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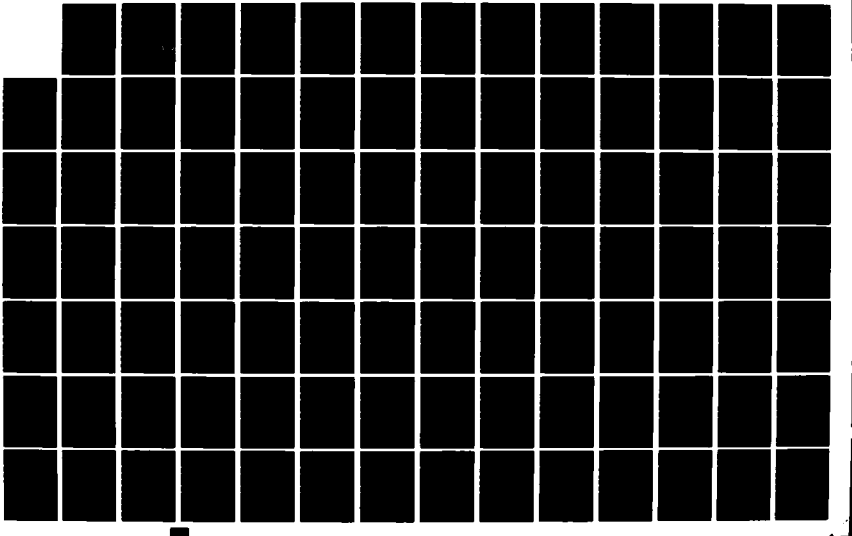

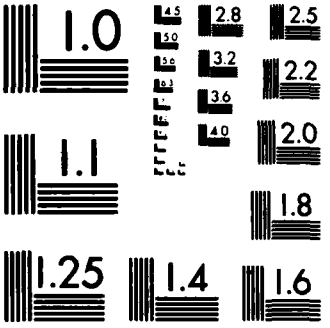

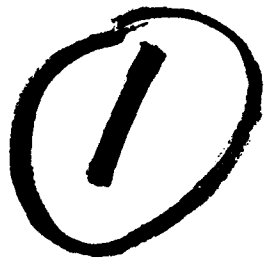

DEVELOPMENT AND VALIDATION OF A METHODOLOGY FOR TESTING TOPICAL ANTIPRURITIC DRUGS USING EXPERIMENTALLY INDUCED PRURITUS

by

Raymond D. Wilkins

A degree paper submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Master of Science in the School of Pharmacy.

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ACKNOWLEDGEMENTS

This paper is dedicated to my wife, Carola, for her patience, confidence, and encouragement; and to my son, Andrew, for his contagious smile.

RAYMOND D. WILKINS. Development and Validation of a Methodology for Testing Topical Antipruritic Drugs Using Experimentally Induced Pruritus (Under the direction of Dr. Bert Spilker).

A new double-blind methodology for testing the efficacy of topical antipruritic drugs was evaluated in a series of four experiments. Hair of rose hips was impregnated with histamine and applied to two or three sites on each forearm of volunteers. Pruritus intensity at each site was measured 2 minutes after application of the hair of rose hips (baseline) and 2, 5, 10, 15 and 20 minutes after application of topical study drugs. Pruritic responses in volunteers treated with hydrocortisone (0.5%) cream, hydrocortisone (0.5%) plus chlorcyclizine (2%) (Mantadil) cream, and placebo cream were evaluated in experiment 1. In experiment 2, volunteers were treated with hydrocortisone plus chlorcyclizine and placebo creams. Dibucaine (1%) ointment, calamine lotion, and their corresponding placebos were evaluated in experiments 3 and 4, respectively. Experiments 1 and 2 included only volunteers naive to the study, whereas experiments 3 and 4 included 9 and 12 repeat volunteers, respectively. In experiment 1, the mean pruritus scores were significantly lower for hydrocortisone (0.5%) plus chlorcyclizine (2%) vs. placebo at the 5 and 10 minute time points ($p<0.017$), but there were no significant differences at any time point in experiment 2. There was a statistically significant decrease in the intensity of pruritus in repeat volunteers following treatment with dibucaine (experiment 3) and calamine (experiment 4) as compared to their respective placebo. This effect was not present in volunteers naive to the study. The methodology was thus validated with experienced volunteers but not with volunteers who had not previously participated in the study.

INTRODUCTION

Pruritus (itching) was defined as "an unpleasant cutaneous sensation provoking the desire to scratch" over 200 years ago,[1] and is a common dermatological complaint for which there often is no completely effective treatment. One cause contributing to this ineffective treatment relates to the lack of a suitable well-controlled methodology for developing effective antipruritic drugs. Methods used to experimentally induce pruritus have included mechanical stimulation, electrical stimulation, natural and synthetic chemical stimulation, combinations of the above,[1,2] and the utilization of allergen patch tests.[3]

The scientific study of experimentally induced pruritus dates to the early 1900's. Titchener showed in 1909 that a pruritic response could be mechanically evoked by punctate stimulation of the skin with a fine hair. This was later confirmed by Shelley and Arthur.[4] This technique, however, has two major shortcomings: (1) it can produce pain depending on the amount of stimulation, and (2) the duration of the pruritic sensation only persists for approximately the length of time that contact is maintained.[4]

Edwards et al produced a local pruritic response through electrical stimulation of the skin.[5] The drawbacks to this method are that it requires specialized equipment, causes a short-duration pruritus (less than 30 seconds), and does not elicit reproducible results within the same subject.

The evaluation of chemical stimulation has focused on the drug histamine. Recently, Spilker et al evaluated the efficacy of a topically applied antihistamine cream applied four hours prior to or two minutes

after an intradermal (I.D.) injection of histamine (unpublished observations). A significant reduction in both wheal and flare diameters due to I.D. histamine was observed at the sites pretreated with the antihistamine cream. The pruritus caused by twice the dose of histamine that caused a 30 second pruritic response at baseline was evaluated. The pruritus was variable both in intensity and duration, usually persisting for no more than five minutes.

The plant substance cowhage (mucuna pruriens) has been reported to produce a combination of chemical and mechanical stimulation which provokes a reproducible pruritus in nearly 100% of individuals tested.[1,4,6,7] Broadbent[6] showed that the mean duration of pruritus produced by cowhage is 9.6 minutes. Studies performed by Shelley and Arthur have proven that the pruritus caused by cowhage is due to release of the proteolytic enzyme mucunain.[8] Graham et al showed that after the pruritic sensation produced by cowhage subsides, it could be revived by agitating or stroking the affected area.[7] Shelley and Arthur were able to produce a pruritus from inactivated cowhage spicules by soaking them in a histamine solution.[4]

Poison Ivy is the allergen patch test most frequently used to elicit a pruritic response. This test is particularly effective in North America where up to 80% of the population are sensitized to poison ivy.[3] There are a number of limitations, however, in the use of poison ivy extracts to produce pruritus. Sensitivities vary greatly between individuals and must be determined prior to entering volunteers into a trial; the trial may require 5 days to conduct; and, the intensity of the pruritus may be too strong for commonly used topical drugs to counteract effectively.

The limitations of these methods prompted us to attempt to define the characteristics of an ideal methodology for testing topical antipruritic drugs, and to develop a methodology consistent with these characteristics. We propose that the ideal methodology should have the following properties:

(1) Rapid onset of experimentally induced pruritus: The pruritus should begin within a few minutes after administering the test material. This is necessary to eliminate the need to have volunteers wait for extended periods before the clinical trial begins, or to have them return for testing at a specified time.

(2) Moderate intensity of pruritus: If the pruritus is too intense it might not allow the drugs being tested to demonstrate efficacy. This would cause a Type II error.* Conversely, if the pruritic intensity is too weak, there might be an abnormally high placebo effect also resulting in a Type II error.

(3) Adequate duration of pruritus: The duration of the pruritus produced must be long enough to allow the drugs being tested to demonstrate activity. A duration of approximately 20 minutes is considered desirable if the presence of an antipruritic effect with rapid onset is being evaluated. A longer duration of pruritus would be required if the duration of a drug's antipruritic effect was being studied. In addition, the pruritus must disappear within a relatively short period of time to minimize the volunteers' discomfort.

(4) The pruritus produced is analogous to that observed in clinical conditions: The experimental method should produce an insult to the skin that mimics at least some aspects of cutaneous disease.

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*A Type II error is defined as the chance of erroneously failing to reject a null hypothesis that is, in fact, false.(10)

(5) The pruritic effect must be reproducible within and between subjects.

(6) The methodology should be simple to perform with readily available equipment, should not require excessive time for the volunteer or investigator, and should be relatively inexpensive to conduct.

(7) The methodology must be validated by testing standard topical antipruritic drugs vs. placebo in a double-blind study.

(8) The methodology should be amenable to further clinical research and drug evaluation.

(9) Data obtained must be quantifiable for statistical analysis.

(10) The methodology must be suitable for use in double-blind clinical trials.

Hair of rose hips impregnated with histamine was used to produce pruritus in the present methodology. Hair of rose hips is the trichome-like part of the fruit of the rosa canina plant. It is sold throughout the U. S. and Europe in novelty shops as "Itching Powder", and elicits pruritus by mechanical stimulation. The trichomes become imbedded in the skin or its cloth cover, and a pruritus results as the cloth rubs against the skin. The pruritus persists only as long as the cloth remains in contact with the skin. Once the cloth is removed the pruritus cannot be reactivated by subsequent stimulation. Histamine has been used as a chemical stimulant to induce pruritus through intradermal injections and application via impregnated cowhage spicules. The proposed methodology incorporates the combination of hair of rose hips' mechanically induced pruritus with chemically induced pruritus through histamine impregnation of trichomes.

This paper describes the development of a methodology that meets

most of the "ideal" criteria, and describes its validation in a series of double-blind clinical experiments with commonly used topical anti-pruritic drugs.

MATERIALS AND METHODS

Study Design

This study consisted of four separate placebo-controlled, double-blind experiments with 20 to 24 volunteers in each experiment. The drugs used and number of volunteers in each experiment are summarized in Table 1:

TABLE 1: Drugs Tested and Number of Volunteers in Each Experiment.

Experiment	Drugs Tested	No. of Volunteers
1	Hydrocortisone (0.5%) plus Chlorcyclizine (2%) Cream, 0.5% Hydrocortisone Cream and Placebo Cream	21
2	Hydrocortisone (0.5%) plus Chlorcyclizine (2%) Cream and Placebo Cream	20
3	Dibucaine Ointment (1%) and Placebo Ointment	20
4	Calamine Lotion and Placebo Lotion	24

In experiments 2, 3 and 4, two sites (3 cm diameter each) were marked on the volar surface of each forearm with a marking pen. One site was located approximately 3 cm above the wrist and the other site was approximately 3 cm below the elbow. In experiment 1, a third site on each forearm was located approximately half-way between the distal and proximal sites and at least 3 cm from either site.

In experiments 2, 3 and 4, the letters A or B were assigned to each site. One letter was assigned to the proximal site and the other letter was assigned to the distal site on the same arm. The letters were reversed on the volunteer's other arm (e.g., left distal = A, left

proximal = B, right distal = B and right proximal = A). The letters assigned to the next volunteer were in the reverse order (i.e., left distal = B, left proximal = A, right distal = A and right proximal = B). In experiment 1, the letters A, B or C were assigned to each site. Each forearm was randomized separately, as were the three sites on each forearm, with codes generated by the Clinical Information and Statistics Department of the Burroughs Wellcome Company.

Identically appearing syringes containing the test drugs were also labelled with the letters A, B (and C in experiment 1). The syringes were filled and labelled by a clinical monitor. The code used to label the syringes was changed daily by the monitor, and the investigator remained blind to the identity of the syringe contents at all times.

After marking the 4 or 6 sites on both forearms, 25 mg of histamine-impregnated hair of rose hips was applied within the marked borders of each site. After application to all sites, a tongue depressor was used to gently rub the hair of rose hips into the skin. Each site was then covered with a 4 cm x 5 cm polyester cloth which was held in place with paper-adhesive tape. After a 2 minute period, the 0 time (baseline) test for pruritus intensity was performed. The site was then uncovered and gently wiped clean with a dry tissue. A 1-1/2 cm ribbon of the test drug or the respective placebo was applied to each site with a syringe. After the test drug or placebo had been applied to all sites, they were rubbed into the skin for 10 seconds. In experiment 4, 0.07 ml of lotion or its placebo was applied. The sites were again covered with the appropriate cloths, and measurements of pruritus intensity were repeated at 2, 5, 10, 15 and 20 minutes after application of the test drugs.

The rating scale consisted of a round dial 9 cm in diameter marked in equal units from 0 to 100 (Appendix 1). The statement "Not at all Itchy" was placed next to the zero, and the statement "Extremely Itchy" was placed next to the number 100. Each tenth unit was numbered sequentially (10, 20, 30, etc.). Two rating scales per page were used for experiments 2, 3 and 4 and three scales per page were used for experiment 1. One page was used to rate the pruritus for each arm, and two pages were used at each time point.

The rating procedure consisted of the investigator lightly stroking the cloth over the site to be rated for two seconds, the volunteer rotating the arm 180 degrees six times, and then the volunteer marking the dial. Volunteers were instructed to rate the pruritus they felt during both the stroking and rotation phases, to sum those two values, and to mark that sum on the dial. There were no instructions regarding restriction of motion between ratings. The volunteers drew a line with a black pen from the center of the dial to the point on the scale which represented their rating. The arm being rated was the arm used for marking the dial (i.e., if the left distal site was being rated, the left hand was used for marking). This procedure was repeated for each test at each site. The sequence for performing the tests and measurements remained constant throughout the study: right proximal, left proximal, right middle (for experiment 1 only), left middle (for experiment 1 only), right distal and left distal.

Volunteers in experiments 3 and 4 were asked at the conclusion of the test which treatment they preferred, and whether they were right-handed or left-handed.

Volunteers

Healthy adults between the ages of 18 and 65 were eligible for admission to the study if they did not have dermatologic disease, clinically significant illness, had not ingested oral antihistamines within six hours or oral steroids within seven days, had not applied topical antihistamines within six hours or topical steroids within 24 hours to the testing areas, and, if female, were not presently pregnant or lactating. Table 2 summarizes demographic information on volunteers.

TABLE 2: Male and Female Volunteer Information for Each Experiment.

	Experiment				Total
	1	2	3	4	
Number of Males	19	17	17	20	73
Number of Females	2	3	3	4	12
Mean Age of Males (±SD)	38 (± 5.6)	38 (±6.3)	37 (±6.2)	40 (±6.6)	38 (±6.2)
Mean Age of Females (±SD)	39 (±13.3)	43 (±6.4)	35 (±6.0)	28 (±4.4)	35 (±8.9)
Repeat Male Volunteers	---	---	8	12	20
Repeat Female Volunteers	---	---	1	0	1

Experiments 1 and 2 involved only volunteers that were naive to the study. Experiment 3 included 11 volunteers that were naive to the study and 9 volunteers that had participated in either experiment 1 or 2. Experiment 4 included 12 volunteers that were naive to the study and 12 that had participated in one of the first three experiments. Volunteers were not allowed to participate in more than two experiments and there was at least a one week wash-out period between the two tests. All

repeat volunteers were chosen at random. The results for the repeat volunteers were compared with the results for the volunteers who had not previously participated to determine if prior experience with the testing procedure had an effect on the volunteer's ability to detect a difference between active drug and placebo.

All volunteers admitted to the study signed an informed consent after having the procedures and risks explained (Appendix 2).

Drugs

Hair of rose hips was obtained from the Pyro Chemie Company of Eitorf-Sieg, West Germany in the form of approximately 300 mg packets of "Juck Pulver" (Itching Powder). The hair of rose hips was soaked in a 1:10,000 solution of histamine diphosphate (Nutritional Biochemical Corp.) for 30 minutes, centrifuged, decanted and allowed to air dry overnight. Each batch was discarded if not used within 72 hours.

The hydrocortisone acetate (0.5%) plus chlorcyclizine HCl (2%) combination (Mantadil® Cream), and the hydrocortisone acetate (0.5%) (Wellcortin® Cream) were manufactured and supplied by the Burroughs Wellcome Company. Dibucaine ointment (1%) (Nupercainal®, Ciba-Geigy) and calamine lotion (Swan Co.) were purchased at a local pharmacy.

The placebo used for experiments 1 and 2 was the Mantadil base (polawax, mineral oil, white petrolatum, methyl paraben and purified water USP) and was prepared by the Burroughs Wellcome Co. The placebo for dibucaine ointment consisted of 40% lanolin and 60% aquaphor (10% hydrated). The calamine placebo was a 15% talc and 2% bentonite magma solution colored with red food coloring. These two placebos were prepared by the Pharmaceutical Manufacturing Section of North Carolina Memorial Hospital.

Randomization Codes

The clinical monitor kept the randomization codes for the test drugs. The monitor's code listed the identity of the study drugs which were coded A, B (or C in experiment 1). The code to be used on each day of the study was also randomized. The investigator's randomization code for experiment 1 listed each patient by number and the corresponding site (right proximal, right distal, right middle, left proximal, left middle and left distal) by letters (A, B, C) where each drug was to be applied. An investigator's randomization code was not required for experiments 2, 3 and 4 since alternate sites (proximal and distal) on different forearms received the same treatment.

Data Analysis

In experiment 1, average responses for each drug treatment, for each volunteer were analyzed by parametric analysis of variance techniques and the treatments were compared using the Bonferroni approach. Treatment differences were declared statistically significant if the one-tailed p-value was less than 0.017 (Experiment data is in Appendix 3).

In experiments 2, 3 and 4, and for evaluating the effect of experience, the pruritus intensity score for each treatment at each time point was subtracted from the corresponding baseline score for each volunteer. This produced a difference from baseline for each treatment (Appendices 4-6). A paired t-test was computed to test the following one-tailed null hypothesis: mean difference from baseline with active drug was less than or equal to mean difference from baseline with placebo. Rejection of this hypothesis indicates that the active drug significantly lowered the pruritus score more than the placebo ($p \leq 0.05$).

RESULTS

The intensity of the pruritus induced by hair of rose hips impregnated with histamine remained relatively constant for at least 20 minutes. The mean pruritic score at baseline for the placebo sites for all 85 volunteers was 33.7 units. The values for placebo responses progressively declined from baseline over the first 15 minutes of the testing period (Table 3). The pruritic response at 15 and 20 minutes was 81% of baseline at the sites treated with placebo.

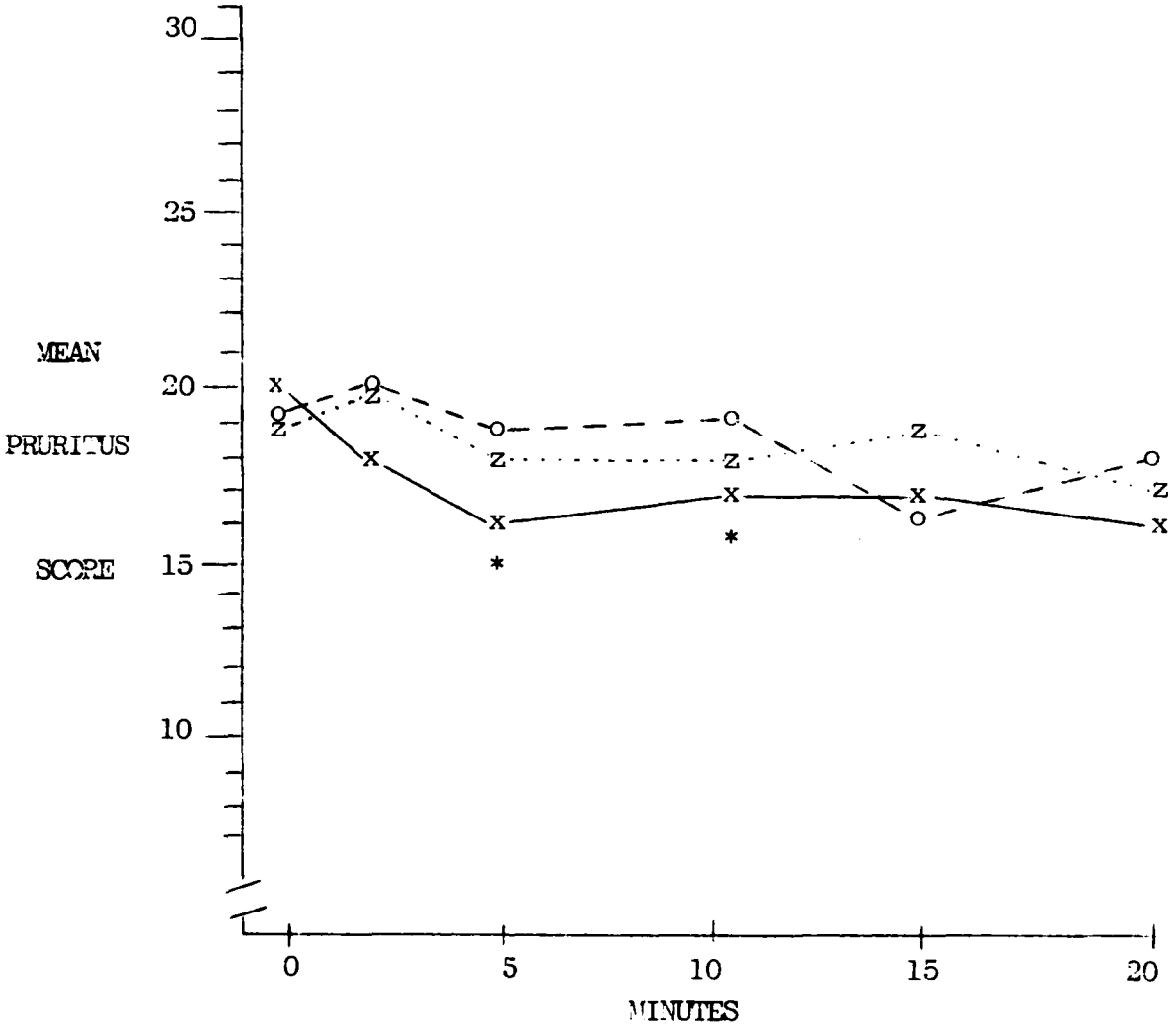
TABLE 3: Mean Pruritus Scores at Sites Treated With Placebo For All Volunteers (n=85)

	Mean Pruritus Score	Percent of Baseline
Baseline	33.7	100
2 minutes	31.2	93
5 minutes	30.3	90
10 minutes	28.4	84
15 minutes	27.4	81
20 minutes	27.2	81

Experiment 1

In experiment 1, hydrocortisone (0.5%) plus chlorcyclizine (2%) cream, hydrocortisone (0.5%) cream and placebo cream were compared using three sites on each forearm of 21 volunteers. Figure 1 shows that hydrocortisone plus chlorcyclizine significantly reduced pruritus scores as compared with placebo at 5 and 10 minutes ($p<0.017$). Hydrocortisone plus chlorcyclizine also had lower, but not significant, pruritus scores than hydrocortisone alone at all time points.

