

THE CUTANEOUS REACTION TO THE BITE OF THE MOSQUITO
AÈDES AEGYPTI (L.) AND ITS ALLEVIATION BY THE
TOPICAL APPLICATION OF AN ANTIHISTAMINIC
CREAM (PYRIBENZAMINE)

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INTRODUCTION

THE cutaneous reaction produced by the bites or stings of those arthropods that attack man may be due to any one of four factors or to a combination of these, as follows: (a) mechanical trauma; (b) secondary infections; (c) injection of toxic substances; (d) response to sensitization.^{1, 2} The trauma inflicted by the delicate mouth parts of mosquitoes is small but, nevertheless, usually produces typical histologic changes in the skin.³ These changes, however, are not sufficiently extensive to be noticeable by the individual. Bites may give rise to pruritus in the area bitten and subsequent scratching often produces marked lesions, which may become secondarily infected. This condition is by no means infrequent in individuals exposed to the vast numbers of biting flies such as occur in northern Canada. Two types of response follow most bites. An immediate reaction begins either while the mosquito is biting or shortly afterward and is characterized by a wheal with erythema and pruritus; a delayed reaction usually begins about twenty-four hours after the bite and consists of an itchy papule. Mellanby⁴ believes that these two reactions are due to sensitization to two different antigens in the insect's saliva. In contrast, Gordon and Crewe³ suggest that the immediate reaction is due to sensitization and is partly the result of the release of histamine, whereas the delayed reaction is caused by a slowly acting poison. These authors also found that in two individuals highly sensitive to the bites of *Aedes aegypti* (L.) the antihistaminic drug Benadryl,[®] taken orally for three days in total daily doses of 150 mg., relieved the pruritus associated with the immediate reaction due to a bite inflicted on the second day, but did not otherwise affect the lesion. Gordon¹ notes that "reports concerning the value of antihistaminic drugs are somewhat contradictory, but it appears that whereas they are of value in controlling general allergic reactions following insect bites they are seldom effective in reducing the severity of the local reaction."

Bowen⁵ found that, in some cases, antihistaminic creams applied to the sites of insect bites relieved the pruritus "in the early urticarial stages, but are of no benefit during the inflammatory or fibrotic stages of the lesion." The same author quoted a personal communication from Dr. Evelyn M. Rockwell, Department of Dermatology, University of Cincinnati, to the effect that antihistaminic creams are of no value and that pruritus is decreased only when

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the drugs are given orally, or locally by iontophoresis. Neither of these workers mentioned the species of insect involved. Strauss⁶ has found that the local application of antihistaminics relieves the reaction produced by the sting of the honeybee. It should be pointed out that this bee's sting introduces poisonous substances, probably including histamine, into the skin, so that the subsequent reactions are of a different nature from those produced by mosquito bites.^{6, 7}

In view of the severe problem caused by biting flies in northern Canada⁸ and elsewhere, it would be of considerable value to have a drug that would relieve the irritation due to bites. Antihistaminics, which are readily available, were considered worthy of a trial. Local application was preferred to oral administration as this would eliminate the undesirable side effects, such as nausea and drowsiness, that not infrequently follow the exhibition of these drugs. The topical application of an antihistaminic cream might be expected to alleviate the reaction to mosquito bites, in part by its inactivation of histamine and in part by its local anesthetic action.

METHODS

To test this, 36 volunteer third-year medical students from the University of Ottawa were exposed to the bites of *A. aegypti*. All these students had previously been bitten by indigenous mosquitoes in Canada (where some species of *Aëdes* commonly occur as pests). As some of the students had been in areas where *A. aegypti* is known to occur, some of them may have been bitten by this species in the past. Of the group studied 16 claimed to be insensitive to mosquito bites whereas the other 20 said they reacted markedly.

Two mosquitoes were allowed to feed to repletion on the flexor aspect of the forearm; the sites of the bites were about six inches apart. One of the areas bitten was left untreated; into the other a 2 per cent Pyribenzamine® cream was rubbed immediately. The reactions were examined several times during the first hour and the students later questioned on their own observations on the reactions.

