THE FAILURE OF THE ANTIHISTAMINE CREAM PYRIBENZAMINE TO ALLEVIATE REACTIONS FROM BITES OF THE MOSQUITO *AEDES AEGYPTI* [1]

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Recently O'Rourke and Murnaghan (1953) have published results to show that a topically applied antihistamine, pyribenzamine, decreases not only pruritus but also the immediate cutaneous reaction to the bites of *Aedes aegypti* (L). Fourteen of thirty reactors experienced relief of pruritus associated with the immediate reaction and four out of five with the delayed reaction. In addition ten out of thirty subjects exhibited reductions in size of the immediate cutaneous reaction.

Previous claims for relief of insect bite reactions through the use of antihistamines have varied and have been based on results obtained with very few subjects or with an unstated number of subjects (Gordon and Crewe, 1948; Salva Miquel, 1949; Straus, 1949; Gordon, 1951; Rockwell and Johnson, 1952). In no report was the number cited as large as employed by O'Rourke and Murnaghan. Studies of the local effects of antihistaminic ointments on the histamine wheal led Perry (1947) and Peck *et al.*, (1950) to conclude that topical application had relatively little effect and that very little if any of the antihistamine is absorbed through the intact skin.

During early phases of an extended study on the nature of the mosquito bite reaction now in progress, sporadic tests with antihistamines were made. These limited tests failed to indicate that any significant relief was obtained. It appeared possible that the results obtained by O'Rourke and Murnaghan might have been influenced by the methods used. In their procedure, two mosquitoes were allowed to feed to repletion on the flexor surface of the forearm at sites about six inches apart. Immediately following, a two per cent pyribenzamine cream was massaged into one of the sites and the other was left untreated as a control. No statement was made as to whether the sites were randomized with respect to treatment. The technique might be criticized on two grounds, namely, the failure to use a control cream, and the apparent lack of randomization. Since no treatment was given the control bite it is apparent that this area was not massaged. Also, the subject appears to have known which site had received the antihistaminic treatment. If this was the case, a well recognized source of bias was permitted which could be reflected in the subject's interpretation of degree of pruritus at each site. Regarding the need for randomization, Becker and Rappaport (1948) have found in ragweed-sensitive subjects that sites near the cubital fossa are more reactive to constant doses of ragweed antigen than sites near the wrist. Similar results were obtained by Swain and Becker (1953) with constant doses of histamine. Presumably mosquito bite reactions might show the same variation. The use of randomization and a control cream also has the advantage of removing bias on the part of the observer of the bite reactions since he will be unaware of the kind of treatment applied at a particular site. Since reactions to mosquito bites exhibit considerable variation even for the individual, it is most important to eliminate as many sources of error as possible.

METHOD. One hundred and twenty-six medical and biology students from Queen's University, Kingston, together

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with twenty associates from this laboratory served as volunteers. Two methods of applying treatment were tried. In the first, O'Rourke and Murnaghan's procedure of applying the antihistamine immediately after the receipt of mosquito bites was followed. Since, however, the application of the antihistamine prior to the test substance (histamine, allergen) appears to be the usual method for assessing antihistamines (Perry 1947; Peck *et al.*, 1950; Feinberg *et al.*, 1950, p. 96), a second test was made employing this procedure.

(1) *Post-biting treatment.* Eighty-two subjects were tested. Mosquitoes were confined individually in 1" x 8" vials. A vial was applied to the flexor surface of each forearm and the mosquitoes were allowed to feed to repletion. Immediately after the subject was bitten, approximately 2 grams of 2 per cent pyribenzamine cream [1] were applied on one bitten area and a similar amount of control cream of comparable consistency (dermabase [2]) was applied on the other. The creams were massaged into the skin over an area of approximately 1.5 inches in diameter centered on the bite. The selection of right or left arm for treatment with antihistamine was random and not known either to the subject or to the observer of the reaction.

(2) *Pre-biting treatment.* Sixty-four subjects were tested. The creams were applied, massaged for three minutes and the areas outlined with a ball-point pen. After an additional seven minutes, the creams were washed off with water, dried and the sites exposed to mosquito bites as in the previous trial.