FIGURE 1: MEAN PRURITUS SCORES FOR EXPERIMENT 1



LEGEND: x——x - Hydrocortisone plus Chlorcyclizine
z·····z - Hydrocortisone
o– – –o - Placebo

All standard deviations for Hydrocortisone plus Chlorcyclizine, Hydrocortisone, and Placebo varied from 19 to 21 (n=21 for each time point).

*$p < 0.017$ for Hydrocortisone plus Chlorcyclizine vs Placebo

Experiment 2

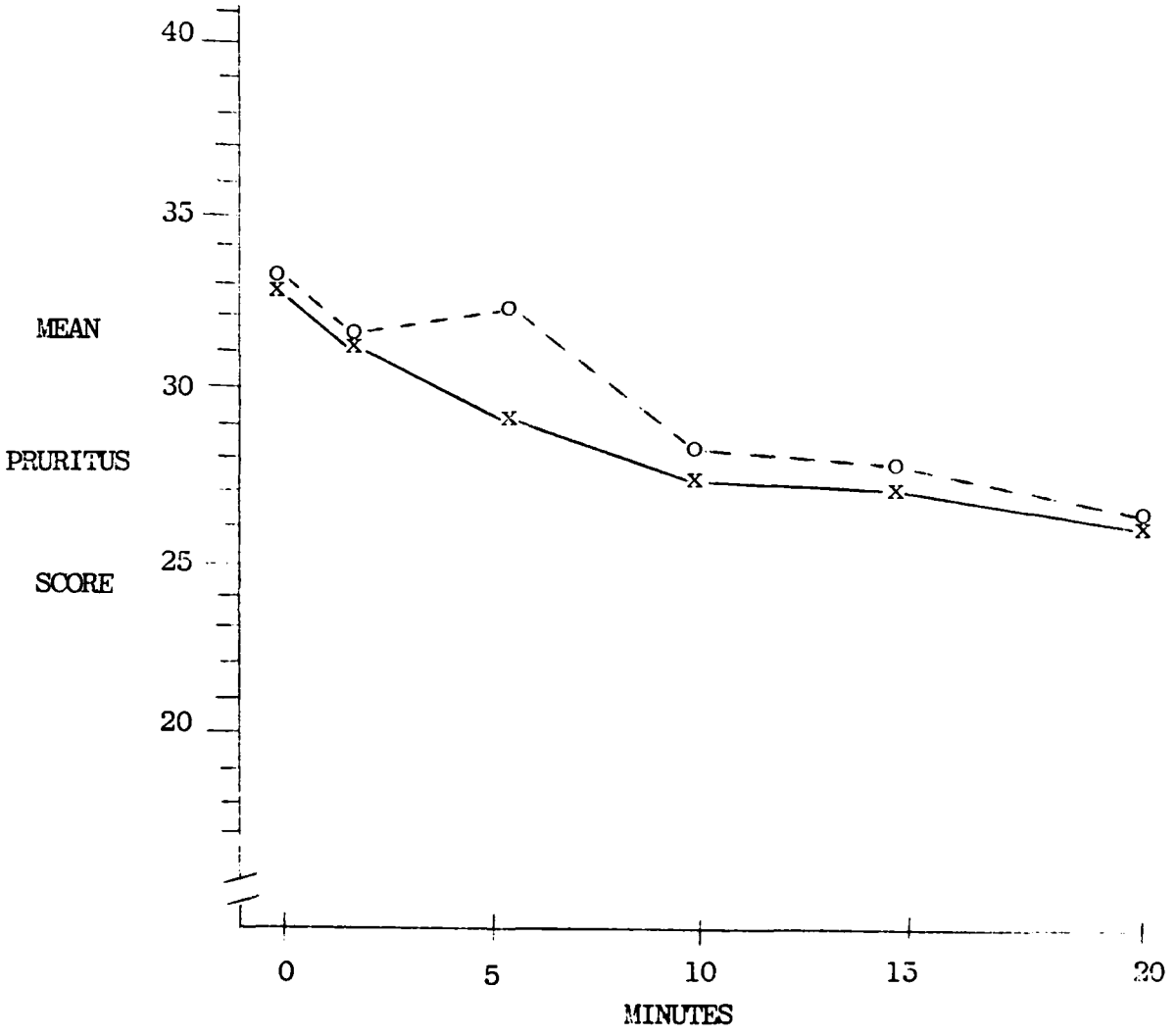
Experiment 2 consisted of comparing hydrocortisone (0.5%) plus chlorcyclizine (2%) cream with placebo cream which were applied at two sites on each forearm of 20 volunteers. The mean pruritus scores for hydrocortisone plus chlorcyclizine were lower than the scores for placebo at 5 and 10 minutes, but there was no significant difference between hydrocortisone plus chlorcyclizine and placebo at any of the time points (Figure 2).

Experiment 3

In experiment 3, dibucaine (1%) ointment and placebo ointment were applied at two sites on each forearm of 20 volunteers. Eleven volunteers were naive to the study and nine volunteers had participated in either experiment 1 or 2. The pooled data for both experienced and non-experienced volunteers showed dibucaine to have statistically significant ($p<=0.05$) lower pruritus scores than placebo at 5 and 10 minutes (Figure 3). The data was analyzed to test whether experienced volunteers were better able to detect a difference between the two study drug treatments than could nonexperienced volunteers. Figure 4 shows the mean pruritus scores for both the experienced and nonexperienced volunteers. Experienced volunteers had statistically significant lower pruritus scores for dibucaine than for placebo at 5, 10, 15 and 20 minutes ($p<=0.05$). There were no significant differences for nonexperienced volunteers. Mean baseline pruritus scores for experienced volunteers were significantly higher ($p<=0.05$) for their second test as compared to their first test at all sites on the forearms.

Volunteers in experiment 3 were asked the question, "If you had

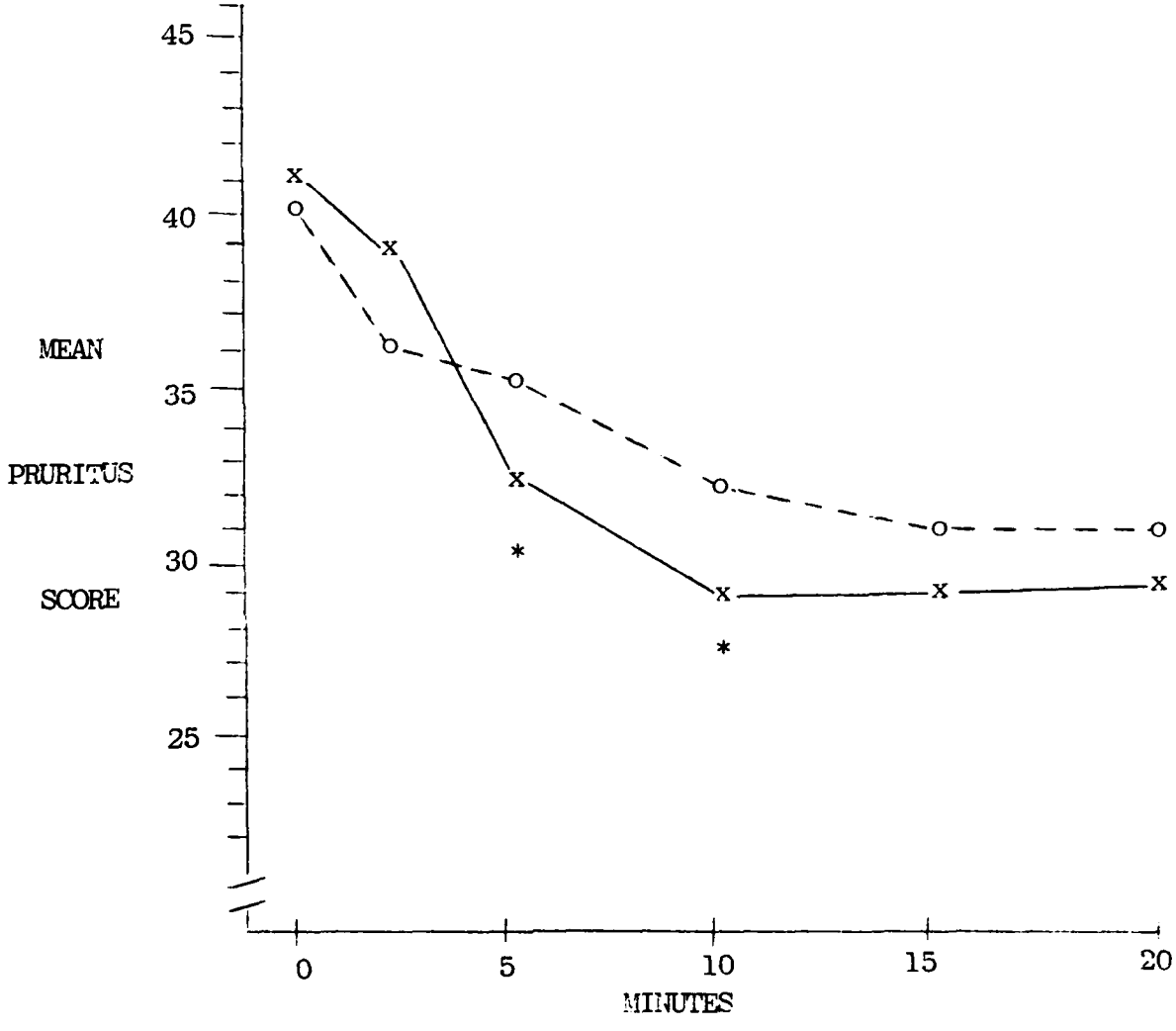
FIGURE 2: MEAN PRURITUS SCORES FOR EXPERIMENT 2



LEGEND: x——x - Hydrocortisone plus Chlorcyclizine
o— — o - Placebo

All standard deviations for Hydrocortisone plus Chlorcyclizine and Placebo varied from 15 to 20 (n=20 for each time point).

FIGURE 3: MEAN PRURITUS SCORES FOR EXPERIMENT 3

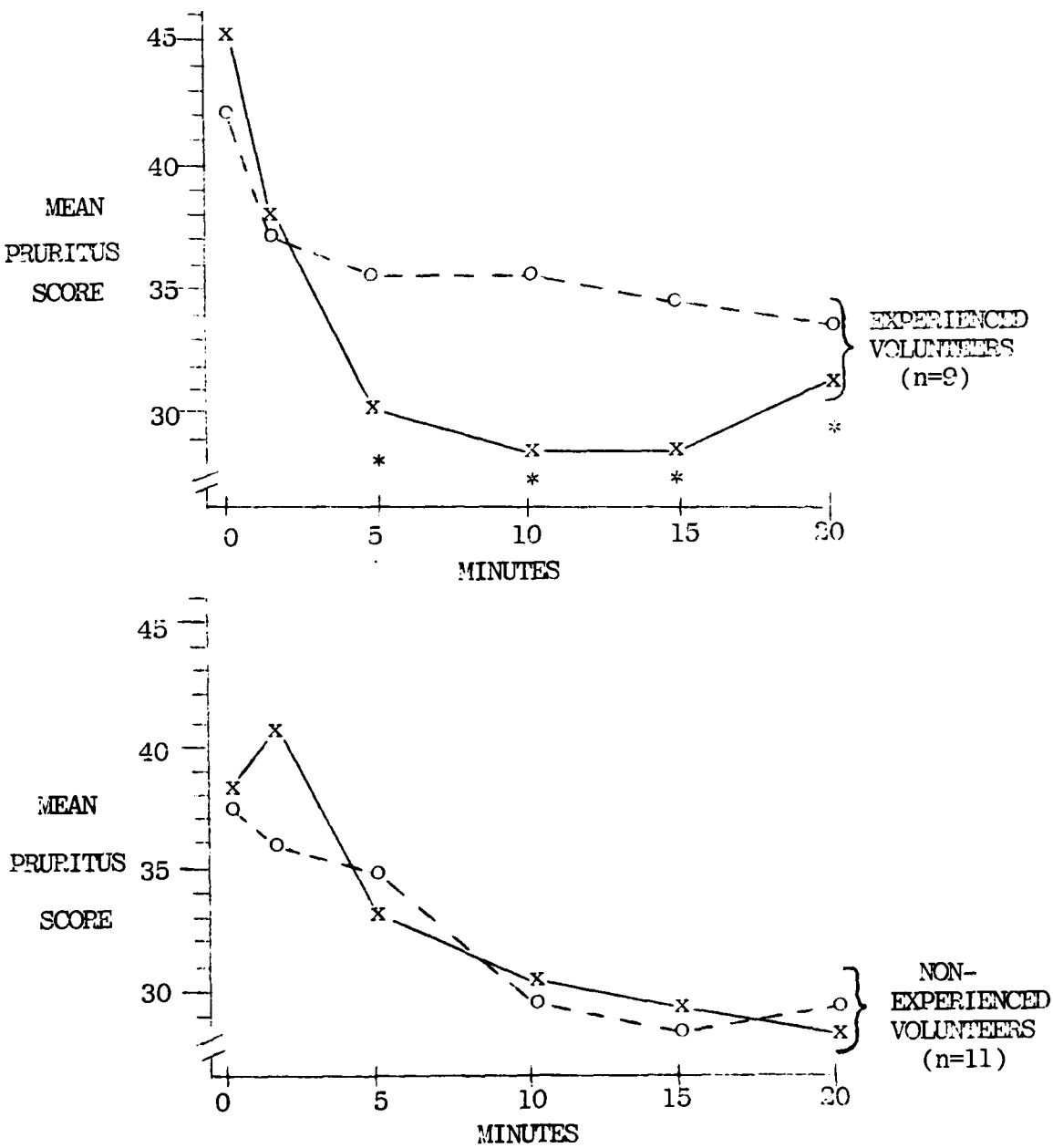


LEGEND: x——x - Dibucaine
o- - -o - Placebo

All standard deviations for Dibucaine and Placebo varied from 12 to 17 (n=20 for each time point).

*p<=0.05

FIGURE 4: MEAN PRURITUS SCORES OF EXPERIENCED AND NONEXPERIENCED VOLUNTEERS FOR EXPERIMENT 3



LEGEND: x——x - Dibucaine
o- - -o - Placebo

All standard deviations for Dibucaine and Placebo varied from 10.8 to 18.4.

*$p \leq 0.05$

to use one of these creams for this type of pruritus for the rest of the day, which one would you choose?" Ten volunteers preferred dibucaine, six preferred placebo, and four had no preference. Of those with a preference, 62.5% preferred dibucaine (not significantly different from 50%). Of the nine experienced volunteers, six preferred dibucaine, two preferred placebo and one had no preference. Of those with a preference, 75% preferred dibucaine (not significantly different from 50%).

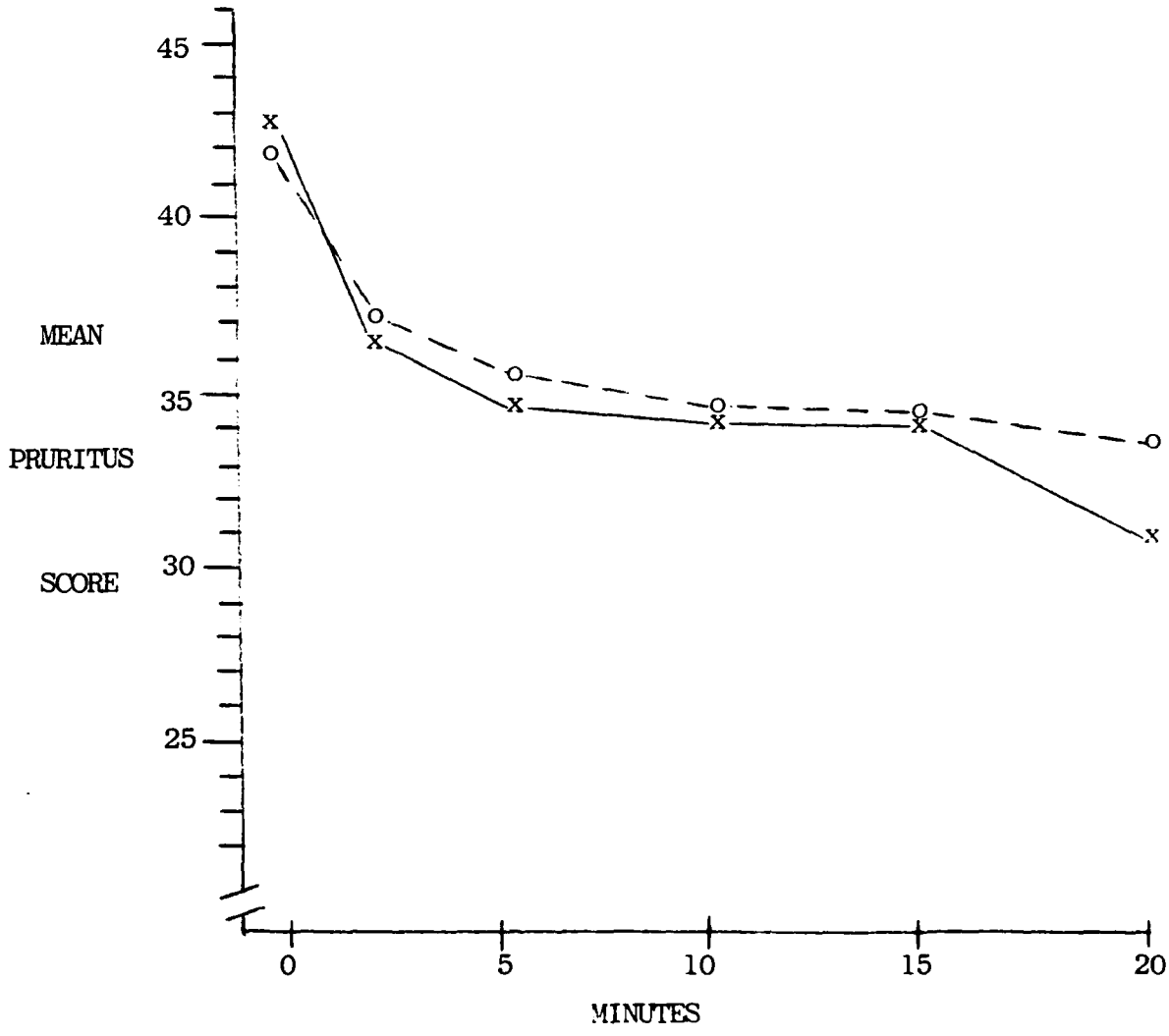
Volunteers were also asked if they were right-handed or left-handed. Baseline scores for both proximal and distal sites were higher for the dominant arm than nondominant arm. The scores were higher for the distal site than the proximal site on each arm, but none of these differences were significant (Appendix 7).

Experiment 4

Calamine lotion and placebo lotion were applied at two sites on each forearm of 24 volunteers. Experiment 4 included an equal number of experienced and nonexperienced volunteers (n=12 for each).