RESULTS

The reactions found are shown in Table I and are compared with the results obtained by Heilesen⁹ as calculated from his figures for the reactions of adults. The results in both series are similar but there is a statistically

TABLE I. THE REACTIONS TO THE FIRST SERIES OF BITES

	PRESENT SERIES		HEILESEN'S ⁹ SERIES	
	NUMBER	PERCENTAGE	NUMBER	PERCENTAGE
Subjects	36	100	31	100
Reactors	30	83	25	81
Nonreactors	6	17	6	19
Immediate reaction only	23*	64	10*	32
Delayed reaction only	5	14	6	19
Immediate and delayed reactions	2†	6	9†	29
Number claiming to be insensitive	16	46	—	—
Number claiming to be sensitive	20	54	—	—

*By χ^2 test, significantly different at 1 per cent level.

†By χ^2 test, significantly different at 5 per cent level.

significant difference between the two series in those that showed an immediate reaction only and in those that had both immediate and delayed reactions. As 14 of Heilesen's subjects had been previously exposed to bites of *A. aegypti*, and 4 of these had been intensively bitten, the differences possibly may be accounted for in this way.

Of the 6 nonreactors in Heilesen's series, 3 became positive after repeated biting; of the 6 in our series 4 gave an immediate reaction when bitten again at the same site after three weeks.

REACTIONS IN THOSE CLAIMING TO BE INSENSITIVE

Among those who claimed to be insensitive 5 showed no reaction when bitten, a higher proportion of nonreactors than in the group that claimed to be sensitive (see Table II) but not significantly different at the 5 per cent level

TABLE II. DIFFERENCES IN THE REACTIONS OF THOSE CLAIMING TO BE INSENSITIVE AND THOSE CLAIMING TO BE SENSITIVE

	CLAIMING TO BE INSENSITIVE		CLAIMING TO BE SENSITIVE	
	NUMBER	PERCENTAGE	NUMBER	PERCENTAGE
Subjects	16	100	20	100
Reactors	11	69	19	95
Nonreactors	5	31	1	5
Immediate reaction only	9	56	14	70
Delayed reaction only	2	12	3	15
Immediate and delayed reactions	0	0	2	10

using the χ^2 test. When these 5 were bitten again three weeks later, only 2 failed to react; the other 3 showed a small wheal after thirty minutes. Of the 9 with immediate reactions 6 complained of pruritus and all had a wheal surrounded by a peripheral erythematous area of varying extent. In addition to the wheal, erythema, and pruritus, 2 of these 6 reactors had marked swelling and induration at the site of the bite. In two cases there were delayed reactions. In one individual a pruritic papule appeared after about twenty-four hours and remained for about ten hours. The other individual had a slight itch twenty-four hours later. Both were retested three months later; the former had a very mild, rapidly disappearing immediate reaction and no delayed reaction, whereas the latter retained his previous reaction. No individual in this group had both immediate and delayed reactions.

REACTIONS IN THOSE CLAIMING TO BE SENSITIVE

Of the 20 individuals who claimed to be sensitive 19 showed some reaction to being bitten, a higher proportion of reactors than in the "insensitive" group, but not significant at the 5 per cent level by the χ^2 test. Immediate reactions occurred in 14 individuals, only 1 of whom had a delayed reaction as well. The reaction was typical in 5 cases; in 4 other cases there was in addition marked induration; in another 4, no pruritus, and in one of these no wheal, merely erythema; whereas in the last case, simply pruritus. The 2 students who showed both immediate and delayed reactions responded immediately by a wheal, erythema, and pruritus, followed after twenty-four

hours by a markedly pruritic papule. In the 3 delayed reactors the reaction began after two to forty-eight hours and consisted of a papule surrounded by erythema, in 1 case accompanied by pruritus and induration. The single nonreactor when bitten again three weeks later developed a small wheal after an interval of thirty minutes.

RESPONSES TO TREATMENT

Table III shows that 18 of the 30 reactors experienced some degree of relief, either subjective or objective, in the treated area. There was no statistically significant difference between the degree of relief experienced by the two groups. Each of the 18 experienced relief of the pruritus either in the immediate reaction (14 individuals) or in the delayed reaction (4 individuals).

TABLE III. RESPONSES TO TREATMENT AMONG THOSE REACTING TO BITES

	TOTAL	PER-CENTAGE	CLAIMING TO BE INSENSITIVE		CLAIMING TO BE SENSITIVE	
			NUMBER	PER-CENTAGE	NUMBER	PER-CENTAGE
Reactors	30	100	11	100	19	100
Number relieved	18	60	5	45	13	68
Immediate reactors	25	100	9	100	16*	100
Number relieved	16	64	4	44	12	75
Delayed reactors	7	100	2	100	5*	100
Number relieved	4	57	1	50	3	60

*Including those showing both immediate and delayed reactions.