Reactions were recorded one-half hour and twenty-four hours after the bites were received. All observations were made by the same person. Wheals and erythema were measured longitudinally and transversely with calipers accurate to 0.1 mm. Wheals were recorded to the nearest tenth millimetre and erythema to the nearest millimetre. The degree of pruritus was recorded by the subject for each arm using +, ++, or +++. These have no absolute comparative value between subjects but merely indicate similarities or differences in pruritus between the two sites for an individual. In the first test, any pruritus which occurred between the beginning of the biting and the application of creams was ignored and pruritus was recorded only if it occurred following the massage of creams.

RESULTS. Not all subjects developed reactions to the bites (numbers positive are shown in Tables 3 and 4). There were also several instances in which immediate reactions developed on one arm but failed to appear on the other. These inconsistent reactions are summarized in Table 1.

TABLE 1.—Variations in immediate reactions between arms of individual subjects

Site	Number of subjects with negative reactions at one site and positive at the other	
	Post-biting	Pre-biting
Antihistamine	6	3
Control	3	4

The occurrence of negative and positive reactions on one individual cannot be correlated with the antihistaminic treatment but only emphasizes the variations in reactions which may occur.

Immediate reactions at the antihistamine and control sites are compared in Table 2 on the basis of mean diameters of wheals and erythema for all reacting subjects. It is apparent from the results that the antihistamine, applied either before or immediately after the bite, had no influence on wheal or erythema. In Table 3, immediate reactions are compared on the basis of numbers of individuals who exhibited particular types of reactions. Table 4 compares delayed reactions also on the basis of numbers of individuals.

[1] Ciba Company Limited, Montreal.

[2] Marcelle Pharmaceuticals, Chicago. This cream is a stabilized emulsion of fatty acid esters and alcohols.

TABLE 2.—Mean diameters of immediate wheals and erythema at sites treated with antihistamine and control creams

	Wheal		Erythema	
	Antihistamine	Control	Antihistamine	Control
Post-biting treatment				
Mean diameter (mm.)	6.8	6.8	32	33
Standard deviation	3.2	3.5	13	12
Pre-biting treatment				
Mean diameter (mm.)	6.1 *	6.5 *	30	31
Standard deviation	3.0	3.1	16	15

* The difference between these diameters was not statistically significant at the 5 per cent level.

TABLE 3.—Comparison, by number of individuals, of immediate reactions at sites treated with antihistamine and control creams

			Unequal reactions at two sites	
	Number of reactors	Equal reaction treated and control sites	Less at control-treated	Less at antihistamine-treated
Post-biting treatment 82 Subjects				
Pruritus	49	16	15	18
Erythema	48	4	24	20
Wheal	71	6	32	33
Subjective estimation	71	39	16	16
Pre-biting treatment 64 Subjects				
Pruritus	47	18	15	14
Erythema	47	4	22	21
Wheal	60	7	24	29
Subjective estimation	60	36	10	14

TABLE 4.—Comparison, by number of individuals, of delayed reactions at sites treated with antihistamine and control creams

			Unequal reactions at two sites	
	Number of reactors	Equal reaction treated and control sites	Less at control-treated	Less at antihistamine-treated
Post-biting treatment				
Pruritus	11	3	3	5
Erythema	24	12	8	4
Papule	59	42	6	11
Subjective estimation	59	43	8	8
Pre-biting treatment				
Pruritus	13	4	5	4
Erythema	33	20	6	7
Papule	50	39	5	6
Subjective estimation	50	37	6	7

The term "Subjective estimation" is here used to mean an over-all evaluation of the total reaction at each site and was made by observing the reactions with both arms held side by side.

DISCUSSION. The above tables show that two per cent pyribenzamine cream has exerted no significant effect on reactions to bites of the mosquito, *A. aegypti*. The disagreement between these results and those published by O'Rourke and Murnaghan can possibly be attributed to differences in technique which have already been discussed. In our test which followed O'Rourke and Murnaghan's method of applying creams after the bites were received, it was frequently noted that massage of either cream decreased or eliminated pruritus. It therefore appears that the massage of a cream is more important in relieving pruritus from mosquito bites than the presence of pyribenzamine in the cream.

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SUMMARY. Two per cent pyribenzamine cream was tested against a control cream, dermabase, for its ability to relieve reactions to mosquito bites. One hundred and forty-six volunteers were used for the test. The creams were employed in two ways, (1) applied immediately after biting and (2) applied ten minutes before biting. In neither method of treatment was the antihistamine superior to the control cream in relieving pruritus or the cutaneous reaction.

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