Experienced volunteers included only those who had participated in one previous experiment. The pooled pruritus score data for all volunteers in experiment 4 showed no significant differences between the pruritus scores for calamine lotion and its placebo lotion at any time point (Figure 5). The data for experienced volunteers showed statistically significant lower pruritus scores for calamine lotion compared with placebo lotion at 2, 10, 15 and 20 minutes ($p \leq 0.05$). The data for nonexperienced volunteers showed no significant differences at any time point (Figure 5). There were no significant differences in mean baseline pruritus scores for the experienced volunteers between

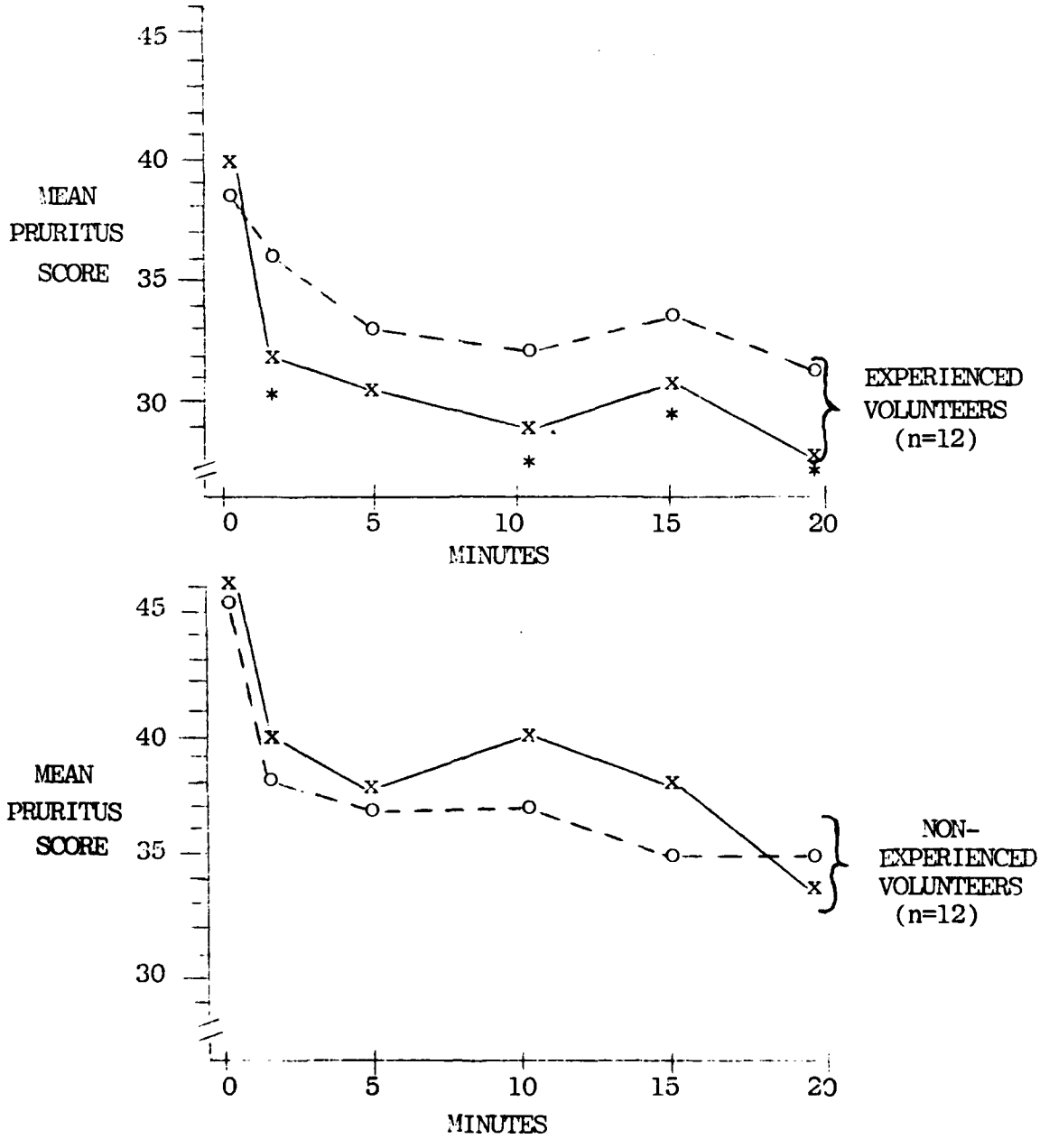
FIGURE 5: MEAN PRURITUS SCORES FOR EXPERIMENT 4



LEGEND: x——x - Calamine
o- - -o - Placebo

All standard deviations for Calamine and Placebo varied from 14 to 20 (n=24 for each time point).

FIGURE 6: MEAN PRURITUS SCORES OF EXPERIENCED AND NONEXPERIENCED VOLUNTEERS FOR EXPERIMENT 4



LEGEND: x——x - Calamine
o- - -o - Placebo

All standard deviations for Calamine and Placebo varied from 13.3 to 23.1.

*p<=0.05

their first and second tests, but the mean score was higher for the second test at both proximal and distal sites.

Volunteers in experiment 4 were asked for their treatment preference and whether they were right-handed or left-handed. Eleven volunteers preferred calamine lotion, eight preferred placebo lotion, and five had no preference. Of those with a preference, 57.9% preferred calamine (not significantly different from 50%). For the twelve experienced volunteers, six preferred calamine, three preferred placebo, and three had no preference. Of those with a preference, 66.7% preferred calamine (not significantly different from 50%). Baseline scores were higher, but not statistically significantly higher, for the distal site than for the proximal site. There was almost no difference in baseline scores between the dominant and nondominant arms (Appendix 7).

Adverse Reactions

Four volunteers experienced mild adverse reactions to the procedure: (1) Rash accompanied by pruritus for five days; (2) erythema at all testing sites without pruritus for four days after the second test; (3) sinus congestion for approximately 4-1/2 hours, however, this effect did not occur on rechallenge; and (4) wheal and erythema with extreme pruritus for three hours.

DISCUSSION

There is no satisfactory methodology at present for accurately and reproducibly testing topical antipruritics in a rapid manner. All methods utilized have significant drawbacks. The objective of this study was to develop a methodology that met most of the criteria established for an ideal methodology (see Introduction), and to validate this methodology with commonly used topical antipruritic drugs.

Pruritus is believed to be a modified form of pain mediated by unmyelinated C fibers.[4, 10] Stimuli that are insufficient in intensity to produce pain may cause pruritus. Shelley and Arthur noted that the relationship of pruritus and burning pain is one of degree.[4] Pruritus may be induced through mechanical, electrical, or chemical stimulations, or by a combination of these as described in the Introduction. The proposed methodology utilizing histamine-impregnated hair of rose hips is based on a combination of mechanical and chemical stimulation.

Initially, the study was designed to test two active drugs and a placebo on each forearm (i.e., three sites per forearm), and experiment 1 was conducted in this manner. It was often difficult, however, for volunteers to distinguish which of the three sites caused the pruritus when one of the treated sites on the forearm was stroked, or when the forearm was moved during the test. This problem was due to the relatively close proximity of the three sites to each other. Thus, volunteers were instructed not to move their arms, and to rate only the pruritus felt at the time the cloth was stroked. This restriction of arm movement may have been responsible for the lower mean pruritus scores observed in

experiment 1 than in the other experiments. It has been reported that there is a difference in sensitivity to stimuli between the dominant and nondominant arms[1], thus, testing only one site per forearm was considered not as desirable as testing two sites per forearm. In experiments 2, 3 and 4, two sites were used per forearm. A rotating motion of the forearm was also incorporated into the protocol to increase the intensity of the pruritic response.

The data from experiments 3 and 4 indicate that volunteer experience is an important factor in the results obtained in this test. Figures 4 and 6 show significant differences between mean pruritus scores for active drug versus placebo in both experiments conducted with experienced volunteers as compared with identical experiments conducted with non-experienced volunteers. The reason for this difference between experienced and nonexperienced volunteers may be due to a better understanding and awareness of the methodology used, to a sensitizing effect of the testing material, or to a combination of both factors. Volunteer participation was limited to a total of two experiments separated by at least one week (wash-out period between experiments ranged between 10 and 41 days). It is not possible at this time to determine the presence or degree of the sensitizing effect. It is believed that a "training effect" increased the awareness of volunteers to enable them to be able to detect a difference between active and placebo drugs. Experienced volunteers had higher mean baseline pruritus scores in their second experiment than in their first. This is most likely due to a better understanding of the methodology used.

The pooled data for all volunteers from experiments 3 and 4 does not adequately validate this methodology because values at only two of

the ten time points tested were significant. A significant difference was noted, however, at eight of the ten time points tested in experienced volunteers. Thus, the results of experiments 3 and 4 validate this methodology with experienced volunteers but not with nonexperienced volunteers.

The proposed methodology generally meets most of the criteria of an ideal methodology proposed in the Introduction.

(1) Rapid onset - Pruritus occurred within two minutes of the application of the test material.

(2) Moderate intensity - Commonly used topical antipruritic drugs were able to significantly reduce the intensity of pruritus in several experiments.

(3) Adequate duration of pruritus - Eighty-one percent of the baseline pruritus persisted for 20 minutes permitting topical drugs to be evaluated.

(4) Analogous to clinically observed conditions - This model is not entirely satisfactory since many clinical conditions cause a pruritus that is more intense and of longer duration than that caused by this model.

(5) Reproducibility of effect - A similar degree of pruritus was demonstrated between volunteers in four separate experiments and within volunteers who participated in two separate experiments.

(6) Validity demonstrated with standard drugs - Dibucaine ointment and calamine lotion were both more active than placebo when the tests were performed with experienced volunteers.

(7) Simple to perform - The tests described in this report required up to 45 minutes per volunteer to complete.

(8) Amenable to further research - The proposed methodology is applicable for further research studies with easily trained volunteers.

(9) Quantifiable data - the rating system used provided easily obtained data that could be analyzed statistically.

(10) Suitable for double-blind clinical trials - The proposed methodology was performed in a double-blind manner.

The limitations of this methodology concern the need for experienced volunteers, the duration of the antipruritic effect observed, and the similarity to clinically observed conditions. Whether the effect observed that was attributed to "experience" with the methodology would also be observed in a third, fourth, or additional study is not known. It is not possible to test the duration of action of topical antipruritic drugs with this methodology.

The novel methodology described was developed for testing topical antipruritic drugs. This methodology has been validated with two commonly used topical antipruritics in experienced volunteers, and may be used to test the efficacy of new topical antipruritic drugs.

REFERENCES

1. Murray FS and Weaver MM. Effects of ipsilateral and contralateral counterirritation on experimentally produced itch in human beings. Journal of Comparative and Physiological Psychology 1975;89(7): 819-826.

2. Keele CA and Armstrong D. Substances producing pain and itch. London: Edward Arnold LTD, 1964.

3. Wendt H and Frosch PJ. Poison Ivy Test. In: Clinico-pharmacological models for the assay of topical corticoids. Basel: S. Karger, 1982.

4. Shelley WB and Arthur RP. The neurohistology and neurophysiology of the itch sensation in man. AMA Archives of Dermatology 1957;76: 296-323.

5. Edwards AE, Shellow WVR, Wright ET, and Dignam TF. Pruritic skin disease, psychological stress, and the itch sensation. Archives of Dermatology 1976;112:339-343.

6. Broadbent JL. Observations on itching produced by cowhage, and on the part played by histamine as a mediator of the itch sensation. British Journal of Pharmacology 1953;8:263-270.

7. Graham DT, Goodell H, and Wolff HG. Neural mechanisms involved in itch, "itchy skin", and tickle sensations. Journal of Clinical Investigations 1951;30:37-49.

8. Shelley WB and Arthur RP. Studies on cowhage (mucuna pruriens) and its pruritogenic proteinase, mucunain. AMA Archives of Dermatology 1955;72:399-406.

9. Colton T. Statistics in medicine. Boston: Little, Brown and Company, 1974.

10. Cormia FE and Kuykendall V. Experimental histamine pruritus II. Nature; Physical and environmental factors influencing development and severity. Journal of Investigative Dermatology 1953;20:429-446.

APPENDIX 2

"INFORMED CONSENT"

COMPARISON OF TOPICAL DIBUCAINE AND PLACEBO

This study involves research to evaluate the anti-irritation and anti-itching properties of topically applied dibucaine ointment compared with a placebo ointment. Your participation in this study will be completed today.

The procedure to be used in this experiment is as follows: Dried histamine-impregnated hair of rose hips powder will be placed on the skin at two different sites on each forearm (a total of four sites), rubbed in for 10 seconds and covered with a cloth. After two minutes, a test to measure the itching at each site will be conducted. The cloth will then be removed, the powder on the skin wiped off, one of the two ointments applied and rubbed in, and the cloth replaced. The same test, consisting of a 2 second finger rub of each site, rotating the arm and recording the sensation of itch and/or irritation, will be done 2, 5, 10, 15 and 20 minutes after the ointments are applied.

Risks or discomforts you may experience in this study include: extremely rare hypersensitivity reaction to the dibucaine, the dibucaine base, or the hair of rose hips; local irritation, a pricking sensation, and itching due to the penetration of the hair of rose hips into the skin. The irritation and itching should not last for more than 30 minutes after the completion of the test.

The confidentiality of records identifying the subject will be maintained within the Burroughs Wellcome Co., with the possible exception that the Food and Drug Administration may inspect the records.

Questions regarding this study should be directed to the investigators; Bert Spilker, M.D., Ph.D. or Ray Wilkins, B.S.

Participation in this study is voluntary and refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled. Furthermore, the subject may discontinue participation at any time without penalty.

I, _____, have read and I understand the preceding
(print name)
statements. I agree to become a subject in this study fully aware of the procedures and risks involved.

_____ _____

Subject's Signature Date

Appendix 2

"INFORMED CONSENT" (Cont'd)

I have explained and defined in detail the research procedures in which the subject has consented to participate.

Investigator	Date

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TABLES

FIGURES

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ACKNOWLEDGEMENTS

This paper is dedicated to my wife, Carola, for her patience, confidence, and encouragement; and to my son, Andrew, for his contagious smile.

INTRODUCTION

Pruritus (itching) was defined as "an unpleasant cutaneous sensation provoking the desire to scratch" over 200 years ago,[1] and is a common dermatological complaint for which there often is no completely effective treatment. One cause contributing to this ineffective treatment relates to the lack of a suitable well-controlled methodology for developing effective antipruritic drugs. Methods used to experimentally induce pruritus have included mechanical stimulation, electrical stimulation, natural and synthetic chemical stimulation, combinations of the above,[1,2] and the utilization of allergen patch tests.[3]

The scientific study of experimentally induced pruritus dates to the early 1900's. Titchener showed in 1909 that a pruritic response could be mechanically evoked by punctate stimulation of the skin with a fine hair. This was later confirmed by Shelley and Arthur.[4] This technique, however, has two major shortcomings: (1) it can produce pain depending on the amount of stimulation, and (2) the duration of the pruritic sensation only persists for approximately the length of time that contact is maintained.[4]

Edwards et al produced a local pruritic response through electrical stimulation of the skin.[5] The drawbacks to this method are that it requires specialized equipment, causes a short-duration pruritus (less than 30 seconds), and does not elicit reproducible results within the same subject.

The evaluation of chemical stimulation has focused on the drug histamine. Recently, Spilker et al evaluated the efficacy of a topically applied antihistamine cream applied four hours prior to or two minutes

after an intradermal (I.D.) injection of histamine (unpublished observations). A significant reduction in both wheal and flare diameters due to I.D. histamine was observed at the sites pretreated with the antihistamine cream. The pruritus caused by twice the dose of histamine that caused a 30 second pruritic response at baseline was evaluated. The pruritus was variable both in intensity and duration, usually persisting for no more than five minutes.

The plant substance cowhage (mucuna pruriens) has been reported to produce a combination of chemical and mechanical stimulation which provokes a reproducible pruritus in nearly 100% of individuals tested.[1,4,6,7] Broadbent[6] showed that the mean duration of pruritus produced by cowhage is 9.6 minutes. Studies performed by Shelley and Arthur have proven that the pruritus caused by cowhage is due to release of the proteolytic enzyme mucunain.[8] Graham et al showed that after the pruritic sensation produced by cowhage subsides, it could be revived by agitating or stroking the affected area.[7] Shelley and Arthur were able to produce a pruritus from inactivated cowhage spicules by soaking them in a histamine solution.[4]

Poison Ivy is the allergen patch test most frequently used to elicit a pruritic response. This test is particularly effective in North America where up to 80% of the population are sensitized to poison ivy.[3] There are a number of limitations, however, in the use of poison ivy extracts to produce pruritus. Sensitivities vary greatly between individuals and must be determined prior to entering volunteers into a trial; the trial may require 5 days to conduct; and, the intensity of the pruritus may be too strong for commonly used topical drugs to counteract effectively.

The limitations of these methods prompted us to attempt to define the characteristics of an ideal methodology for testing topical antipruritic drugs, and to develop a methodology consistent with these characteristics. We propose that the ideal methodology should have the following properties:

(1) Rapid onset of experimentally induced pruritus: The pruritus should begin within a few minutes after administering the test material. This is necessary to eliminate the need to have volunteers wait for extended periods before the clinical trial begins, or to have them return for testing at a specified time.

(2) Moderate intensity of pruritus: If the pruritus is too intense it might not allow the drugs being tested to demonstrate efficacy. This would cause a Type II error.* Conversely, if the pruritic intensity is too weak, there might be an abnormally high placebo effect also resulting in a Type II error.

(3) Adequate duration of pruritus: The duration of the pruritus produced must be long enough to allow the drugs being tested to demonstrate activity. A duration of approximately 20 minutes is considered desirable if the presence of an antipruritic effect with rapid onset is being evaluated. A longer duration of pruritus would be required if the duration of a drug's antipruritic effect was being studied. In addition, the pruritus must disappear within a relatively short period of time to minimize the volunteers' discomfort.

(4) The pruritus produced is analogous to that observed in clinical conditions: The experimental method should produce an insult to the skin that mimics at least some aspects of cutaneous disease.

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*A Type II error is defined as the chance of erroneously failing to reject a null hypothesis that is, in fact, false.(10)

(5) The pruritic effect must be reproducible within and between subjects.

(6) The methodology should be simple to perform with readily available equipment, should not require excessive time for the volunteer or investigator, and should be relatively inexpensive to conduct.

(7) The methodology must be validated by testing standard topical antipruritic drugs vs. placebo in a double-blind study.

(8) The methodology should be amenable to further clinical research and drug evaluation.

(9) Data obtained must be quantifiable for statistical analysis.

(10) The methodology must be suitable for use in double-blind clinical trials.

Hair of rose hips impregnated with histamine was used to produce pruritus in the present methodology. Hair of rose hips is the trichome-like part of the fruit of the rosa canina plant. It is sold throughout the U. S. and Europe in novelty shops as "Itching Powder", and elicits pruritus by mechanical stimulation. The trichomes become imbedded in the skin or its cloth cover, and a pruritus results as the cloth rubs against the skin. The pruritus persists only as long as the cloth remains in contact with the skin. Once the cloth is removed the pruritus cannot be reactivated by subsequent stimulation. Histamine has been used as a chemical stimulant to induce pruritus through intradermal injections and application via impregnated cowhage spicules. The proposed methodology incorporates the combination of hair of rose hips' mechanically induced pruritus with chemically induced pruritus through histamine impregnation of trichomes.

This paper describes the development of a methodology that meets

most of the "ideal" criteria, and describes its validation in a series of double-blind clinical experiments with commonly used topical anti-pruritic drugs.

MATERIALS AND METHODS

Study Design

This study consisted of four separate placebo-controlled, double-blind experiments with 20 to 24 volunteers in each experiment. The drugs used and number of volunteers in each experiment are summarized in Table 1:

TABLE 1: Drugs Tested and Number of Volunteers in Each Experiment.

Experiment	Drugs Tested	No. of Volunteers
1	Hydrocortisone (0.5%) plus Chlorcyclizine (2%) Cream, 0.5% Hydrocortisone Cream and Placebo Cream	21
2	Hydrocortisone (0.5%) plus Chlorcyclizine (2%) Cream and Placebo Cream	20
3	Dibucaine Ointment (1%) and Placebo Ointment	20
4	Calamine Lotion and Placebo Lotion	24

In experiments 2, 3 and 4, two sites (3 cm diameter each) were marked on the volar surface of each forearm with a marking pen. One site was located approximately 3 cm above the wrist and the other site was approximately 3 cm below the elbow. In experiment 1, a third site on each forearm was located approximately half-way between the distal and proximal sites and at least 3 cm from either site.

In experiments 2, 3 and 4, the letters A or B were assigned to each site. One letter was assigned to the proximal site and the other letter was assigned to the distal site on the same arm. The letters were reversed on the volunteer's other arm (e.g., left distal = A, left

proximal = B, right distal = B and right proximal = A). The letters assigned to the next volunteer were in the reverse order (i.e., left distal = B, left proximal = A, right distal = A and right proximal = B). In experiment 1, the letters A, B or C were assigned to each site. Each forearm was randomized separately, as were the three sites on each forearm, with codes generated by the Clinical Information and Statistics Department of the Burroughs Wellcome Company.

Identically appearing syringes containing the test drugs were also labelled with the letters A, B (and C in experiment 1). The syringes were filled and labelled by a clinical monitor. The code used to label the syringes was changed daily by the monitor, and the investigator remained blind to the identity of the syringe contents at all times.

