

## **Clinical Background of Conditions Caused by Mosquito Bites in Children and the Effect of Tranilast upon the Related Symptoms**

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Many pediatricians often encounter children suffering from extreme swelling following mosquito bites. Our study attempted to make the definition of the mosquito-bite-induced condition. For the diagnosis of mosquito bites, 35 children served as the subjects of this study. They visited our department or the Pediatric Allergy Clinic of Toda Chuo General Hospital with major complaints of symptoms that ensued after being bitten by mosquitoes. Nursery school children who were bitten by mosquitoes served as controls and their responses were comparatively examined. The median maximum diameter of swelling after the mosquito bites is 1.5 cm and the swelling lasts about 3 days in the control group. In case of mosquito-bite-induced condition, the swelling after the mosquito bites exceeds 3 cm or more and lasts over 7 days. The effect of tranilast administration was evaluated on those cases judged to have been suffering from the mosquito-bite-induced conditions. After medication, the median maximum diameter and duration of swelling after mosquito bite was reduced. It was concluded from the results of our study that the reaction of the mosquito-bite-induced condition tended to be greater than the control group. Tranilast administration will be effective against the mosquito-bite-induced condition.

**Key words:** delayed reaction, immediate reaction, insect bite, mosquito-bite-induced condition, tranilast

### **Introduction**

It is suspected that many pediatricians encounter children suffering from extreme swelling following mosquito bites in their pediatric outpatient clinic. However, there are no definitions or therapeutic standards for this condition.

For the diagnosis of mosquito bites (hereafter called the mosquito-bite-induced condition), nursery school children who were bitten by mosquitoes served as controls and their responses were comparatively examined. The effect of tranilast administration was evaluated on those cases judged to have been suffering from the mosquito-bite-induced conditions.

### **Subjects and Methods**

Thirty-five children served as the subjects of this study. They visited our department or the Pediatric Allergy Clinic of Toda Chuo General Hospital with major complaints of symptoms that ensued after being bitten by mosquitoes. They were treated as those suffering from the mosquito-bite-induced condition and were performed a questionnaire to elicit their reaction to the mosquito bites (Fig. 1). All of them were undertaken a blood sample examination for eosinophil count, total IgE and specific IgE antibodies for house dust, mite, egg white, cow's milk, soybean, wheat, moth and mosquito.

A survey was conducted among 128 children (68 boys and 60 girls) who attended either of two nurs-

Do you suffer from any allergic diseases? Circle those that apply. (asthma, allergic rhinitis, atopic dermatitis, allergic conjunctivitis, food allergy, and urticaria)

1. When bitten by a mosquito:
  - (i) How big was the swelling? Maximum diameter ( ) cm
  - (ii) How long does it stay swollen? About ( ) days
2. What happens after you are bitten by a mosquito?
 

Circle those that apply.

  - a. Swelling appears 1/2 to 1 hour after the sting but it subsides on the following day.
  - b. Swelling does not become obvious until the next day but the symptom exacerbates thereafter.
  - c. Swelling becomes eminent on the same day followed by exacerbation. It requires time for recovery.
  - d. Blister forms at the site of the bite.
  - e. The skin is damaged from scratching and remains moist with oozing. Recovery is slow.
3. Did vaccination leave a hard subcutaneous lump that persisted for days? (yes or no)  
If the answer is yes, specify the type of vaccination. ( )
4. Do any of the parents, siblings, or grandparents suffer from the complications of mosquito bites? (yes or no)
5. What kind of treatment did you receive after being stung by a mosquito?  
( )
6. Have you ever contracted another disease? ( )

**Fig. 1** Questions posed in the questionnaire  
Thirty-five children of mosquito-bite-induced condition group (n=35) and control group (n=128) were performed the questionnaire to elicit their reaction to the mosquito bites.

eries in Arakawa Ward by using same questionnaire to elicit their reactions to the mosquito bites (Fig. 1). All responded negatively on the question about past illnesses, including immunodeficiency, which was asked in question 6. All served as the controls to be compared against those who suffered from the mosquito-bite-induced condition. The questionnaires were filled out by guardians of their memory.

Tranilast was administered to those suffering from mosquito-bite-induced condition and the subsequent clinical course was observed. Nineteen children who had been receiving oral anti-allergy agents were switched to tranilast. The dosage of tranilast was 5 mg per bodyweight (kg) and the dosage period was 12 weeks in summer season. Investigation was done after 3 weeks. At the same time,

their guardians were requested to evaluate the efficacy of the medication by applying a 5-point scale.

The age of the children serving as controls ranged from 9 months to 6 years and 7 months (mean, 3 years and 8 months), while the range for the clinical patients was from 10 months to 12 years (mean, 3 years and 8 months). There was no significant difference in age between the 2 groups. Informed consent was obtained from all patients and the control cases.

The statistical analyses of the data were performed by chi-square test and Student's t-test. P values less than 0.05 were considered significant.

## Results

### 1. Percentages of allergic diseases complicating mosquito-bite-induced condition (Fig. 2)

Among those suffering from the mosquito-bite-induced condition, 100% reported experiences with allergic conditions because of consulting the allergy clinic. Among the controls also, 38 children (29.7%) suffered from allergic conditions. Of the allergic conditions in both groups, asthma and atopic dermatitis were predominant (amounting to 11.7% even in the control group, a figure slightly higher than the national average).