In addition, 10 of the immediate reactors had reductions in the size and duration of the tissue reaction in the treated area. This relief was greatest in those who showed the most marked reactions in the control area; thus, of the 6 reactors who had marked induration in the control area 3 had no induration and 2 had very little induration in the treated area. In no case did treatment produce objective relief in the delayed reaction although in 4 of the 5 cases in which pruritus occurred in the control area it was absent in the treated area.

ALLEVIATION OF PRURITUS

As pruritus is the most significant subjective reaction to mosquito bites and provokes scratching, which may lead to secondary infection, the effect of treatment on its occurrence is shown in Table IV. The treatment relieved or abolished the pruritus in 80 per cent of the cases. Twenty-one individuals suffered from pruritus and one of them complained of it in both immediate and delayed reactions.

TABLE IV. EFFECTS OF TREATMENT ON THE DEVELOPMENT OF PRURITUS

REACTION	PRURITUS PRESENT IN THE CONTROL AREA	PRURITUS ABSENT IN THE TREATED AREA	PRURITUS RELIEVED IN THE TREATED AREA	PRURITUS EITHER ABSENT OR RELIEVED IN THE TREATED AREA
Immediate	17	7 (41%)	7 (41%)	14 (82%)
Delayed	5	4 (80%)	0	4 (80%)
Total	22	11 (50%)	7 (32%)	18 (82%)

To determine whether the alleviation of the pruritus afforded by the Pyribenzamine® was due solely to its local anesthetic action, a further series of observations were made on the 21 students who complained of pruritus immediately after being bitten. Three mosquitoes were allowed to feed to repletion on the flexor aspect of the forearm; the sites of the bites were about four inches apart. One site was treated with the Pyribenzamine® cream, the second with a freshly prepared 1 per cent Nupercaine® (dibucaine) cream (chosen because it is one of the most potent local anesthetics), and the third area left as a control.

The results are shown in Table V. In 3 individuals the reactions have become altered: in 2 cases the delayed reaction did not recur and was replaced by an immediate one, and in the third case, although a delayed reaction occurred, there was no itch as there had been on the previous occasion. The two preparations appear to be equally effective in the relief of pruritus since there is no significant difference between the two groups. We have already noted, however, that in some cases the severity of the reaction and the extent of induration are also reduced after the application of the Pyribenzamine® cream. Of the 21 pairs of treated reactions shown in Table V, in 9 cases the least se-

TABLE V. EFFECTS OF TWO DIFFERENT TREATMENTS ON THE DEVELOPMENT OF PRURITUS

TREATMENT	PRURITUS PRESENT IN CONTROL LESION	PRURITUS ABSENT IN TREATED AREA	PRURITUS RELIEVED IN TREATED AREA	PRURITUS EITHER ABSENT OR RELIEVED IN TREATED AREA
<i>Immediate Reaction</i>				
Pyribenzamine® 2%	18 (100%)	9 (50%)	8 (44%)	17 (94%)
Nupercaine® 1%	18 (100%)	7 (38%)	10 (56%)	17 (94%)
<i>Delayed Reaction</i>				
Pyribenzamine® 2%	3 (100%)	3 (100%)	—	3 (100%)
Nupercaine® 1%	3 (100%)	2 (66%)	0	2 (66%)

vere was that treated with Pyribenzamine®. In the remaining cases there was no appreciable difference between the lesions. The more severe the reaction in the control area the more marked was the relief in the area treated with the antihistaminic.

These results indicate that the application of either Pyribenzamine® or Nupercaine® cream to mosquito bites is useful: not only will individuals be subjectively relieved but also secondary infections that generally result from scratching will be considerably reduced. In view of its effect on the severity of the lesion the antihistaminic appears to be more useful than the local anesthetic.

SUMMARY

The reactions of 36 medical students to the bites of the mosquito *Aedes aegypti* (L.) are described.

Treatment of the area bitten, immediately after the bite was received, with an antihistaminic cream (2 per cent Pyribenzamine®) diminished the severity of the reaction in 60 per cent of reactors. This drug and a local anesthetic cream (1 per cent Nupercaine®) were compared and each was very

effective, relieving the pruritus in over 80 per cent of cases. As the anti-histaminic was also effective in reducing the severity of the lesions, it was considered slightly superior to the local anesthetic.

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