After marking the 4 or 6 sites on both forearms, 25 mg of histamine-impregnated hair of rose hips was applied within the marked borders of each site. After application to all sites, a tongue depressor was used to gently rub the hair of rose hips into the skin. Each site was then covered with a 4 cm x 5 cm polyester cloth which was held in place with paper-adhesive tape. After a 2 minute period, the 0 time (baseline) test for pruritus intensity was performed. The site was then uncovered and gently wiped clean with a dry tissue. A 1-1/2 cm ribbon of the test drug or the respective placebo was applied to each site with a syringe. After the test drug or placebo had been applied to all sites, they were rubbed into the skin for 10 seconds. In experiment 4, 0.07 ml of lotion or its placebo was applied. The sites were again covered with the appropriate cloths, and measurements of pruritus intensity were repeated at 2, 5, 10, 15 and 20 minutes after application of the test drugs.

The rating scale consisted of a round dial 9 cm in diameter marked in equal units from 0 to 100 (Appendix 1). The statement "Not at all Itchy" was placed next to the zero, and the statement "Extremely Itchy" was placed next to the number 100. Each tenth unit was numbered sequentially (10, 20, 30, etc.). Two rating scales per page were used for experiments 2, 3 and 4 and three scales per page were used for experiment 1. One page was used to rate the pruritus for each arm, and two pages were used at each time point.

The rating procedure consisted of the investigator lightly stroking the cloth over the site to be rated for two seconds, the volunteer rotating the arm 180 degrees six times, and then the volunteer marking the dial. Volunteers were instructed to rate the pruritus they felt during both the stroking and rotation phases, to sum those two values, and to mark that sum on the dial. There were no instructions regarding restriction of motion between ratings. The volunteers drew a line with a black pen from the center of the dial to the point on the scale which represented their rating. The arm being rated was the arm used for marking the dial (i.e., if the left distal site was being rated, the left hand was used for marking). This procedure was repeated for each test at each site. The sequence for performing the tests and measurements remained constant throughout the study: right proximal, left proximal, right middle (for experiment 1 only), left middle (for experiment 1 only), right distal and left distal.

Volunteers in experiments 3 and 4 were asked at the conclusion of the test which treatment they preferred, and whether they were right-handed or left-handed.

Volunteers

Healthy adults between the ages of 18 and 65 were eligible for admission to the study if they did not have dermatologic disease, clinically significant illness, had not ingested oral antihistamines within six hours or oral steroids within seven days, had not applied topical antihistamines within six hours or topical steroids within 24 hours to the testing areas, and, if female, were not presently pregnant or lactating. Table 2 summarizes demographic information on volunteers.

TABLE 2: Male and Female Volunteer Information for Each Experiment.

	Experiment				Total
	1	2	3	4	
Number of Males	19	17	17	20	73
Number of Females	2	3	3	4	12
Mean Age of Males (±SD)	38 (± 5.6)	38 (±6.3)	37 (±6.2)	40 (±6.6)	38 (±6.2)
Mean Age of Females (±SD)	39 (±13.3)	43 (±6.4)	35 (±6.0)	28 (±4.4)	35 (±8.9)
Repeat Male Volunteers	---	---	8	12	20
Repeat Female Volunteers	---	---	1	0	1

Experiments 1 and 2 involved only volunteers that were naive to the study. Experiment 3 included 11 volunteers that were naive to the study and 9 volunteers that had participated in either experiment 1 or 2. Experiment 4 included 12 volunteers that were naive to the study and 12 that had participated in one of the first three experiments. Volunteers were not allowed to participate in more than two experiments and there was at least a one week wash-out period between the two tests. All

repeat volunteers were chosen at random. The results for the repeat volunteers were compared with the results for the volunteers who had not previously participated to determine if prior experience with the testing procedure had an effect on the volunteer's ability to detect a difference between active drug and placebo.

All volunteers admitted to the study signed an informed consent after having the procedures and risks explained (Appendix 2).

Drugs

Hair of rose hips was obtained from the Pyro Chemie Company of Eitorf-Sieg, West Germany in the form of approximately 300 mg packets of "Juck Pulver" (Itching Powder). The hair of rose hips was soaked in a 1:10,000 solution of histamine diphosphate (Nutritional Biochemical Corp.) for 30 minutes, centrifuged, decanted and allowed to air dry overnight. Each batch was discarded if not used within 72 hours.

The hydrocortisone acetate (0.5%) plus chlorcyclizine HCl (2%) combination (Mantadil® Cream), and the hydrocortisone acetate (0.5%) (Wellcortin® Cream) were manufactured and supplied by the Burroughs Wellcome Company. Dibucaine ointment (1%) (Nupercainal®, Ciba-Geigy) and calamine lotion (Swan Co.) were purchased at a local pharmacy.

The placebo used for experiments 1 and 2 was the Mantadil base (polawax, mineral oil, white petrolatum, methyl paraben and purified water USP) and was prepared by the Burroughs Wellcome Co. The placebo for dibucaine ointment consisted of 40% lanolin and 60% aquaphor (10% hydrated). The calamine placebo was a 15% talc and 2% bentonite magma solution colored with red food coloring. These two placebos were prepared by the Pharmaceutical Manufacturing Section of North Carolina Memorial Hospital.

Randomization Codes

The clinical monitor kept the randomization codes for the test drugs. The monitor's code listed the identity of the study drugs which were coded A, B (or C in experiment 1). The code to be used on each day of the study was also randomized. The investigator's randomization code for experiment 1 listed each patient by number and the corresponding site (right proximal, right distal, right middle, left proximal, left middle and left distal) by letters (A, B, C) where each drug was to be applied. An investigator's randomization code was not required for experiments 2, 3 and 4 since alternate sites (proximal and distal) on different forearms received the same treatment.

Data Analysis

In experiment 1, average responses for each drug treatment, for each volunteer were analyzed by parametric analysis of variance techniques and the treatments were compared using the Bonferroni approach. Treatment differences were declared statistically significant if the one-tailed p-value was less than 0.017 (Experiment data is in Appendix 3).

In experiments 2, 3 and 4, and for evaluating the effect of experience, the pruritus intensity score for each treatment at each time point was subtracted from the corresponding baseline score for each volunteer. This produced a difference from baseline for each treatment (Appendices 4-6). A paired t-test was computed to test the following one-tailed null hypothesis: mean difference from baseline with active drug was less than or equal to mean difference from baseline with placebo. Rejection of this hypothesis indicates that the active drug significantly lowered the pruritus score more than the placebo ($p \leq 0.05$).

RESULTS

The intensity of the pruritus induced by hair of rose hips impregnated with histamine remained relatively constant for at least 20 minutes. The mean pruritic score at baseline for the placebo sites for all 85 volunteers was 33.7 units. The values for placebo responses progressively declined from baseline over the first 15 minutes of the testing period (Table 3). The pruritic response at 15 and 20 minutes was 81% of baseline at the sites treated with placebo.

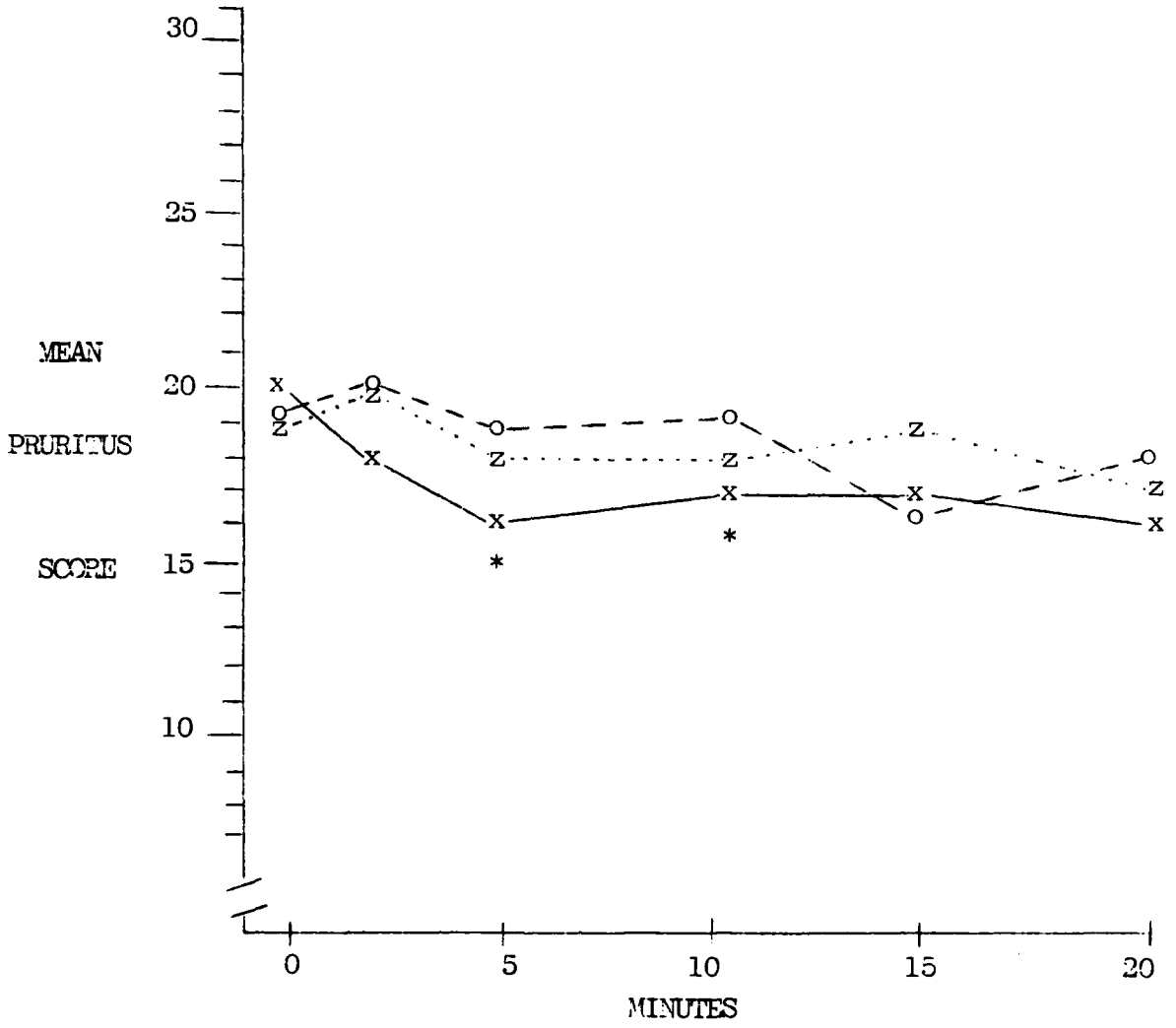
TABLE 3: Mean Pruritus Scores at Sites Treated With Placebo For All Volunteers (n=85)

	Mean Pruritus Score	Percent of Baseline
Baseline	33.7	100
2 minutes	31.2	93
5 minutes	30.3	90
10 minutes	28.4	84
15 minutes	27.4	81
20 minutes	27.2	81

Experiment 1

In experiment 1, hydrocortisone (0.5%) plus chlorcyclizine (2%) cream, hydrocortisone (0.5%) cream and placebo cream were compared using three sites on each forearm of 21 volunteers. Figure 1 shows that hydrocortisone plus chlorcyclizine significantly reduced pruritus scores as compared with placebo at 5 and 10 minutes ($p<0.017$). Hydrocortisone plus chlorcyclizine also had lower, but not significant, pruritus scores than hydrocortisone alone at all time points.

FIGURE 1: MEAN PRURITUS SCORES FOR EXPERIMENT 1



LEGEND: x——x - Hydrocortisone plus Chlorcyclizine
z·····z - Hydrocortisone
o– – –o - Placebo

All standard deviations for Hydrocortisone plus Chlorcyclizine, Hydrocortisone, and Placebo varied from 19 to 21 (n=21 for each time point).

*$p < 0.017$ for Hydrocortisone plus Chlorcyclizine vs Placebo

Experiment 2

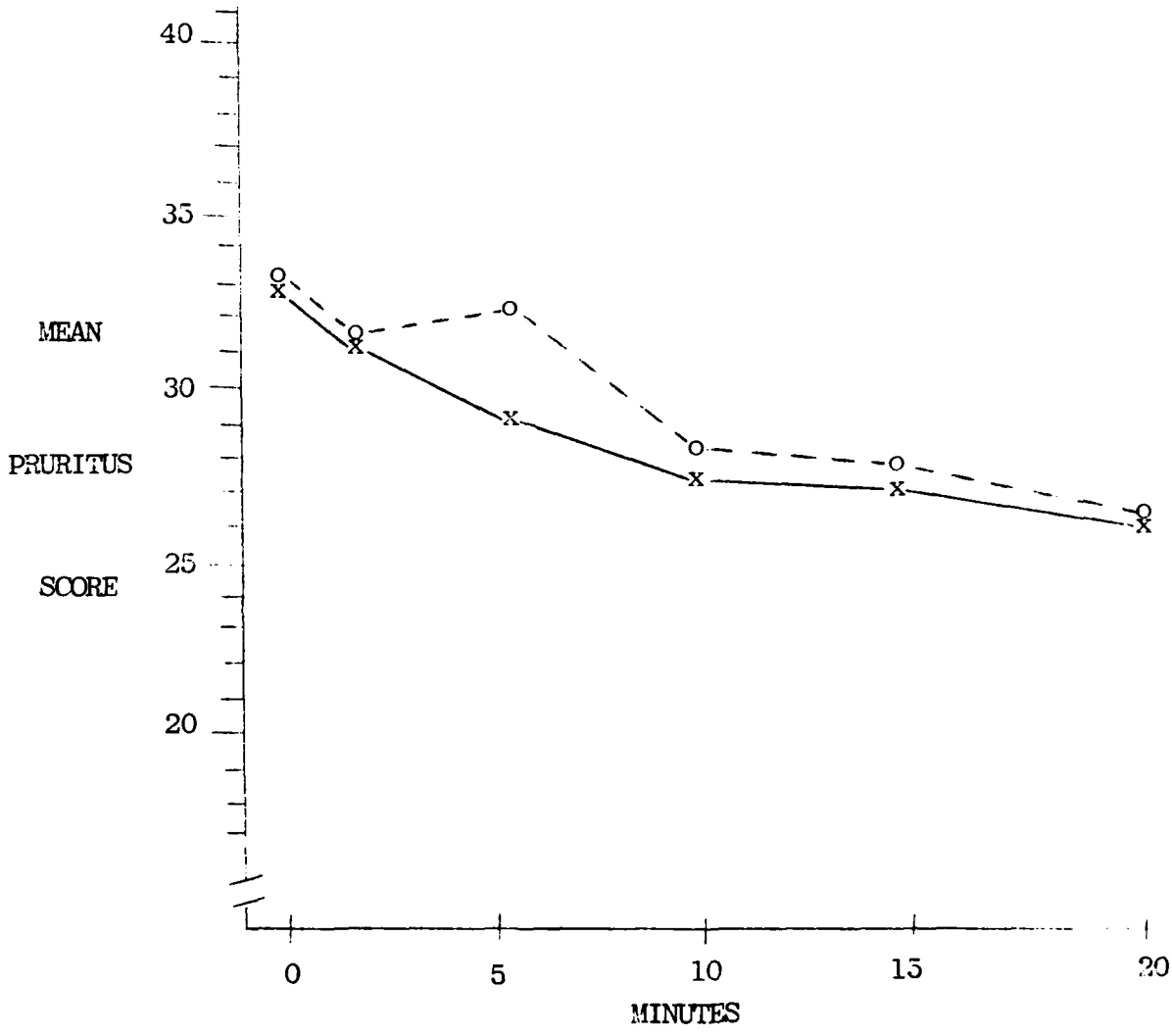
Experiment 2 consisted of comparing hydrocortisone (0.5%) plus chlorcyclizine (2%) cream with placebo cream which were applied at two sites on each forearm of 20 volunteers. The mean pruritus scores for hydrocortisone plus chlorcyclizine were lower than the scores for placebo at 5 and 10 minutes, but there was no significant difference between hydrocortisone plus chlorcyclizine and placebo at any of the time points (Figure 2).

Experiment 3

In experiment 3, dibucaine (1%) ointment and placebo ointment were applied at two sites on each forearm of 20 volunteers. Eleven volunteers were naive to the study and nine volunteers had participated in either experiment 1 or 2. The pooled data for both experienced and non-experienced volunteers showed dibucaine to have statistically significant ($p<=0.05$) lower pruritus scores than placebo at 5 and 10 minutes (Figure 3). The data was analyzed to test whether experienced volunteers were better able to detect a difference between the two study drug treatments than could nonexperienced volunteers. Figure 4 shows the mean pruritus scores for both the experienced and nonexperienced volunteers. Experienced volunteers had statistically significant lower pruritus scores for dibucaine than for placebo at 5, 10, 15 and 20 minutes ($p<=0.05$). There were no significant differences for nonexperienced volunteers. Mean baseline pruritus scores for experienced volunteers were significantly higher ($p<=0.05$) for their second test as compared to their first test at all sites on the forearms.

Volunteers in experiment 3 were asked the question, "If you had

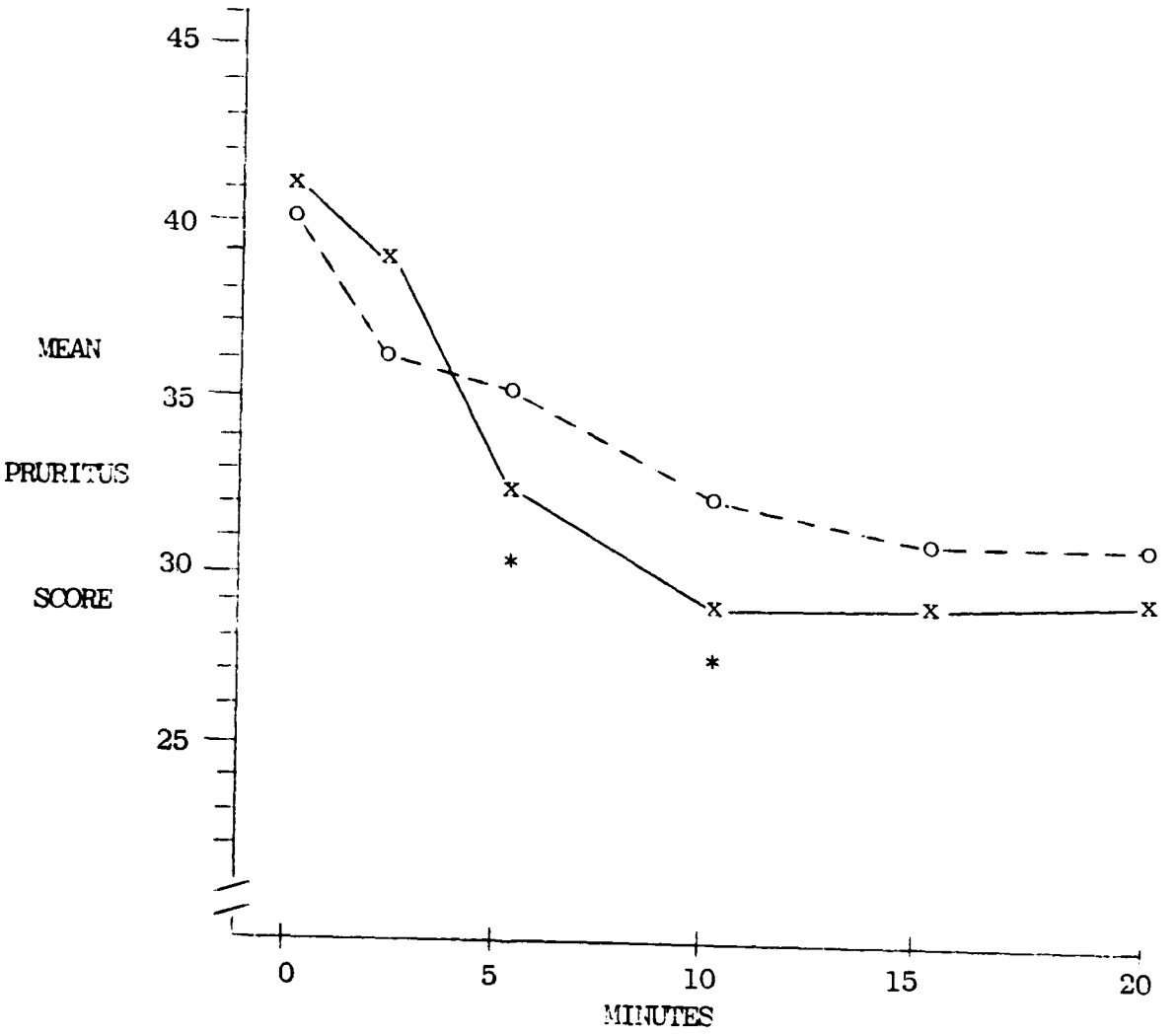
FIGURE 2: MEAN PRURITUS SCORES FOR EXPERIMENT 2



LEGEND: x——x - Hydrocortisone plus Chlorcyclizine
o— —o - Placebo

All standard deviations for Hydrocortisone plus Chlorcyclizine and Placebo varied from 15 to 20 (n=20 for each time point).

