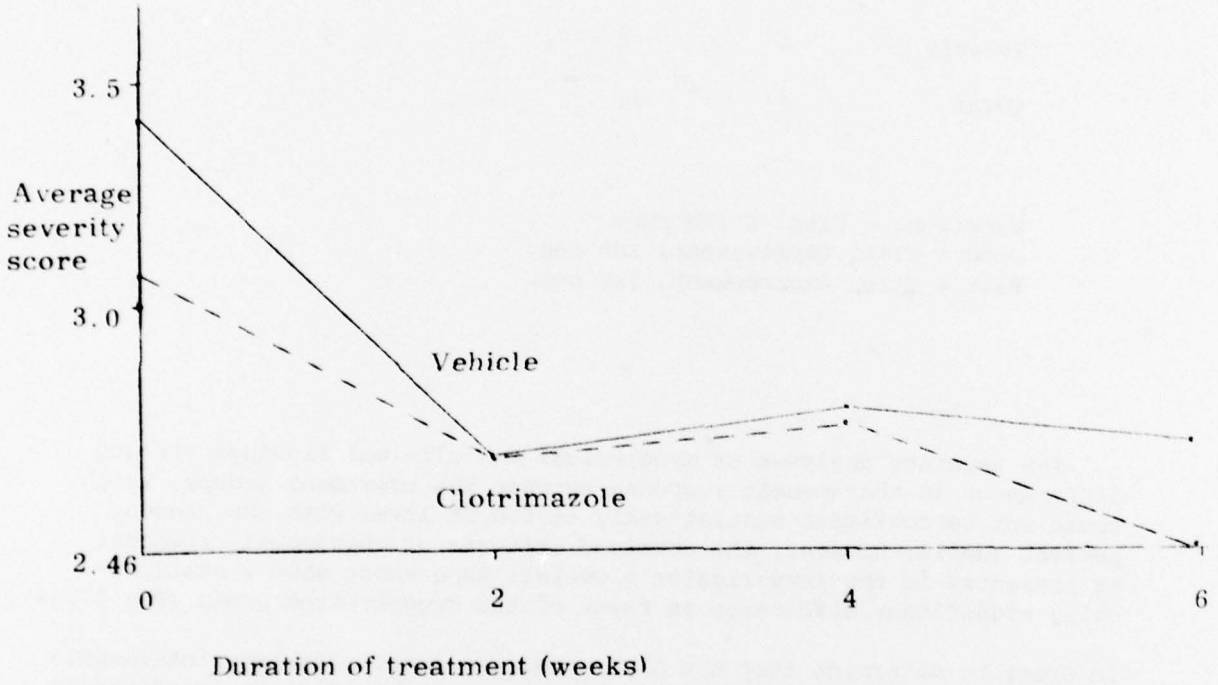


Table 9

Distribution of Patients by Treatment Group vs.
Investigator's Assessment of Therapeutic Results.

	Excellent	Good	Fair	No Response
Bay 5097	2	7	3	2
Vehicle	0	4	3	5
TOTAL	2	11	6	7

Excellent = Clin. & lab cure
Good = Clin. improvement, lab neg.
Fair = Clin. improvement, lab pos.

The separate analyses of mycological and clinical findings yielded differences in therapeutic response between the treatment groups, which could not be confirmed statistically at the 5% level with the present patient sample; however, the combined criteria of therapeutic response as presented in the Investigator's Overall Assessment show a statistically significant difference in favor of the drug-treated group ($P = 0.044$).

In order to determine that the higher success rate following clotrimazole therapy, as compared with vehicle therapy, was not obtained in an inordinately large number of patients with either less chronic or less severe infection, the results of this multicentric study were evaluated collectively.

STATISTICAL ANALYSIS

Statistical evaluation of the data was carried out via a series of nonparametric Wilcoxon Tests or Fischer's Exact Probability Tests.* The advantage of the nonparametric approach is that the assumption regarding the

*Nonparametric Statistics, John E. Walsh, D. Van Nostrand & Co., 1962, Vol. 1-3.

underlying requirements of parametric tests need not be met. The probability values tend to be more conservative, and one can be more confident about the individual probability values which are calculated.

CONCLUSIONS

A total of 30 patients entered the trial and were evaluated for tolerance. A minor adverse reaction, mild burning on application of clotrimazole solution, was reported.

Results from 26 patients were evaluated for efficacy; 14 of them had been treated with the active drug, and 12 with the vehicle.

Topical treatment with 1% clotrimazole solution, generally for six weeks but ranging from four to eight weeks, led to mycological cure with clinical cure or improvement in 64% of patients with plantar hyperkeratotic tinea pedis.

Thus, 1% clotrimazole solution in polyethylene glycol proved to be an effective therapeutic agent; it also proved to be more effective than the vehicle alone.

Incidence and kind of adverse reactions was quite acceptable.

PREVENTION OF BURN WOUND INFECTION

We continue to monitor the environment and intensively study individual cases in our Burn Unit. The problem of training all members of the staff in infection control measures is a continuous one, due to rotation of personnel, particularly surgical residents. We are more than ever convinced that control of the environment results in lower infection rates, and that an understanding of the entire ecosystem of the unit is a valuable approach

Like Dr. Kominos at Mary Hospital in Pittsburgh, we also found that the Waring blender, used to propare milk shakes, was a potent source of Pseudomonas aeruginosa. 10^6 bacteria per ml were obtained when sterile water was added to the blender and spun for 20 seconds.

Another hazardous source of Pseudomonas aeruginosa appeared in the nebulizers of respiratory therapy equipment, which were accidentally filled with tap water instead of sterile distilled water.

By routinely monitoring burn wounds by culture, we are able to detect the emergence of new species or strains of bacteria. The first truly gentamicin/penicillin resistant strain of P. aeruginosa appeared in the unit following the treatment of one child with topical gentamicin, a practice which we consider an extreme ecological hazard.

We appear to be able to control Pseudomonas infections by removing wet sources, frequently searching for hazardous practices (tap water in nebulizers, recirculating whirlpool baths, etc.) orientation of new personnel and removing all uncooked foods from the diet. We are now able to pyocine type strains and identify other species of Pseudomonas. The ability to identify unusual aquatic bacteria is helpful in spearating pathogens from saprophytes and preparing to quickly identify outbreaks of burn infections by bacteria previously considered non-pathogens.

We currently face a problem with multiple drug resistant Klebsiella pneumoniae. We have not yet identified an environmental source, but the same organism has recently emerged in the nursery, surgical intensive care, and now the Burn Unit. We are working with a new culture medium which looks promising as a selective medium for K. pneumoniae. One patient, who was close to death and extremely toxic following K. pneumoniae invasion of his burns, lungs and blood stream, was treated with BBK8 following unsuccessful therapy with gentamicin and colisten. This highly resistant organism is sensitive in vitro to BBK8, a new aminoglycoside antibiotic, and this drug appears to have a future in the management of these infections. Our young man survived and is now well on the road to complete recovery.

During this contract year we have conducted a large study on the effect of an antibacterial soap on the prevention of common skin infections.

This study was conducted in collaboration with industry, and the Food and Drug Administration.

The results contribute significantly to our understanding of common bacterial skin infections and the role which antibacterial soaps may play in their prevention, and we consider this work to be directly relevant to military dermatology.

The study is currently under review by the Food and Drug Administration, which is expected to make its findings known in September or October.

We therefore, feel it would be inappropriate to release the data before the Food and Drug Administration has issued its findings. Our complete report will, however, be submitted to the U.S. Army R. & D. Command at the earlist opportunity.

PUBLICATIONS SUPPORTED BY THIS CONTRACT

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