FIGURE 3: MEAN PRURITUS SCORES FOR EXPERIMENT 3

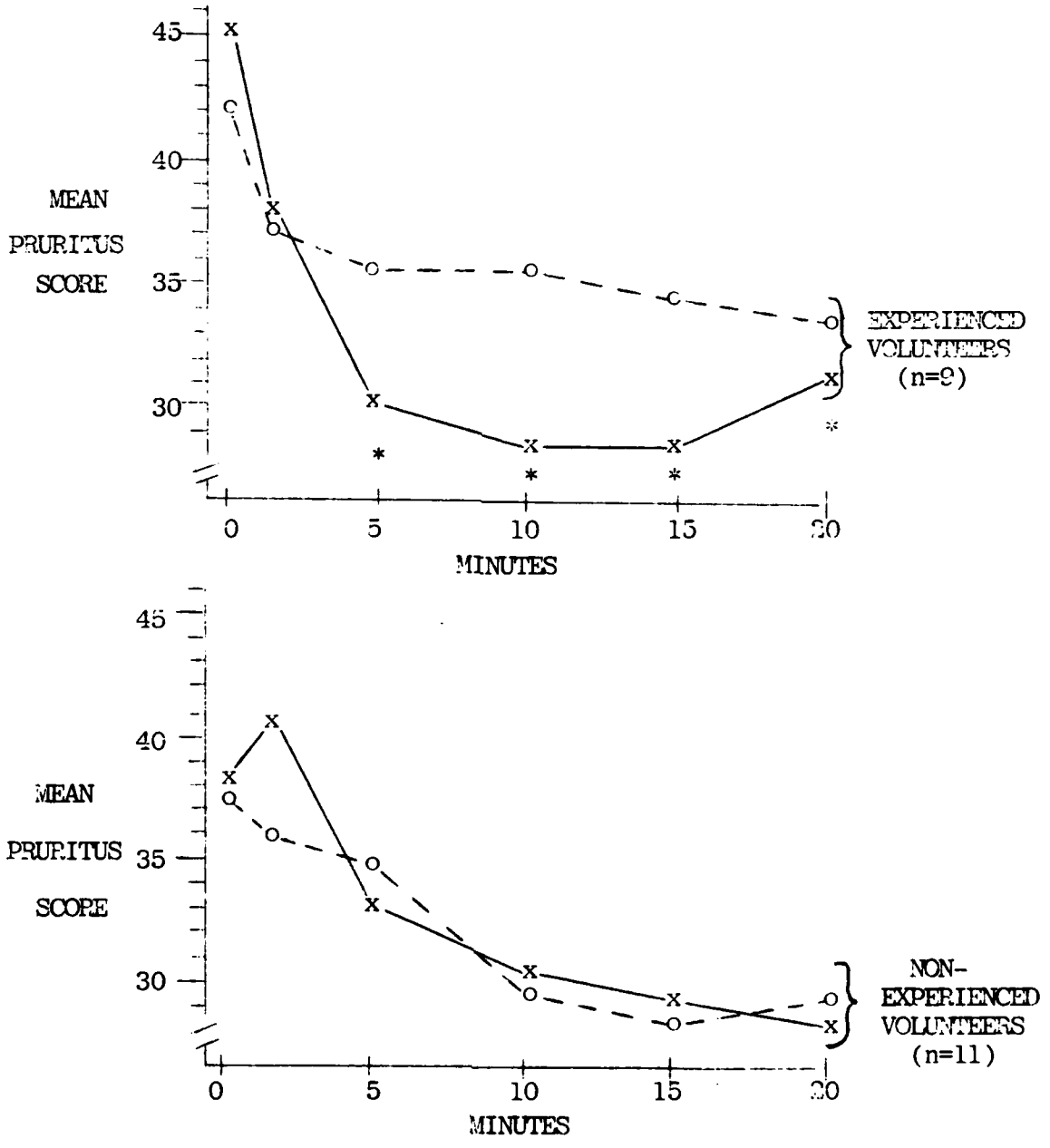


LEGEND: x——x - Dibucaine
o- - -o - Placebo

All standard deviations for Dibucaine and Placebo varied from 12 to 17 (n=20 for each time point).

*p<=0.05

FIGURE 4: MEAN PRURITUS SCORES OF EXPERIENCED AND NONEXPERIENCED VOLUNTEERS FOR EXPERIMENT 3



LEGEND: x——x - Dibucaine
o- - -o - Placebo

All standard deviations for Dibucaine and Placebo varied from 10.8 to 18.4.

*p<=0.05

to use one of these creams for this type of pruritus for the rest of the day, which one would you choose?" Ten volunteers preferred dibucaine, six preferred placebo, and four had no preference. Of those with a preference, 62.5% preferred dibucaine (not significantly different from 50%). Of the nine experienced volunteers, six preferred dibucaine, two preferred placebo and one had no preference. Of those with a preference, 75% preferred dibucaine (not significantly different from 50%).

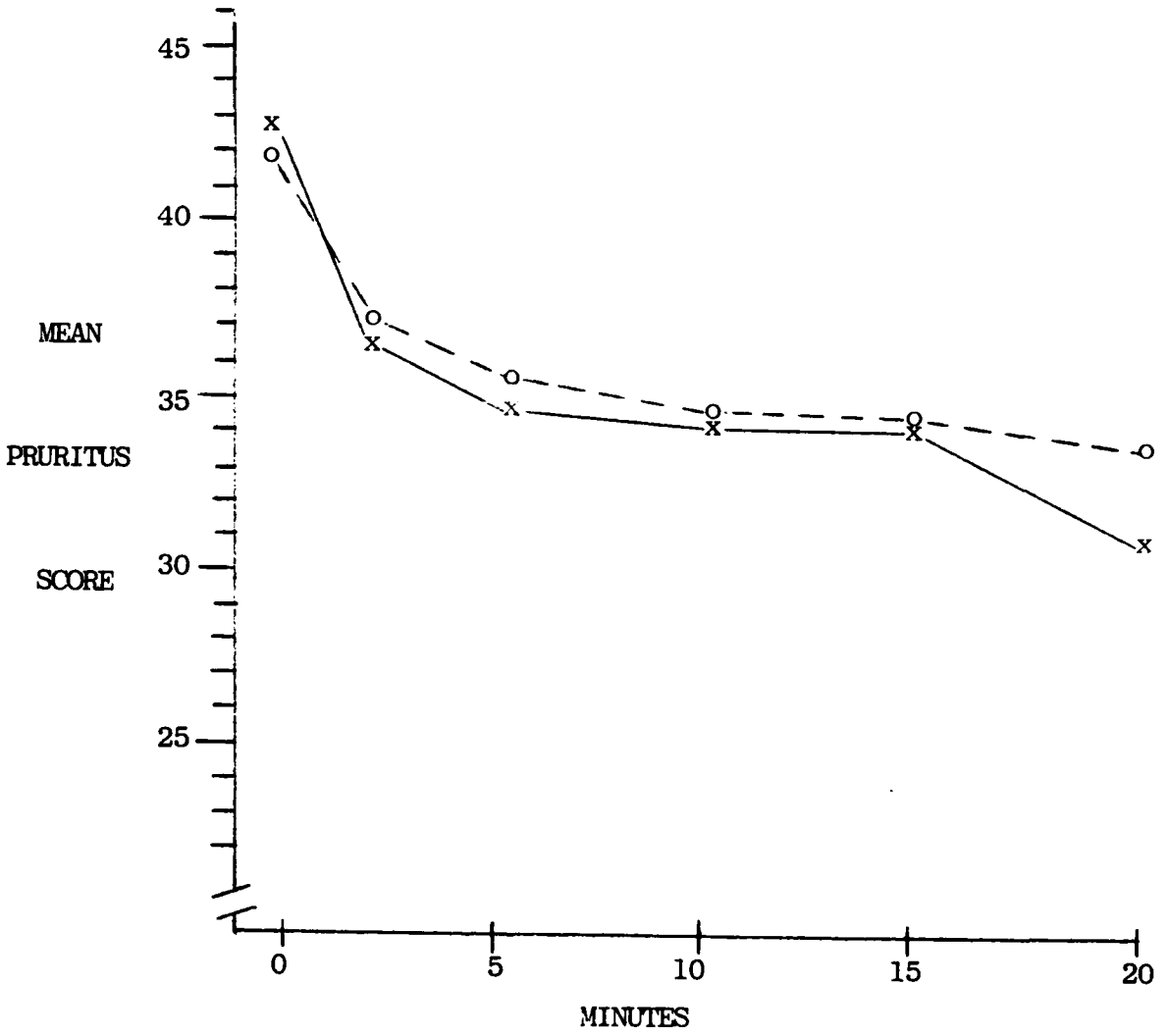
Volunteers were also asked if they were right-handed or left-handed. Baseline scores for both proximal and distal sites were higher for the dominant arm than nondominant arm. The scores were higher for the distal site than the proximal site on each arm, but none of these differences were significant (Appendix 7).

Experiment 4

Calamine lotion and placebo lotion were applied at two sites on each forearm of 24 volunteers. Experiment 4 included an equal number of experienced and nonexperienced volunteers (n=12 for each).

Experienced volunteers included only those who had participated in one previous experiment. The pooled pruritus score data for all volunteers in experiment 4 showed no significant differences between the pruritus scores for calamine lotion and its placebo lotion at any time point (Figure 5). The data for experienced volunteers showed statistically significant lower pruritus scores for calamine lotion compared with placebo lotion at 2, 10, 15 and 20 minutes ($p \leq 0.05$). The data for nonexperienced volunteers showed no significant differences at any time point (Figure 5). There were no significant differences in mean baseline pruritus scores for the experienced volunteers between

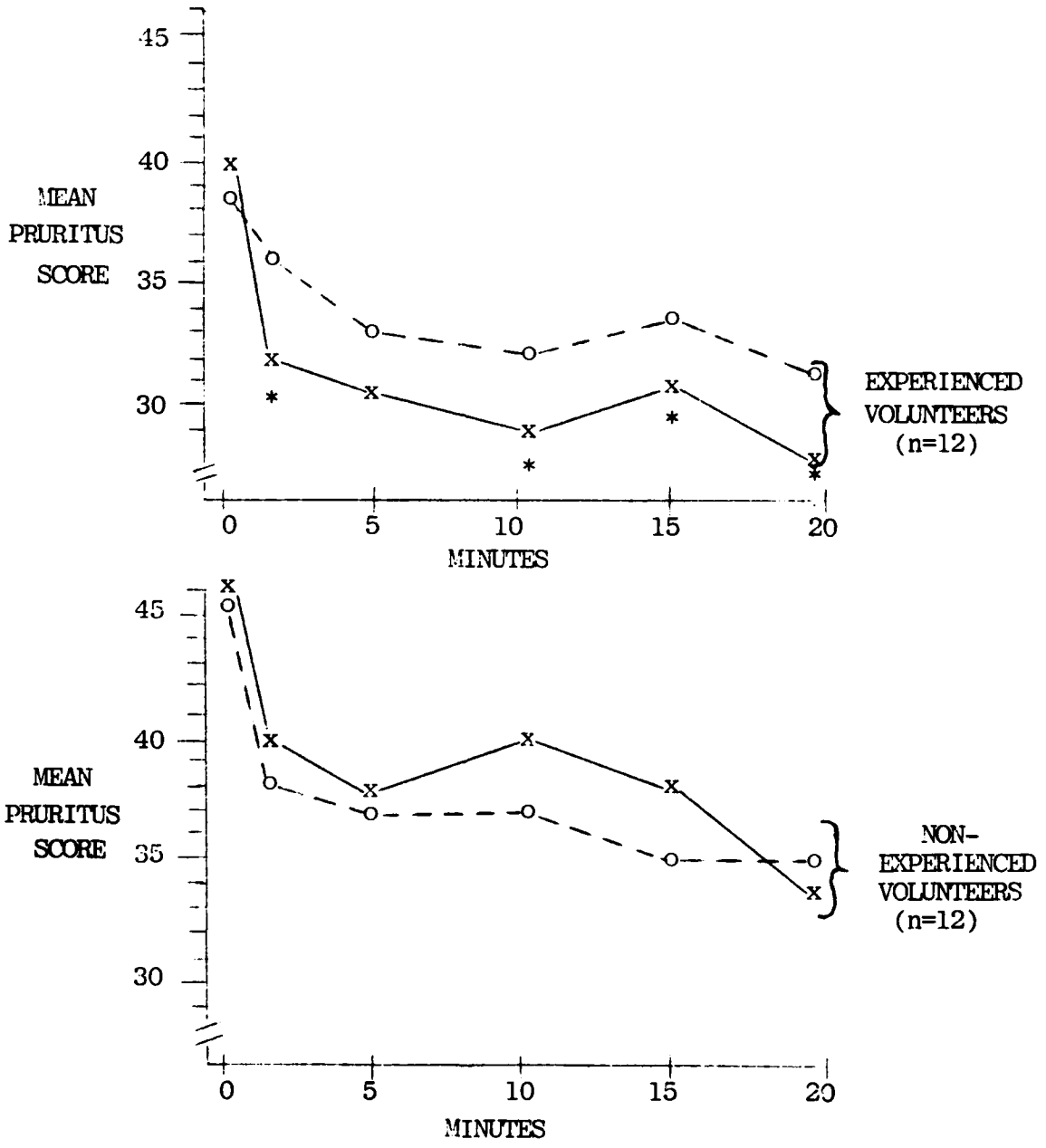
FIGURE 5: MEAN PRURITUS SCORES FOR EXPERIMENT 4



LEGEND: x——x - Calamine
o- - -o - Placebo

All standard deviations for Calamine and Placebo varied from 14 to 20 (n=24 for each time point).

FIGURE 6: MEAN PRURITUS SCORES OF EXPERIENCED AND NONEXPERIENCED VOLUNTEERS FOR EXPERIMENT 4



LEGEND: x——x - Calamine
o- - -o - Placebo

All standard deviations for Calamine and Placebo varied from 13.3 to 23.1.

*p<=0.05

their first and second tests, but the mean score was higher for the second test at both proximal and distal sites.

Volunteers in experiment 4 were asked for their treatment preference and whether they were right-handed or left-handed. Eleven volunteers preferred calamine lotion, eight preferred placebo lotion, and five had no preference. Of those with a preference, 57.9% preferred calamine (not significantly different from 50%). For the twelve experienced volunteers, six preferred calamine, three preferred placebo, and three had no preference. Of those with a preference, 66.7% preferred calamine (not significantly different from 50%). Baseline scores were higher, but not statistically significantly higher, for the distal site than for the proximal site. There was almost no difference in baseline scores between the dominant and nondominant arms (Appendix 7).

Adverse Reactions

Four volunteers experienced mild adverse reactions to the procedure: (1) Rash accompanied by pruritus for five days; (2) erythema at all testing sites without pruritus for four days after the second test; (3) sinus congestion for approximately 4-1/2 hours, however, this effect did not occur on rechallenge; and (4) wheal and erythema with extreme pruritus for three hours.

DISCUSSION

There is no satisfactory methodology at present for accurately and reproducibly testing topical antipruritics in a rapid manner. All methods utilized have significant drawbacks. The objective of this study was to develop a methodology that met most of the criteria established for an ideal methodology (see Introduction), and to validate this methodology with commonly used topical antipruritic drugs.

Pruritus is believed to be a modified form of pain mediated by unmyelinated C fibers.[4, 10] Stimuli that are insufficient in intensity to produce pain may cause pruritus. Shelley and Arthur noted that the relationship of pruritus and burning pain is one of degree.[4] Pruritus may be induced through mechanical, electrical, or chemical stimulations, or by a combination of these as described in the Introduction. The proposed methodology utilizing histamine-impregnated hair of rose hips is based on a combination of mechanical and chemical stimulation.

Initially, the study was designed to test two active drugs and a placebo on each forearm (i.e., three sites per forearm), and experiment 1 was conducted in this manner. It was often difficult, however, for volunteers to distinguish which of the three sites caused the pruritus when one of the treated sites on the forearm was stroked, or when the forearm was moved during the test. This problem was due to the relatively close proximity of the three sites to each other. Thus, volunteers were instructed not to move their arms, and to rate only the pruritus felt at the time the cloth was stroked. This restriction of arm movement may have been responsible for the lower mean pruritus scores observed in

experiment 1 than in the other experiments. It has been reported that there is a difference in sensitivity to stimuli between the dominant and nondominant arms[1], thus, testing only one site per forearm was considered not as desirable as testing two sites per forearm. In experiments 2, 3 and 4, two sites were used per forearm. A rotating motion of the forearm was also incorporated into the protocol to increase the intensity of the pruritic response.

The data from experiments 3 and 4 indicate that volunteer experience is an important factor in the results obtained in this test. Figures 4 and 6 show significant differences between mean pruritus scores for active drug versus placebo in both experiments conducted with experienced volunteers as compared with identical experiments conducted with non-experienced volunteers. The reason for this difference between experienced and nonexperienced volunteers may be due to a better understanding and awareness of the methodology used, to a sensitizing effect of the testing material, or to a combination of both factors. Volunteer participation was limited to a total of two experiments separated by at least one week (wash-out period between experiments ranged between 10 and 41 days). It is not possible at this time to determine the presence or degree of the sensitizing effect. It is believed that a "training effect" increased the awareness of volunteers to enable them to be able to detect a difference between active and placebo drugs. Experienced volunteers had higher mean baseline pruritus scores in their second experiment than in their first. This is most likely due to a better understanding of the methodology used.

The pooled data for all volunteers from experiments 3 and 4 does not adequately validate this methodology because values at only two of

the ten time points tested were significant. A significant difference was noted, however, at eight of the ten time points tested in experienced volunteers. Thus, the results of experiments 3 and 4 validate this methodology with experienced volunteers but not with nonexperienced volunteers.

The proposed methodology generally meets most of the criteria of an ideal methodology proposed in the Introduction.

(1) Rapid onset - Pruritus occurred within two minutes of the application of the test material.

(2) Moderate intensity - Commonly used topical antipruritic drugs were able to significantly reduce the intensity of pruritus in several experiments.

(3) Adequate duration of pruritus - Eighty-one percent of the baseline pruritus persisted for 20 minutes permitting topical drugs to be evaluated.

(4) Analogous to clinically observed conditions - This model is not entirely satisfactory since many clinical conditions cause a pruritus that is more intense and of longer duration than that caused by this model.

(5) Reproducibility of effect - A similar degree of pruritus was demonstrated between volunteers in four separate experiments and within volunteers who participated in two separate experiments.

(6) Validity demonstrated with standard drugs - Dibucaine ointment and calamine lotion were both more active than placebo when the tests were performed with experienced volunteers.

(7) Simple to perform - The tests described in this report required up to 45 minutes per volunteer to complete.

(8) Amenable to further research - The proposed methodology is applicable for further research studies with easily trained volunteers.

(9) Quantifiable data - the rating system used provided easily obtained data that could be analyzed statistically.

(10) Suitable for double-blind clinical trials - The proposed methodology was performed in a double-blind manner.

The limitations of this methodology concern the need for experienced volunteers, the duration of the antipruritic effect observed, and the similarity to clinically observed conditions. Whether the effect observed that was attributed to "experience" with the methodology would also be observed in a third, fourth, or additional study is not known. It is not possible to test the duration of action of topical antipruritic drugs with this methodology.

The novel methodology described was developed for testing topical antipruritic drugs. This methodology has been validated with two commonly used topical antipruritics in experienced volunteers, and may be used to test the efficacy of new topical antipruritic drugs.

REFERENCES

1. Murray FS and Weaver MM. Effects of ipsilateral and contralateral counterirritation on experimentally produced itch in human beings. Journal of Comparative and Physiological Psychology 1975;89(7): 819-826.

2. Keele CA and Armstrong D. Substances producing pain and itch. London: Edward Arnold LTD, 1964.

3. Wendt H and Frosch PJ. Poison Ivy Test. In: Clinico-pharmacological models for the assay of topical corticoids. Basel: S. Karger, 1982.

4. Shelley WB and Arthur RP. The neurohistology and neurophysiology of the itch sensation in man. AMA Archives of Dermatology 1957;76: 296-323.

5. Edwards AE, Shellow WVR, Wright ET, and Dignam TF. Pruritic skin disease, psychological stress, and the itch sensation. Archives of Dermatology 1976;112:339-343.

6. Broadbent JL. Observations on itching produced by cowhage, and on the part played by histamine as a mediator of the itch sensation. British Journal of Pharmacology 1953;8:263-270.

7. Graham DT, Goodell H, and Wolff HG. Neural mechanisms involved in itch, "itchy skin", and tickle sensations. Journal of Clinical Investigations 1951;30:37-49.

8. Shelley WB and Arthur RP. Studies on cowhage (mucuna pruriens) and its pruritogenic proteinase, mucunain. AMA Archives of Dermatology 1955;72:399-406.

9. Colton T. Statistics in medicine. Boston: Little, Brown and Company, 1974.

10. Cormia FE and Kuykendall V. Experimental histamine pruritus II. Nature; Physical and environmental factors influencing development and severity. Journal of Investigative Dermatology 1953;20:429-446.

APPENDIX 1

BURROUGHS WELLCOME CO.

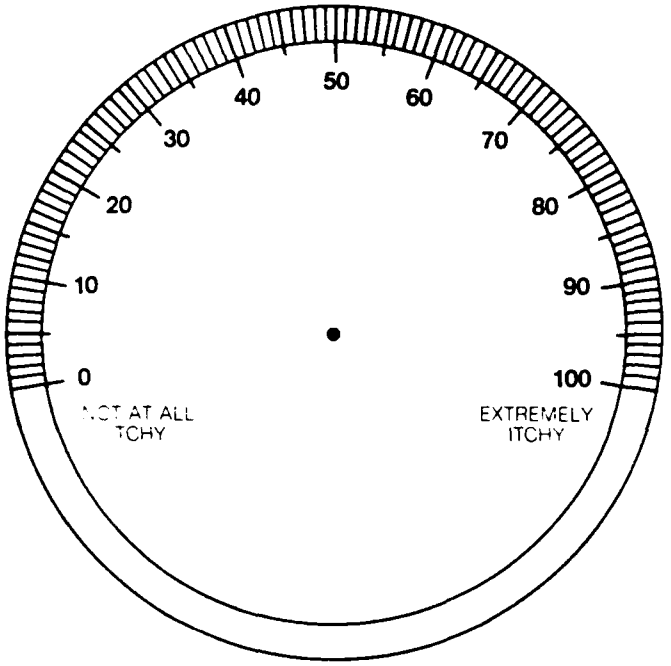
COMPARISON OF TOPICAL EFFECTS OF MANTADIL, WELLCORTIN AND PLACEBO

MINUTE: Control ARM: Left

USE BLACK INK

Q-13	MANTADIL
Protocol No. 02	Study No. 01
Section RESP	Dept. CR

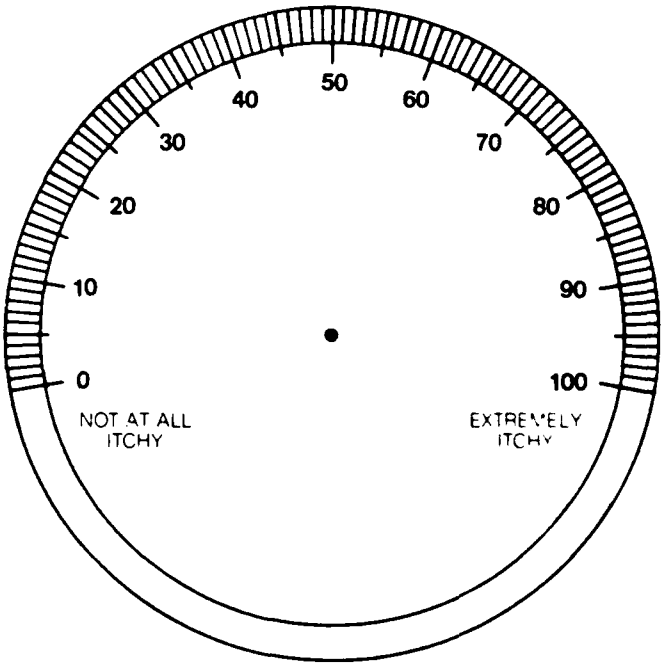
VOLUNTEER'S INITIALS __/__/__ (F M L) | VOLUNTEER'S NO. _____ | DATE __/__/__ (M D Y)



CREAM A

SITE _____

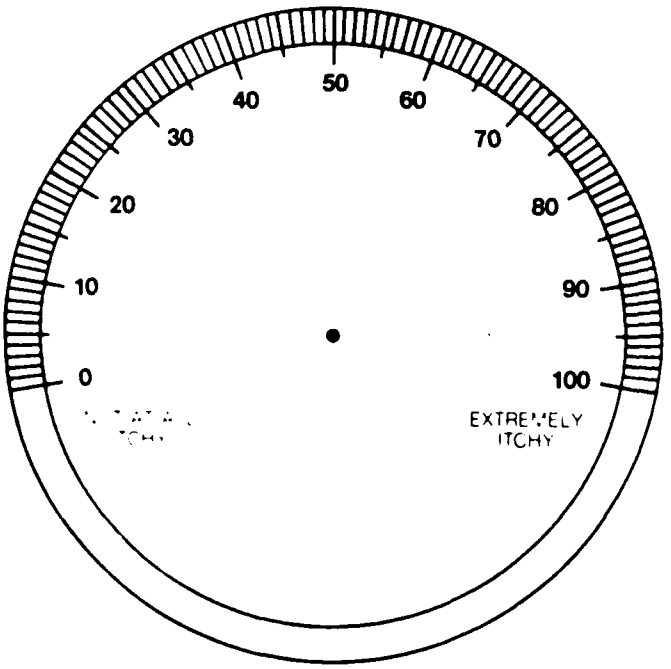
ITCH SCORE_____



CREAM B

SITE _____

ITCH SCORE_____



CREAM C

SITE _____

ITCH SCORE_____

_____

Investigator's Initials

APPENDIX 2

"INFORMED CONSENT"

COMPARISON OF TOPICAL DIBUCAINE AND PLACEBO

This study involves research to evaluate the anti-irritation and anti-itching properties of topically applied dibucaine ointment compared with a placebo ointment. Your participation in this study will be completed today.

The procedure to be used in this experiment is as follows: Dried histamine-impregnated hair of rose hips powder will be placed on the skin at two different sites on each forearm (a total of four sites), rubbed in for 10 seconds and covered with a cloth. After two minutes, a test to measure the itching at each site will be conducted. The cloth will then be removed, the powder on the skin wiped off, one of the two ointments applied and rubbed in, and the cloth replaced. The same test, consisting of a 2 second finger rub of each site, rotating the arm and recording the sensation of itch and/or irritation, will be done 2, 5, 10, 15 and 20 minutes after the ointments are applied.

Risks or discomforts you may experience in this study include: extremely rare hypersensitivity reaction to the dibucaine, the dibucaine base, or the hair of rose hips; local irritation, a pricking sensation, and itching due to the penetration of the hair of rose hips into the skin. The irritation and itching should not last for more than 30 minutes after the completion of the test.

The confidentiality of records identifying the subject will be maintained within the Burroughs Wellcome Co., with the possible exception that the Food and Drug Administration may inspect the records.

Questions regarding this study should be directed to the investigators; Bert Spilker, M.D., Ph.D. or Ray Wilkins, B.S.

Participation in this study is voluntary and refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled. Furthermore, the subject may discontinue participation at any time without penalty.

I, _____, have read and I understand the preceding
(print name)
statements. I agree to become a subject in this study fully aware of the procedures and risks involved.

_____ _____
Subject's Signature Date

Appendix 2

"INFORMED CONSENT" (Cont'd)

I have explained and defined in detail the research procedures in which the subject has consented to participate.

_____ _____

Investigator Date

APPENDIX 3

TABLE 4: Pruritus Score Summary Statistics for Experiment 1.

	Minute					
	0	2	5	10	15	20
Mantadil						
n	21	21	21	21	21	21
Mean Pruritus Score	20	18	16	17	17	16
S.D.	20	19	20	20	20	21
Minimum Pruritus Score	2	2	2	0	0	0
Maximum Pruritus Score	39	85	89	86	86	88
Hydrocortisone						
n	21	21	21	21	21	21
Mean Pruritus Score	19	20	18	18	19	17
S.D.	19	20	20	20	20	20
Minimum Pruritus Score	2	0	0	0	0	0
Maximum Pruritus Score	90	90	90	92	90	89
Placebo						
n	21	21	21	21	21	21
Mean Pruritus Score	19	20	19	19	16	18
S.D.	19	20	19	20	19	20
Minimum Pruritus Score	0	1	1	2	2	0
Maximum Pruritus Score	90	90	85	87	88	86

APPENDIX 3

Pruritus Score Data for Experiment 1

VOL. #	SITE		TREATMENT	MINUTE	PRURITUS SCORE	
	LEFT ARM	RIGHT ARM			L	R
1	MIDDLE	PROXIMAL	MANTADIL	0	9	14
				2	8	9
				5	2	12
				10	6	3
				15	5	8
				20	4	5
	DISTAL	MIDDLE	PLACEBO	0	8	0
				2	4	3
				5	8	4
				10	7	4
				15	7	5
				20	6	3
	PROXIMAL	DISTAL	HYDROCORTISONE	0	4	20
				2	4	13
				5	7	21
				10	5	23
				15	8	13
				20	8	14
2	DISTAL	DISTAL	MANTADIL	0	25	40
				2	7	8
				5	15	22
				10	17	14
				15	11	20
				20	23	25
	MIDDLE	PROXIMAL	PLACEBO	0	10	10
				2	6	6
				5	10	5
				10	10	10
				15	10	10
				20	11	8
	PROXIMAL	MIDDLE	HYDROCORTISONE	0	10	20
				2	6	20
				5	8	6
				10	7	8
				15	8	10
				20	10	9

Appendix 3

Pruritus Score Data for Experiment 1 (Cont'd)

VOL. #	SITE		TREATMENT	MINUTE	PRURITUS SCORE	
	LEFT ARM	RIGHT ARM			L	R
3	DISTAL	PROXIMAL	MANTADIL	0	9	5
				2	5	5
				5	2	10
				10	1	2
				15	1	18
				20	2	3
	MIDDLE	MIDDLE	PLACEBO	0	15	10
				2	15	15
				5	7	4
				10	15	3
				15	11	2
				20	11	9
	PROXIMAL	DISTAL	HYDROCORTISONE	0	10	20
				2	10	1
				5	10	2
				10	5	1
				15	12	3
				20	8	5
4	DISTAL	MIDDLE	MANTADIL	0	15	20
				2	27	30
				5	30	25
				10	27	27
				15	20	20
				20	20	22
	MIDDLE	DISTAL	PLACEBO	0	26	15
				2	30	25
				5	27	30
				10	30	27
				15	20	25
				20	20	25
	PROXIMAL	PROXIMAL	HYDROCORTISONE	0	15	15
				2	27	30
				5	30	27
				10	25	20
				15	25	15
				20	20	22

Appendix 3

Pruritus Score Data for Experiment 1 (Cont'd)

VOL. #	SITE		TREATMENT	MINUTE	PRURITUS SCORE	
	LEFT ARM	RIGHT ARM			L	R
5	PROXIMAL	PROXIMAL	MANTADIL	0	0	9
				2	10	20
				5	2	2
				10	0	5
				15	4	7
				20	0	5
	MIDDLE	MIDDLE	PLACEBO	0	0	21
				2	4	3
				5	0	5
				10	7	15
				15	4	0
				20	0	0
	DISTAL	DISTAL	HYDROCORTISONE	0	5	10
				2	0	0
				5	0	0
				10	0	0
				15	0	7
				20	0	0
6	DISTAL	PROXIMAL	MANTADIL	0	4	0
				2	3	0
				5	4	1
				10	5	0
				15	4	3
				20	4	5
	MIDDLE	DISTAL	PLACEBO	0	1	1
				2	1	1
				5	1	2
				10	4	3
				15	2	3
				20	1	2
	PROXIMAL	MIDDLE	HYDROCORTISONE	0	0	3
				2	1	1
				5	1	0
				10	2	0
				15	0	0
				20	1	0

Appendix 3

Pruritus Score Data for Experiment 1 (Cont'd)

VOL. #	SITE		TREATMENT	MINUTE	PRURITUS SCORE	
	LEFT ARM	RIGHT ARM			L	R
7	DISTAL	DISTAL	MANTADIL	0	15	18
				2	7	14
				5	3	7
				10	3	5
				15	6	14
				20	3	6
	PROXIMAL	MIDDLE	PLACEBO	0	14	16
				2	18	10
				5	10	13
				10	16	18
				15	13	7
				20	13	7
	MIDDLE	PROXIMAL	HYDROCORTISONE	0	17	14
				2	23	18
				5	7	15
				10	20	16
				15	15	16
				20	4	11
8	DISTAL	DISTAL	MANTADIL	0	87	90
				2	80	90
				5	85	92
				10	82	90
				15	80	92
				20	82	93
	PROXIMAL	PROXIMAL	PLACEBO	0	90	90
				2	90	90
				5	85	85
				10	87	87
				15	86	90
				20	85	87
	MIDDLE	MIDDLE	HYDROCORTISONE	0	90	90
				2	90	90
				5	90	90
				10	92	92
				15	90	90
				20	88	90

Appendix 3

Pruritus Score Data for Experiment 1 (Cont'd)

VOL. #	SITE		TREATMENT	MINUTE	PRURITUS SCORE	
	LEFT ARM	RIGHT ARM			L	R
9	MIDDLE	MIDDLE	MANTADIL	0	5	10
				2	7	2
				5	7	8
				10	5	10
				15	5	8
				20	5	7
	PROXIMAL	DISTAL	PLACEBO	0	5	6
				2	5	7
				5	5	10
				10	2	7
				15	5	7
				20	2	5
	DISTAL	PROXIMAL	HYDROCORTISONE	0	15	10
				2	7	5
				5	7	12
				10	5	7
				15	7	10
				20	7	5
10	MIDDLE	DISTAL	MANTADIL	0	0	3
				2	0	5
				5	2	2
				10	0	2
				15	0	3
				20	1	2
	PROXIMAL	PROXIMAL	PLACEBO	0	0	0
				2	1	1
				5	0	1
				10	1	2
				15	2	2
				20	3	3
	DISTAL	MIDDLE	HYDROCORTISONE	0	0	3
				2	0	1
				5	0	0
				10	0	1
				15	0	1
				20	2	1

Appendix 3

Pruritus Score Data for Experiment 1 (Cont'd)

VOL. #	SITE		TREATMENT	MINUTE	PRURITUS SCORE	
	LEFT ARM	RIGHT ARM			L	R
11	DISTAL	MIDDLE	MANTADIL	0	15	25
				2	10	5
				5	5	10
				10	0	20
				15	5	5
				20	5	5
	MIDDLE	DISTAL	PLACEBO	0	25	20
				2	20	20
				5	21	25
				10	30	20
				15	15	25
				20	30	20
	PROXIMAL	PROXIMAL	HYDROCORTISONE	0	25	30
				2	30	30
				5	25	25
				10	30	30
				15	25	35
				20	31	34
12	MIDDLE	DISTAL	MANTADIL	0	30	40
				2	40	20
				5	29	30
				10	45	45
				15	50	35
				20	60	30
	PROXIMAL	MIDDLE	PLACEBO	0	29	34
				2	20	30
				5	30	30
				10	45	35
				15	35	35
				20	45	35
	DISTAL	PROXIMAL	HYDROCORTISONE	0	21	30
				2	15	25
				5	19	40
				10	15	35
				15	40	40
				20	20	50

Appendix 3

Pruritus Score Data for Experiment 1 (Cont'd)

VOL. #	SITE		TREATMENT	MINUTE	PRURITUS SCORE	
	LEFT ARM	RIGHT ARM			L	R
13	DISTAL	DISTAL	MANTADIL	0	0	20
				2	0	15
				5	0	5
				10	0	0
				15	0	0
				20	0	0
	PROXIMAL	PROXIMAL	PLACEBO	0	5	10
				2	40	20
				5	35	40
				10	9	4
				15	10	5
				20	5	5
	MIDDLE	MIDDLE	HYDROCORTISONE	0	31	20
				2	40	40
				5	20	20
				10	20	20
				15	21	20
				20	31	30
14	MIDDLE	PROXIMAL	MANTADIL	0	5	5
				2	2	4
				5	3	3
				10	3	1
				15	4	5
				20	2	4
	DISTAL	MIDDLE	PLACEBO	0	11	10
				2	8	7
				5	9	11
				10	9	6
				15	9	5
				20	7	6
	PROXIMAL	DISTAL	HYDROCORTISONE	0	5	7
				2	4	7
				5	2	3
				10	5	6
				15	9	7
				20	3	6

Appendix 3

Pruritus Score Data for Experiment 1 (Cont'd)

VOL. #	SITE		TREATMENT	MINUTE	PRURITUS SCORE	
	LEFT ARM	RIGHT ARM			L	R
15	MIDDLE	PROXIMAL	MANTADIL	0	1	20
				2	10	20
				5	5	25
				10	10	22
				15	7	15
				20	8	10
	DISTAL	MIDDLE	PLACEBO	0	6	17
				2	5	25
				5	10	15
				10	3	2
				15	3	7
				20	5	12
	PROXIMAL	DISTAL	HYDROCORTISONE	0	0	20
				2	5	15
				5	5	25
				10	5	22
				15	7	14
				20	5	16
16	DISTAL	DISTAL	MANTADIL	0	29	40
				2	25	36
				5	25	35
				10	20	47
				15	29	41
				20	14	39
	MIDDLE	PROXIMAL	PLACEBO	0	25	23
				2	25	25
				5	24	29
				10	33	40
				15	10	30
				20	14	35
	PROXIMAL	MIDDLE	HYDROCORTISONE	0	10	6
				2	20	14
				5	19	13
				10	10	34
				15	5	24
				20	3	10

Appendix 3

Pruritus Score Data for Experiment 1 (Cont'd)

VOL. #	SITE		TREATMENT	MINUTE	PRURITUS SCORE	
	LEFT ARM	RIGHT ARM			L	R
17	PROXIMAL	DISTAL	MANTADIL	0	5	5
				2	6	9
				5	5	7
				10	5	5
				15	5	5
				20	8	4
	MIDDLE	PROXIMAL	PLACEBO	0	5	0
				2	8	6
				5	5	6
				10	3	5
				15	4	3
				20	3	10
	DISTAL	MIDDLE	HYDROCORTISONE	0	5	7
				2	7	7
				5	4	5
				10	6	5
				15	5	4
				20	9	5
18	PROXIMAL	PROXIMAL	MANTADIL	0	15	14
				2	19	9
				5	17	9
				10	25	15
				15	23	18
				20	25	10
	MIDDLE	DISTAL	PLACEBO	0	15	29
				2	35	13
				5	26	15
				10	30	15
				15	16	14
				20	26	11
	DISTAL	MIDDLE	HYDROCORTISONE	0	10	10
				2	14	15
				5	8	10
				10	10	19
				15	8	27
				20	9	21

Appendix 3

Pruritus Score Data for Experiment 1 (Cont'd)

VOL. #	SITE		TREATMENT	MINUTE	PRURITUS SCORE	
	LEFT ARM	RIGHT ARM			L	R
19	MIDDLE	DISTAL	MANTADIL	0	40	45
				2	34	38
				5	36	35
				10	35	31
				15	40	40
				20	36	39
	PROXIMAL	PROXIMAL	PLACEBO	0	29	36
				2	35	36
				5	33	28
				10	30	25
				15	28	32
				20	32	30
	DISTAL	MIDDLE	HYDROCORTISONE	0	35	28
				2	42	42
				5	34	43
				10	39	36
				15	37	40
				20	37	39
20	DISTAL	DISTAL	MANTADIL	0	15	35
				2	20	35
				5	8	20
				10	6	16
				15	6	15
				20	5	10
	PROXIMAL	PROXIMAL	PLACEBO	0	41	30
				2	40	40
				5	36	30
				10	30	30
				15	25	30
				20	35	35
	MIDDLE	MIDDLE	HYDROCORTISONE	0	40	25
				2	30	30
				5	30	25
				10	25	20
				15	25	5
				20	10	4

Appendix 3

Pruritus Score Data for Experiment 1 (Cont'd)

VOL. #	SITE		TREATMENT	MINUTE	PRURITUS SCORE	
	LEFT ARM	RIGHT ARM			L	R
21	DISTAL	MIDDLE	MANTADIL	0	25	40
				2	30	21
				5	25	15
				10	30	15
				15	35	20
				20	34	20
	PROXIMAL	DISTAL	PLACEBO	0	25	25
				2	15	14
				5	30	15
				10	30	25
				15	15	25
				20	30	26
	MIDDLE	PROXIMAL	HYDROCORTISONE	0	30	25
				2	30	30
				5	24	20
				10	15	20
				15	30	25
				20	30	25

APPENDIX 4

TABLE 5: Pruritus Score Summary Statistics for Experiment 2.

	Minute					
	0	2	5	10	15	20
Mantadil						
n	20	20	20	20	20	20
Mean Pruritus Score	33	31	29	27	27	26
S.D.	20	19	15	17	15	15
Minimum Pruritus Score	5	4	2	2	3	3
Maximum Pruritus Score	73	71	57	62	52	56
Placebo						
n	20	20	20	20	20	20
Mean Pruritus Score	33	31	32	28	23	26
S.D.	20	19	18	16	15	15
Minimum Pruritus Score	3	0	1	0	1	1
Maximum Pruritus Score	78	66	63	56	56	54

APPENDIX 4

Pruritus Score Data for Experiment 2

VOL. #	SITE		TREATMENT	MINUTE	PRURITUS SCORE	
	LEFT ARM	RIGHT ARM			L	R
M01	DISTAL	PROXIMAL	MANTADIL	0	25	41
				2	20	35
				5	25	35
				10	30	30
				15	25	35
				20	20	34
	PROXIMAL	DISTAL	PLACEBO	0	31	30
				2	30	30
				5	35	30
				10	30	25
				15	26	25
				20	30	25
M02	PROXIMAL	DISTAL	MANTADIL	0	35	26
				2	30	25
				5	35	25
				10	29	25
				15	32	22
				20	27	22
	DISTAL	PROXIMAL	PLACEBO	0	35	30
				2	35	30
				5	35	30
				10	34	30
				15	36	30
				20	35	30
M03	DISTAL	PROXIMAL	MANTADIL	0	62	22
				2	40	22
				5	50	22
				10	31	19
				15	70	13
				20	26	15
	PROXIMAL	DISTAL	PLACEBO	0	34	50
				2	27	55
				5	40	70
				10	25	60
				15	20	60
				20	14	45

Appendix 4

Pruritus Score Data for Experiment 2 (Cont'd)

VOL. #	SITE		TREATMENT	MINUTE	PRURITUS SCORE	
	LEFT ARM	RIGHT ARM			L	R
M04	PROXIMAL	DISTAL	MANTADIL	0	30	75
				2	30	68
				5	29	55
				10	24	58
				15	22	54
				20	31	50
	DISTAL	PROXIMAL	PLACEBO	0	50	60
				2	44	57
				5	50	54
				10	51	61
				15	35	59
				20	45	51
M05	DISTAL	PROXIMAL	MANTADIL	0	20	10
				2	21	9
				5	28	20
				10	14	8
				15	15	5
				20	15	4
	PROXIMAL	DISTAL	PLACEBO	0	15	25
				2	15	27
				5	19	20
				10	11	17
				15	18	17
				20	14	19
M06	DISTAL	PROXIMAL	MANTADIL	0	20	20
				2	20	46
				5	23	27
				10	11	20
				15	10	11
				20	3	3
	PROXIMAL	DISTAL	PLACEBO	0	34	45
				2	20	20
				5	33	21
				10	30	24
				15	23	19
				20	18	15

Appendix 4

Pruritus Score Data for Experiment 2 (Cont'd)

VOL. #	SITE		TREATMENT	MINUTE	PRURITUS SCORE	
	LEFT ARM	RIGHT ARM			L	R
M07	PROXIMAL	DISTAL	MANTADIL	0	55	65
				2	51	62
				5	57	41
				10	46	50
				15	45	47
				20	47	48
	DISTAL	PROXIMAL	PLACEBO	0	61	59
				2	60	60
				5	56	54
				10	39	37
				15	35	38
				20	32	38
M08	DISTAL	PROXIMAL	MANTADIL	0	10	20
				2	3	7
				5	3	1
				10	2	1
				15	12	7
				20	5	8
	PROXIMAL	DISTAL	PLACEBO	0	15	18
				2	4	4
				5	0	5
				10	2	2
				15	0	1
				20	1	1
M09	PROXIMAL	DISTAL	MANTADIL	0	60	85
				2	61	81
				5	50	51
				10	54	69
				15	44	60
				20	42	70
	DISTAL	PROXIMAL	PLACEBO	0	86	70
				2	65	60
				5	66	60
				10	45	51
				15	65	46
				20	65	42

Appendix 4

Pruritus Score Data for Experiment 2 (Cont'd)

VOL. #	SITE		TREATMENT	MINUTE	PRURITUS SCORE	
	LEFT ARM	RIGHT ARM			L	R
M10	DISTAL	PROXIMAL	MANTADIL	0	68	70
				2	69	68
				5	56	57
				10	60	50
				15	55	40
				20	45	40
	PROXIMAL	DISTAL	PLACEBO	0	74	58
				2	65	67
				5	50	60
				10	50	50
				15	49	45
				20	45	50
M11	PROXIMAL	DISTAL	MANTADIL	0	40	40
				2	21	35
				5	23	31
				10	18	26
				15	21	31
				20	23	28
	DISTAL	PROXIMAL	PLACEBO	0	30	40
				2	20	20
				5	26	29
				10	28	29
				15	24	30
				20	25	21
M12	DISTAL	PROXIMAL	MANTADIL	0	45	9
				2	39	10
				5	37	14
				10	30	13
				15	20	9
				20	30	10
	PROXIMAL	DISTAL	PLACEBO	0	51	20
				2	29	10
				5	39	10
				10	32	8
				15	29	21
				20	20	9

Appendix 4

Pruritus Score Data for Experiment 2 (Cont'd)

VOL. #	SITE		TREATMENT	MINUTE	PRURITUS SCORE	
	LEFT ARM	RIGHT ARM			L	R
M13	PROXIMAL	DISTAL	MANTADIL	0	19	34
				2	26	38
				5	36	44
				10	26	40
				15	30	45
				20	29	45
	DISTAL	PROXIMAL	PLACEBO	0	22	19
				2	32	34
				5	22	35
				10	23	38
				15	26	36
				20	17	39
M14	DISTAL	PROXIMAL	MANTADIL	0	35	15
				2	30	15
				5	27	15
				10	19	14
				15	34	30
				20	33	33
	PROXIMAL	DISTAL	PLACEBO	0	12	25
				2	29	20
				5	20	19
				10	30	29
				15	31	31
				20	41	30
M15	DISTAL	PROXIMAL	MANTADIL	0	3	10
				2	3	5
				5	1	3
				10	6	1
				15	10	7
				20	20	8
	PROXIMAL	DISTAL	PLACEBO	0	1	11
				2	0	0
				5	1	0
				10	0	0
				15	3	2
				20	2	0

Appendix 4

Pruritus Score Data for Experiment 2 (Cont'd)

VOL. #	SITE		TREATMENT	MINUTE	PRURITUS SCORE	
	LEFT ARM	RIGHT ARM			L	R
M16	PROXIMAL	DISTAL	MANTADIL	0	10	0
				2	5	5
				5	6	0
				10	10	0
				15	5	0
				20	5	0
	DISTAL	PROXIMAL	PLACEBO	0	5	0
				2	10	4
				5	5	5
				10	0	3
				15	5	0
				20	4	4
M17	DISTAL	PROXIMAL	MANTADIL	0	30	50
				2	21	28
				5	25	31
				10	20	34
				15	20	25
				20	20	24
	PROXIMAL	DISTAL	PLACEBO	0	40	30
				2	20	30
				5	29	41
				10	31	14
				15	19	25
				20	19	15
M18	PROXIMAL	DISTAL	MANTADIL	0	40	49
				2	30	41
				5	26	30
				10	23	30
				15	26	39
				20	36	18
	DISTAL	PROXIMAL	PLACEBO	0	50	31
				2	39	26
				5	39	21
				10	35	26
				15	46	26
				20	40	20

Appendix 4

Pruritus Score Data for Experiment 2 (Cont'd)

VOL. #	SITE		TREATMENT	MINUTE	PRURITUS SCORE	
	LEFT ARM	RIGHT ARM			L	R
M19	PROXIMAL	DISTAL	MANTADIL	0	0	9
				2	16	21
				5	28	25
				10	19	20
				15	22	20
				20	20	23
	DISTAL	PROXIMAL	PLACEBO	0	10	0
				2	10	26
				5	19	31
				10	16	25
				15	14	23
				20	20	25
M20	PROXIMAL	DISTAL	MANTADIL	0	40	40
				2	40	37
				5	45	37
				10	47	38
				15	35	37
				20	41	35
	DISTAL	PROXIMAL	PLACEBO	0	36	20
				2	48	45
				5	45	47
				10	40	35
				15	45	32
				20	25	30

Appendix 4

Difference from Baseline for Experiment 2

MINUTE	PATIENT	MANTADIL	PLACEBO	DIFF (M-P)
2	M01	5.5	0.5	5.0
	M02	3.0	0.0	3.0
	M03	11.0	1.0	10.0
	M04	3.5	4.5	- 1.0
	M05	0.0	- 1.0	1.0
	M06	-13.0	19.5	-32.5
	M07	3.5	0.0	3.5
	M08	10.0	12.5	- 2.5
	M09	1.5	15.5	-14.0
	M10	0.5	0.0	0.5
	M11	12.0	15.0	- 3.0
	M12	2.5	16.0	-13.5
	M13	- 5.5	-12.5	7.0
	M14	2.5	- 6.0	8.5
	M15	2.5	6.0	- 3.5
	M16	0.0	- 4.5	4.5
	M17	15.5	10.0	5.5
	M18	9.0	8.0	1.0
	M19	-14.0	-13.0	- 1.0
	M20	1.5	-18.5	20.0
5	M01	3.0	- 2.0	5.0
	M02	0.5	0.0	0.5
	M03	6.0	-13.0	19.0
	M04	10.5	3.0	7.5
	M05	- 9.0	0.5	- 9.5
	M06	- 5.0	12.5	-17.5
	M07	11.0	5.0	6.0
	M08	13.0	14.0	- 1.0
	M09	22.0	15.0	7.0
	M10	12.5	11.0	1.5
	M11	13.0	7.5	5.5
	M12	1.5	11.0	- 9.5
	M13	-13.5	- 8.0	- 5.5
	M14	4.0	- 1.0	5.0
	M15	4.5	5.5	- 1.0
	M16	2.0	- 2.5	4.5
	M17	12.0	0.0	12.0
	M18	16.5	10.5	6.0
	M19	-22.0	-20.0	- 2.0
	M20	- 1.0	-18.0	17.0

Appendix 4

Difference from Baseline for Experiment 2 (Cont'd)

MINUTE	PATIENT	MANTADIL	PLACEBO	DIFF (M-P)
10	M01	3.0	3.0	0.0
	M02	3.5	0.5	3.0
	M03	17.0	- 0.5	17.5
	M04	11.5	- 1.0	12.5
	M05	4.0	6.0	- 2.0
	M06	4.5	12.5	- 8.0
	M07	12.0	22.0	-10.0
	M08	13.5	14.5	- 1.0
	M09	11.0	30.0	-19.0
	M10	14.0	16.0	- 2.0
	M11	18.0	6.5	11.5
	M12	5.5	15.5	-10.0
	M13	- 6.5	-10.0	3.5
	M14	8.5	-11.0	19.5
	M15	3.0	6.0	- 3.0
	M16	0.0	1.0	- 1.0
	M17	13.0	12.5	0.5
	M18	18.0	10.0	8.0
	M19	-15.0	-15.5	0.5
	M20	- 2.5	- 9.5	7.0
15	M01	3.0	5.0	- 2.0
	M02	3.5	- 0.5	4.0
	M03	0.5	2.0	- 1.5
	M04	14.5	8.0	6.5
	M05	5.0	2.5	2.5
	M06	9.5	18.5	- 9.0
	M07	14.0	23.5	- 9.5
	M08	5.5	16.0	-10.5
	M09	20.5	22.5	- 2.0
	M10	21.5	19.0	2.5
	M11	14.0	8.0	6.0
	M12	12.5	10.5	2.0
	M13	-11.0	-10.5	- 0.5
	M14	- 7.0	-12.5	5.5
	M15	- 2.0	3.5	- 5.5
	M16	2.5	0.0	2.5
	M17	17 5	13.0	4.5
	M18	12.0	4.5	7.5
	M19	-16.5	-13.5	- 3.0
	M20	4.0	-10.5	14.5

Appendix 4

Difference from Baseline for Experiment 2 (Cont'd)

MINUTE	PATIENT	MANTADIL	PLACEBO	DIFF (M-P)
20	M01	6.0	3.0	3.0
	M02	6.0	0.0	6.0
	M03	21.5	12.5	9.0
	M04	12.0	7.0	5.0
	M05	5.5	3.5	2.0
	M06	17.0	23.0	- 6.0
	M07	12.5	25.0	-12.5
	M08	8.5	15.5	- 7.0
	M09	16.5	24.5	- 8.0
	M10	26.5	18.5	8.0
	M11	14.5	12.0	2.5
	M12	7.0	21.0	-14.0
	M13	-10.5	- 7.5	- 3.0
	M14	- 8.0	-17.0	9.0
	M15	- 7.5	5.0	-12.5
	M16	2.5	- 1.5	4.0
	M17	18.0	18.0	0.0
	M18	17.5	10.5	7.0
	M19	-17.0	-17.5	0.5
	M20	2.0	0.5	1.5

APPENDIX 5

TABLE 6: Pruritus Score Summary Statistics for Experiment 3.

	Minute					
	0	2	5	10	15	20
Dibucaine						
n	20	20	20	20	20	20
Mean Pruritus Score	41	39	32	29	29	29
S.D.	17	15	13	13	12	14
Minimum Pruritus Score	13	16	9	10	7	9
Maximum Pruritus Score	80	70	55	53	51	60
Placebo						
n	20	20	20	20	20	20
Mean Pruritus Score	40	36	35	32	31	31
S.D.	16	13	15	14	14	14
Minimum Pruritus Score	13	13	12	11	8	6
Maximum Pruritus Score	70	58	60	67	59	53

APPENDIX 5

Pruritus Score Data for Experiment 3

VOL. #	SITE		TREATMENT	MINUTE	PRURITUS SCORE	
	LEFT ARM	RIGHT ARM			L	R
D01	DISTAL	PROXIMAL	DIBUCAINE	0	46	60
				2	47	50
				5	47	51
				10	49	48
				15	48	53
				20	47	55
	PROXIMAL	DISTAL	PLACEBO	0	50	65
				2	37	43
				5	41	40
				10	40	40
				15	42	43
				20	41	43
D02	PROXIMAL	DISTAL	DIBUCAINE	0	30	41
				2	45	45
				5	36	37
				10	39	30
				15	29	22
				20	33	37
	DISTAL	PROXIMAL	PLACEBO	0	40	30
				2	25	24
				5	18	20
				10	20	11
				15	23	19
				20	34	33
D03	DISTAL	PROXIMAL	DIBUCAINE	0	65	70
				2	65	65
				5	50	60
				10	55	50
				15	35	36
				20	17	30
	PROXIMAL	DISTAL	PLACEBO	0	50	80
				2	40	66
				5	40	69
				10	30	50
				15	30	41
				20	35	50

Appendix 5

Pruritus Score Data for Experiment 3 (Cont'd)

VOL. #	SITE		TREATMENT	MINUTE	PRURITUS SCORE	
	LEFT ARM	RIGHT ARM			L	R
D04	PROXIMAL	DISTAL	DIBUCAINE	0	30	40
				2	35	25
				5	25	20
				10	20	25
				15	20	30
				20	25	25
	DISTAL	PROXIMAL	PLACEBO	0	30	35
				2	20	40
				5	25	35
				10	25	35
				15	25	35
				20	30	35
D05	DISTAL	PROXIMAL	DIBUCAINE	0	52	37
				2	18	23
				5	11	7
				10	9	11
				15	4	9
				20	14	19
	PROXIMAL	DISTAL	PLACEBO	0	29	54
				2	17	50
				5	20	23
				10	13	19
				15	6	12
				20	4	7
D06	PROXIMAL	DISTAL	DIBUCAINE	0	69	70
				2	43	49
				5	35	50
				10	38	54
				15	31	39
				20	31	50
	DISTAL	PROXIMAL	PLACEBO	0	70	70
				2	45	50
				5	50	51
				10	45	50
				15	60	57
				20	52	51

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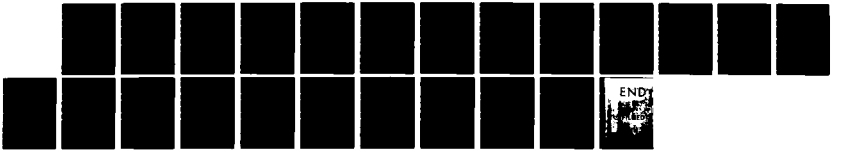
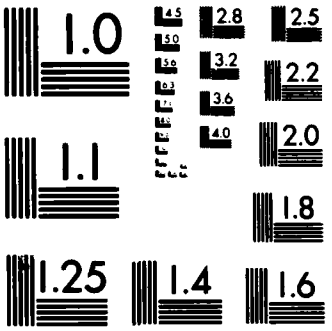
UNCLASSIFIED AFIT/CI/NR-83-52T F/G 6/15 NL





Appendix 5

Pruritus Score Data for Experiment 3 (Cont'd)

VOL. #	SITE		TREATMENT	MINUTE	PRURITUS SCORE	
	LEFT ARM	RIGHT ARM			L	R
D07	PROXIMAL	DISTAL	DIBUCAINE	0	10	21
				2	10	21
				5	10	15
				10	11	11
				15	8	12
				20	7	11
	DISTAL	PROXIMAL	PLACEBO	0	10	15
				2	16	10
				5	13	10
				10	12	10
				15	8	8
				20	10	5
D08	DISTAL	PROXIMAL	DIBUCAINE	0	36	23
				2	37	20
				5	19	22
				10	20	13
				15	33	14
				20	31	12
	PROXIMAL	DISTAL	PLACEBO	0	18	36
				2	17	29
				5	18	25
				10	17	33
				15	14	28
				20	15	29
D09	PROXIMAL	DISTAL	DIBUCAINE	0	40	60
				2	55	65
				5	40	50
				10	40	55
				15	40	60
				20	38	55
	DISTAL	PROXIMAL	PLACEBO	0	65	40
				2	65	50
				5	60	50
				10	65	35
				15	55	30
				20	55	25

Appendix 5

Pruritus Score Data for Experiment 3 (Cont'd)

VOL. #	SITE		TREATMENT	MINUTE	PRURITUS SCORE	
	LEFT ARM	RIGHT ARM			L	R
D10	DISTAL	PROXIMAL	DIBUCAINE	0	16	10
				2	31	19
				5	24	11
				10	25	9
				15	15	24
				20	20	25
	PROXIMAL	DISTAL	PLACEBO	0	15	10
				2	20	8
				5	10	18
				10	20	33
				15	15	34
				20	10	14
D11	PROXIMAL	DISTAL	DIBUCAINE	0	41	45
				2	45	25
				5	20	20
				10	15	25
				15	20	25
				20	15	10
	DISTAL	PROXIMAL	PLACEBO	0	50	39
				2	40	50
				5	26	35
				10	20	15
				15	20	20
				20	15	15
D12	DISTAL	PROXIMAL	DIBUCAINE	0	44	40
				2	44	40
				5	45	36
				10	40	29
				15	41	32
				20	35	31
	PROXIMAL	DISTAL	PLACEBO	0	35	45
				2	34	45
				5	35	41
				10	35	41
				15	33	42
				20	35	42

Appendix 5

Pruritus Score Data for Experiment 3 (Cont'd)

VOL. #	SITE		TREATMENT	MINUTE	PRURITUS SCORE	
	LEFT ARM	RIGHT ARM			L	R
D13	PROXIMAL	DISTAL	DIBUCAINE	0	80	79
				2	64	76
				5	40	47
				10	50	40
				15	46	42
				20	55	65
	DISTAL	PROXIMAL	PLACEBO	0	45	90
				2	47	50
				5	60	60
				10	65	69
				15	56	59
				20	56	49
D14	DISTAL	PROXIMAL	DIBUCAINE	0	46	40
				2	45	30
				5	41	28
				10	31	29
				15	25	30
				20	35	32
	PROXIMAL	DISTAL	PLACEBO	0	37	50
				2	25	50
				5	38	45
				10	41	44
				15	40	34
				20	39	47
D15	PROXIMAL	DISTAL	DIBUCAINE	0	43	41
				2	36	37
				5	35	35
				10	33	30
				15	38	35
				20	31	35
	DISTAL	PROXIMAL	PLACEBO	0	39	50
				2	36	42
				5	29	41
				10	29	32
				15	35	35
				20	35	30

Appendix 5

Pruritus Score Data for Experiment 3 (Cont'd)

VOL. #	SITE		TREATMENT	MINUTE	PRURITUS SCORE	
	LEFT ARM	RIGHT ARM			L	R
D16	DISTAL	PROXIMAL	DIBUCAINE	0	30	36
				2	30	29
				5	25	26
				10	21	24
				15	19	26
				20	12	14
	PROXIMAL	DISTAL	PLACEBO	0	25	30
				2	33	35
				5	30	30
				10	40	38
				15	35	30
				20	33	34
D17	PROXIMAL	DISTAL	DIBUCAINE	0	36	39
				2	33	33
				5	29	32
				10	27	31
				15	29	31
				20	33	37
	DISTAL	PROXIMAL	PLACEBO	0	35	29
				2	33	37
				5	36	32
				10	33	26
				15	30	30
				20	31	32
D18	PROXIMAL	DISTAL	DIBUCAINE	0	30	31
				2	44	39
				5	29	46
				10	30	34
				15	30	40
				20	35	40
	DISTAL	PROXIMAL	PLACEBO	0	25	35
				2	40	29
				5	40	30
				10	40	40
				15	30	29
				20	45	40

Appendix 5

Pruritus Score Data for Experiment 3 (Cont'd)

VOL. #	SITE		TREATMENT	MINUTE	PRURITUS SCORE	
	LEFT ARM	RIGHT ARM			L	R
D19	DISTAL	PROXIMAL	DIBUCAINE	0	51	20
				2	61	31
				5	50	30
				10	37	15
				15	39	21
				20	20	40
	PROXIMAL	DISTAL	PLACEBO	0	20	31
				2	51	50
				5	50	60
				10	15	29
				15	30	41
				20	20	29
D20	PROXIMAL	DISTAL	DIBUCAINE	0	25	35
				2	18	23
				5	17	13
				10	13	11
				15	12	8
				20	12	8
	DISTAL	PROXIMAL	PLACEBO	0	31	38
				2	20	18
				5	20	21
				10	20	20
				15	7	14
				20	9	20

Appendix 5

Difference from Baseline for Experiment 3

MINUTE	EXP?	PATIENT	DIBUCAINE	PLACEBO	DIFF (D-P)
2	NO	D01	4.5	17.5	-13.0
		D02	- 9.5	10.5	-20.0
		D03	2.5	12.0	- 9.5
		D07	0.0	- 0.5	0.5
		D09	-10.0	- 5.0	- 5.0
		D10	-12.0	- 1.5	-10.5
		D11	8.0	- 0.5	8.5
		D14	5.5	6.0	- 0.5
		D18	-11.0	- 4.5	- 6.5
		D19	-10.5	-25.0	14.5
		D20	9.5	15.5	- 6.0
	YES	D04	5.0	2.5	2.5
		D05	24.0	8.0	16.0
		D06	23.5	22.5	1.0
		D08	1.0	4.0	- 3.0
		D12	0.0	0.5	- 0.5
		D13	9.5	19.0	- 9.5
		D15	5.5	5.5	0.0
		D16	3.5	- 6.5	10.0
		D17	4.5	- 3.0	7.5
5	NO	D01	4.0	17.0	-13.0
		D02	- 1.0	16.0	-17.0
		D03	12.5	10.5	2.0
		D07	3.0	1.0	2.0
		D09	5.0	- 2.5	7.5
		D10	- 4.5	- 1.5	- 3.0
		D11	23.0	14.0	9.0
		D14	8.5	2.0	6.5
		D18	- 7.0	- 5.0	- 2.0
		D19	- 4.5	-29.5	25.0
		D20	15.0	14.0	1.0
	YES	D04	12.5	2.5	10.0
		D05	35.5	20.0	15.5
		D06	27.0	19.5	7.5
		D08	9.0	5.5	3.5
		D12	1.5	2.0	- 0.5
		D13	36.0	7.5	28.5
		D15	7.0	9.5	- 2.5
		D16	7.5	- 2.5	10.0
		D17	7.0	- 2.0	9.0

Appendix 5

Difference from Baseline for Experiment 3 (Cont'd)

MINUTE	EXP?	PATIENT	DIBUCAINE	PLACEBO	DIFF (D-P)
10	NO	D01	4.5	17.5	-13.0
		D02	1.0	19.5	-18.5
		D03	15.0	25.0	-10.0
		D07	4.5	1.5	3.0
		D09	2.5	2.5	0.0
		D10	- 4.0	-14.0	10.0
		D11	23.0	27.0	- 4.0
		D14	13.0	1.0	12.0
		D18	- 1.5	-10.0	8.5
		D19	9.5	3.5	6.0
		D20	18.0	14.5	3.5
	YES	D04	12.5	2.5	10.0
		D05	34.5	25.5	9.0
		D06	23.5	22.5	1.0
		D08	13.0	2.0	11.0
		D12	7.5	2.0	5.5
		D13	34.5	0.5	34.0
		D15	10.5	14.0	- 3.5
		D16	10.5	-11.5	22.0
		D17	8.5	2.5	6.0
15	NO	D01	2.5	15.0	-12.5
		D02	10.0	14.0	- 4.0
		D03	32.0	29.5	2.5
		D07	5.5	4.5	1.0
		D09	0.0	10.0	-10.0
		D10	- 6.5	-12.0	5.5
		D11	20.5	24.5	- 4.0
		D14	15.5	6.5	9.0
		D18	- 4.5	0.5	- 5.0
		D19	5.5	-10.0	15.5
		D20	20.0	24.0	- 4.0
	YES	D04	10.0	2.5	7.5
		D05	38.0	32.5	5.5
		D06	34.5	11.5	23.0
		D08	6.0	6.0	0.0
		D12	5.5	2.5	3.0
		D13	35.5	10.0	25.5
		D15	5.5	9.5	- 4.0
		D16	10.5	- 5.0	15.5
		D17	7.5	2.0	5.5

Appendix 5

Difference from Baseline for Experiment 3 (Cont'd)

MINUTE	EXP?	PATIENT	DIBUCAINE	PLACEBO	DIFF (D-P)
20	NO	D01	2.0	15.5	-13.5
		D02	0.5	1.5	- 1.0
		D03	44.0	22.5	21.5
		D07	6.5	5.0	1.5
		D09	3.5	12.5	- 9.0
		D10	- 9.5	0.5	-10.0
		D11	30.5	29.5	1.0
		D14	9.5	0.5	9.0
		D18	- 7.0	-12.5	5.5
		D19	5.5	1.0	4.5
		D20	20.0	20.0	0.0
	YES	D04	10.0	0.0	10.0
		D05	28.0	36.0	- 8.0
		D06	29.0	18.5	10.5
		D08	8.0	5.0	3.0
		D12	9.0	1.5	7.5
		D13	19.5	15.0	4.5
		D15	9.0	12.0	- 3.0
		D16	20.0	- 6.0	26.0
		D17	2.5	0.5	2.0

APPENDIX 6

TABLE 7: Pruritus Score Summary Statistics for Experiment 4.

	Minute					
	0	2	5	10	15	20
Calamine						
n	24	24	24	24	24	24
Mean Pruritus Score	43	36	34	34	34	30
S.D.	20	16	17	16	18	16
Minimum Pruritus Score	10	10	11	13	7	6
Maximum Pruritus Score	90	83	85	85	85	68
Placebo						
n	24	24	24	24	24	24
Mean Pruritus Score	42	37	35	34	34	33
S.D.	18	15	16	14	15	15
Minimum Pruritus Score	11	11	6	12	5	2
Maximum Pruritus Score	87	78	84	72	73	69

APPENDIX 6

Pruritus Score Data for Experiment 4

VOL. #	SITE		TREATMENT	MINUTE	PRURITUS SCORE	
	LEFT ARM	RIGHT ARM			L	R
C01	DISTAL	PROXIMAL	CALAMINE	0	23	15
				2	13	10
				5	18	15
				10	15	10
				15	10	22
				20	15	10
	PROXIMAL	DISTAL	PLACEBO	0	21	20
				2	21	20
				5	16	12
				10	20	18
				15	23	20
				20	18	15
C02	PROXIMAL	DISTAL	CALAMINE	0	41	45
				2	50	45
				5	39	40
				10	39	46
				15	45	40
				20	46	44
	DISTAL	PROXIMAL	PLACEBO	0	40	60
				2	37	50
				5	42	50
				10	37	51
				15	37	53
				20	39	42
C03	DISTAL	PROXIMAL	CALAMINE	0	70	60
				2	55	50
				5	50	55
				10	40	50
				15	48	50
				20	50	50
	PROXIMAL	DISTAL	PLACEBO	0	50	64
				2	50	61
				5	46	42
				10	40	37
				15	45	55
				20	50	55

Appendix 6

Pruritus Score Data for Experiment 4 (Cont'd)

VOL. #	SITE		TREATMENT	MINUTE	PRURITUS SCORE	
	LEFT ARM	RIGHT ARM			L	R
C04	PROXIMAL	DISTAL	CALAMINE	0	90	90
				2	80	85
				5	80	89
				10	85	85
				15	85	85
				20	65	70
	DISTAL	PROXIMAL	PLACEBO	0	95	79
				2	75	81
				5	97	70
				10	73	70
				15	75	70
				20	67	71
C05	PROXIMAL	DISTAL	CALAMINE	0	40	70
				2	40	40
				5	45	40
				10	40	50
				15	40	40
				20	30	35
	DISTAL	PROXIMAL	PLACEBO	0	50	60
				2	30	30
				5	30	40
				10	40	40
				15	20	30
				20	10	40
C06	DISTAL	PROXIMAL	CALAMINE	0	35	25
				2	30	25
				5	31	26
				10	33	24
				15	30	25
				20	30	32
	PROXIMAL	DISTAL	PLACEBO	0	30	30
				2	35	36
				5	38	35
				10	30	35
				15	37	39
				20	40	38

Appendix 6

Pruritus Score Data for Experiment 4 (Cont'd)

VOL. #	SITE		TREATMENT	MINUTE	PRURITUS SCORE	
	LEFT ARM	RIGHT ARM			L	R
C07	PROXIMAL	DISTAL	CALAMINE	0	41	54
				2	47	20
				5	35	29
				10	40	48
				15	47	44
				20	42	34
	DISTAL	PROXIMAL	PLACEBO	0	39	50
				2	37	37
				5	36	39
				10	27	37
				15	31	26
				20	33	35
C08	DISTAL	PROXIMAL	CALAMINE	0	41	72
				2	20	28
				5	11	29
				10	30	34
				15	24	40
				20	10	37
	PROXIMAL	DISTAL	PLACEBO	0	51	50
				2	53	39
				5	46	40
				10	40	32
				15	41	40
				20	64	28
C09	PROXIMAL	DISTAL	CALAMINE	0	0	20
				2	4	16
				5	3	18
				10	12	19
				15	2	12
				20	1	10
	DISTAL	PROXIMAL	PLACEBO	0	21	0
				2	21	0
				5	9	2
				10	12	11
				15	8	1
				20	3	1

Appendix 6

Pruritus Score Data for Experiment 4 (Cont'd)

VOL. #	SITE		TREATMENT	MINUTE	PRURITUS SCORE	
	LEFT ARM	RIGHT ARM			L	R
C10	PROXIMAL	DISTAL	CALAMINE	0	50	46
				2	49	30
				5	46	28
				10	39	41
				15	59	29
				20	56	31
	DISTAL	PROXIMAL	PLACEBO	0	26	40
				2	20	29
				5	32	22
				10	34	27
				15	40	19
				20	44	24
C11	DISTAL	PROXIMAL	CALAMINE	0	30	30
				2	30	50
				5	22	40
				10	23	33
				15	20	32
				20	9	33
	PROXIMAL	DISTAL	PLACEBO	0	40	40
				2	30	32
				5	29	44
				10	39	44
				15	40	41
				20	40	35
C12	PROXIMAL	DISTAL	CALAMINE	0	20	20
				2	20	20
				5	30	5
				10	20	5
				15	20	5
				20	30	10
	DISTAL	PROXIMAL	PLACEBO	0	15	20
				2	20	40
				5	15	40
				10	10	40
				15	5	35
				20	10	30

Appendix 6

Pruritus Score Data for Experiment 4 (Cont'd)

VOL. #	SITE		TREATMENT	MINUTE	PRURITUS SCORE	
	LEFT ARM	RIGHT ARM			L	R
C13	DISTAL	PROXIMAL	CALAMINE	0	30	5
				2	15	19
				5	23	15
				10	16	10
				15	25	7
				20	5	6
	PROXIMAL	DISTAL	PLACEBO	0	4	20
				2	15	19
				5	10	8
				10	15	20
				15	17	10
				20	10	8
C14	PROXIMAL	DISTAL	CALAMINE	0	50	30
				2	30	39
				5	29	27
				10	25	29
				15	30	30
				20	9	30
	DISTAL	PROXIMAL	PLACEBO	0	30	40
				2	29	40
				5	26	35
				10	19	29
				15	19	35
				20	15	25
C15	DISTAL	PROXIMAL	CALAMINE	0	65	60
				2	34	50
				5	25	35
				10	39	55
				15	35	47
				20	34	40
	PROXIMAL	DISTAL	PLACEBO	0	35	50
				2	40	40
				5	29	35
				10	47	32
				15	42	28
				20	38	25

Appendix 6

Pruritus Score Data for Experiment 4 (Cont'd)

VOL. #	SITE		TREATMENT	MINUTE	PRURITUS SCORE	
	LEFT ARM	RIGHT ARM			L	R
C16	PROXIMAL	DISTAL	CALAMINE	0	53	58
				2	52	56
				5	51	51
				10	56	58
				15	57	57
				20	52	51
	DISTAL	PROXIMAL	PLACEBO	0	55	55
				2	55	51
				5	54	51
				10	49	49
				15	50	49
				20	51	50
C17	DISTAL	PROXIMAL	CALAMINE	0	75	31
				2	30	25
				5	24	15
				10	36	15
				15	18	9
				20	21	5
	PROXIMAL	DISTAL	PLACEBO	0	55	39
				2	40	39
				5	41	44
				10	35	26
				15	30	27
				20	63	34
C18	DISTAL	PROXIMAL	CALAMINE	0	34	16
				2	20	24
				5	20	23
				10	32	19
				15	18	30
				20	15	26
	PROXIMAL	DISTAL	PLACEBO	0	40	20
				2	32	22
				5	30	26
				10	28	21
				15	19	25
				20	18	24

Appendix 6

Pruritus Score Data for Experiment 4 (Cont'd)

VOL. #	SITE		TREATMENT	MINUTE	PRURITUS SCORE	
	LEFT ARM	RIGHT ARM			L	R
C19	PROXIMAL	DISTAL	CALAMINE	0	50	80
				2	40	60
				5	44	51
				10	40	30
				15	39	70
				20	40	61
	DISTAL	PROXIMAL	PLACEBO	0	70	61
				2	39	60
				5	45	60
				10	59	55
				15	54	60
				20	40	55
C20	DISTAL	PROXIMAL	CALAMINE	0	30	30
				2	40	30
				5	30	50
				10	32	29
				15	40	30
				20	30	25
	PROXIMAL	DISTAL	PLACEBO	0	42	50
				2	40	19
				5	20	21
				10	40	16
				15	28	25
				20	20	25
C21	PROXIMAL	DISTAL	CALAMINE	0	30	61
				2	33	51
				5	50	50
				10	29	41
				15	21	51
				20	30	44
	DISTAL	PROXIMAL	PLACEBO	0	51	30
				2	41	27
				5	43	26
				10	46	34
				15	30	51
				20	46	32

Appendix 6

Pruritus Score Data for Experiment 4 (Cont'd)

VOL. #	SITE		TREATMENT	MINUTE	PRURITUS SCORE	
	LEFT ARM	RIGHT ARM			L	R
C22	DISTAL	PROXIMAL	CALAMINE	0	15	25
				2	17	30
				5	22	35
				10	28	37
				15	20	20
				20	10	18
	PROXIMAL	DISTAL	PLACEBO	0	31	28
				2	25	35
				5	22	31
				10	28	30
				15	30	35
				20	20	25
C23	PROXIMAL	DISTAL	CALAMINE	0	60	75
				2	50	59
				5	50	45
				10	35	40
				15	45	45
				20	40	42
	DISTAL	PROXIMAL	PLACEBO	0	60	70
				2	50	60
				5	38	50
				10	45	50
				15	45	50
				20	35	50
C24	DISTAL	PROXIMAL	CALAMINE	0	40	25
				2	30	27
				5	11	20
				10	21	20
				15	22	23
				20	16	20
	PROXIMAL	DISTAL	PLACEBO	0	20	49
				2	20	30
				5	22	25
				10	10	19
				15	20	34
				20	14	34

Appendix 6

Difference from Baseline for Experiment 4

MINUTE	EXP?	PATIENT	CALAMINE	PLACEBO	DIFF (C-P)
2	NO	C02	- 4.5	6.5	-11.0
		C03	12.5	1.5	11.0
		C04	7.5	9.0	- 1.5
		C05	15.0	25.0	-10.0
		C07	14.0	7.5	6.5
		C09	0.0	0.0	0.0
		C10	8.5	8.5	0.0
		C11	-10.0	9.0	-19.0
		C15	20.5	2.5	18.0
		C17	25.5	7.5	18.0
		C20	- 5.0	16.5	-21.5
		C22	- 3.5	- 0.5	- 3.0
	YES	C01	7.5	0.0	7.5
		C06	2.5	- 5.5	8.0
		C08	32.5	4.5	28.0
		C12	0.0	-12.5	12.5
		C13	0.5	- 5.0	5.5
		C14	5.5	0.5	5.0
		C16	1.5	2.0	- 0.5
		C18	3.0	3.0	0.0
		C19	15.0	16.0	- 1.0
		C21	3.5	6.5	- 3.0
		C23	13.0	10.0	3.0
		C24	4.0	9.5	- 5.5

Appendix 6

Difference from Baseline for Experiment 4 (Cont'd)

MINUTE	EXP?	PATIENT	CALAMINE	PLACEBO	DIFF (C-P)
5	NO	C02	3.5	4.0	- 0.5
		C03	12.5	13.0	- 0.5
		C04	5.5	3.5	2.0
		C05	12.5	20.0	- 7.5
		C07	15.5	7.0	8.5
		C09	- 0.5	5.0	- 5.5
		C10	11.0	6.0	5.0
		C11	- 1.0	3.5	- 4.5
		C15	32.5	10.5	22.0
		C17	33.5	4.5	29.0
		C20	-10.0	25.5	-35.5
		C22	- 8.5	3.0	-11.5
	YES	C01	2.5	6.5	- 4.0
		C06	1.5	- 6.5	8.0
		C08	36.5	7.5	29.0
		C12	2.5	-10.0	12.5
		C13	- 1.5	3.0	- 4.5
		C14	12.0	4.5	7.5
		C16	4.5	2.5	2.0
		C18	3.5	2.0	1.5
		C19	17.5	13.0	4.5
		C21	- 4.5	6.0	-10.5
		C23	20.0	21.0	- 1.0
		C24	17.0	11.0	6.0

Appendix 6

Difference from Baseline for Experiment 4 (Cont'd)

MINUTE	EXP?	PATIENT	CALAMINE	PLACEBO	DIFF (C-P)
10	NO	C02	0.5	6.0	- 5.5
		C03	20.0	18.5	1.5
		C04	5.0	15.5	-10.5
		C05	10.0	15.0	- 5.0
		C07	3.5	12.5	- 9.0
		C09	- 5.5	- 1.0	- 4.5
		C10	8.0	2.5	5.5
		C11	2.0	- 1.5	3.5
		C15	15.5	3.0	12.5
		C17	27.5	16.5	11.0
		C20	- 0.5	18.0	-18.5
		C22	-12.5	0.5	-13.0
	YES	C01	6.5	1.5	5.0
		C06	1.5	- 2.5	4.0
		C08	24.5	14.5	10.0
		C12	7.5	- 7.5	15.0
		C13	4.5	- 5.5	10.0
		C14	13.0	11.0	2.0
		C16	- 1.5	6.0	- 7.5
		C18	- 0.5	5.5	- 6.0
		C19	30.0	8.5	21.5
		C21	10.5	0.5	10.0
		C23	30.0	17.5	12.5
		C24	12.0	20.0	- 8.0

Appendix 6

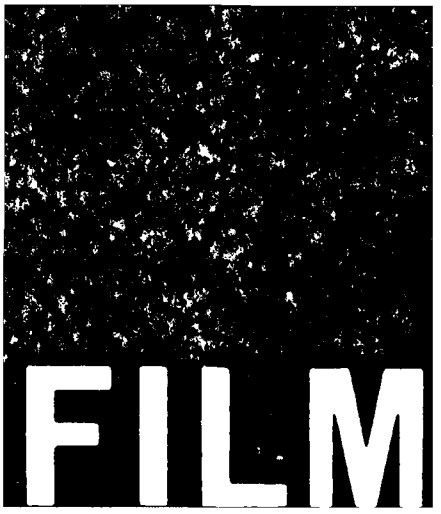
Difference from Baseline for Experiment 4 (Cont'd)

MINUTE	EXP?	PATIENT	CALAMINE	PLACEBO	DIFF (C-P)
15	NO	C02	0.5	5.0	- 4.5
		C03	16.0	7.0	9.0
		C04	5.0	14.5	- 9.5
		C05	15.0	30.0	-15.0
		C07	2.0	16.0	-14.0
		C09	3.0	6.0	- 3.0
		C10	4.0	3.5	0.5
		C11	4.0	- 0.5	4.5
		C15	21.5	7.5	14.0
		C17	39.5	18.5	21.0
		C20	- 5.0	19.5	-24.5
		C22	0.0	- 3.0	3.0
	YES	C01	3.0	- 1.0	4.0
		C06	2.5	- 8.0	10.5
		C08	24.5	10.0	14.5
		C12	7.5	- 2.5	10.0
		C13	1.5	- 1.5	3.0
		C14	10.0	8.0	2.0
		C16	- 1.5	5.5	- 7.0
		C18	1.0	8.0	- 7.0
		C19	10.5	8.5	2.0
		C21	9.5	0.0	9.5
		C23	22.5	17.5	5.0
		C24	10.0	7.5	2.5

Appendix 6

Difference from Baseline for Experiment 4 (Cont'd)

MINUTE	EXP?	PATIENT	CALAMINE	PLACEBO	DIFF (C-P)
20	NO	C02	- 2.0	9.5	-11.5
		C03	15.0	4.5	10.5
		C04	22.5	18.0	4.5
		C05	22.5	30.0	- 7.5
		C07	9.5	10.5	- 1.0
		C09	4.5	8.5	- 4.0
		C10	4.5	- 1.0	5.5
		C11	9.0	2.5	6.5
		C15	25.5	11.0	14.5
		C17	40.0	- 1.5	41.5
		C20	2.5	23.5	-21.0
		C22	6.0	7.0	- 1.0
	YES	C01	6.5	4.0	2.5
		C06	- 1.0	- 9.0	8.0
		C08	33.0	4.5	28.5
		C12	0.0	- 2.5	2.5
		C13	12.0	3.0	9.0
		C14	20.5	15.0	5.5
		C16	4.0	4.5	- 0.5
		C18	4.5	9.0	- 4.5
		C19	14.5	18.0	- 3.5
		C21	8.5	1.5	7.0
		C23	26.5	22.5	4.0
		C24	14.5	10.5	4.0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