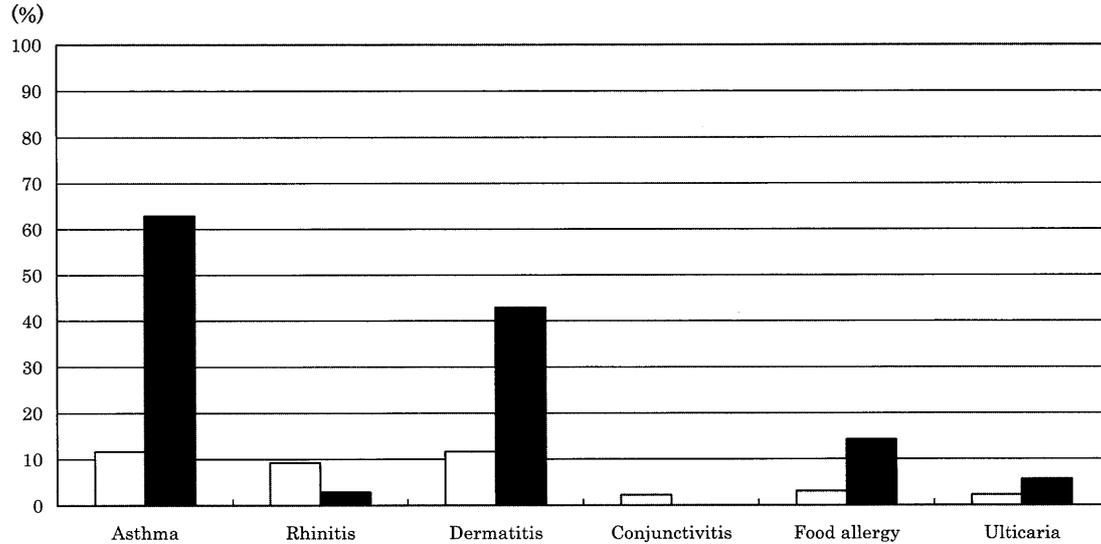
When all results of the survey were tabulated, no significant difference was noted between the two groups, with or without allergic disease, in the control group.

### 2. Comparison of the changes following mosquito bites

The maximum diameter of the swelling caused by mosquito bites in most of those in the control group was around 1 cm, and the median was 1.5 cm. In most of those the group with mosquito-bite-induced conditions, the maximum diameter of the swelling was 3 cm, the median was 3 cm. The reaction tended to be greater in the latter group (Fig. 3).

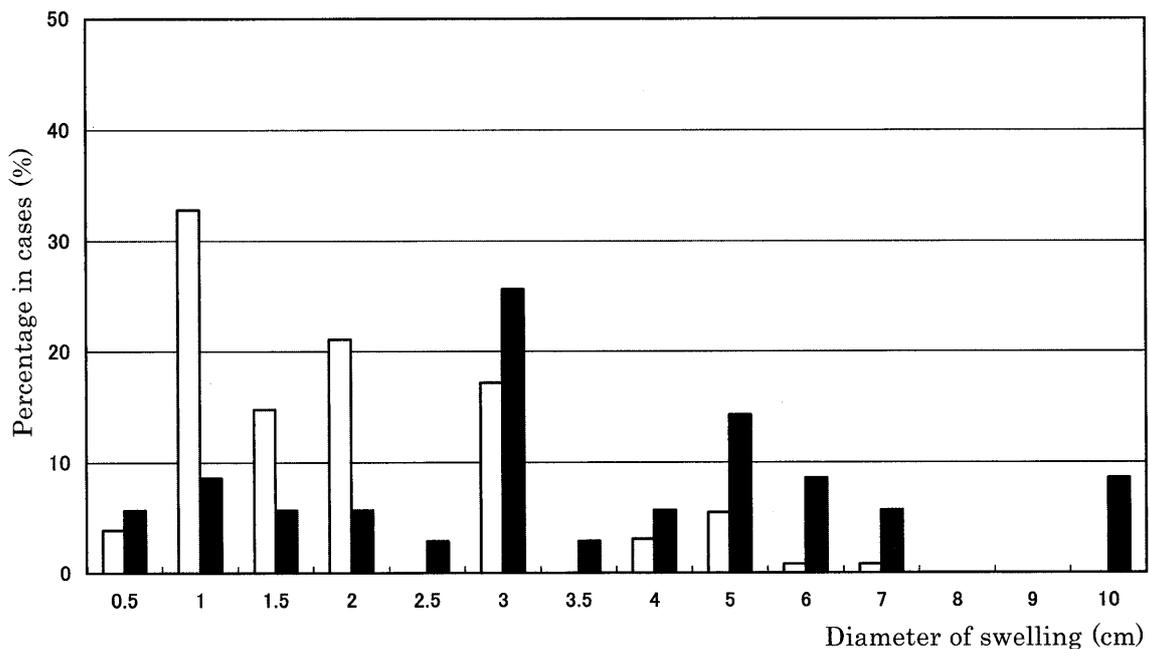
After the bite, the swelling also persisted for a longer period in the group with the mosquito-bite-induced conditions than in the control group, and its median duration was 7 days in the former group as opposed to only 3 days in the latter group (Fig. 4).

The relationship between swelling diameter and duration of swelling after the mosquito bite is



**Fig. 2** Percentages of allergic diseases complicating

All (100%) of the cases with the mosquito-bite-induced condition (■) reported experiences with allergic diseases. Thirty-eight children (29.7%) of the control cases (□) suffered from allergic diseases.

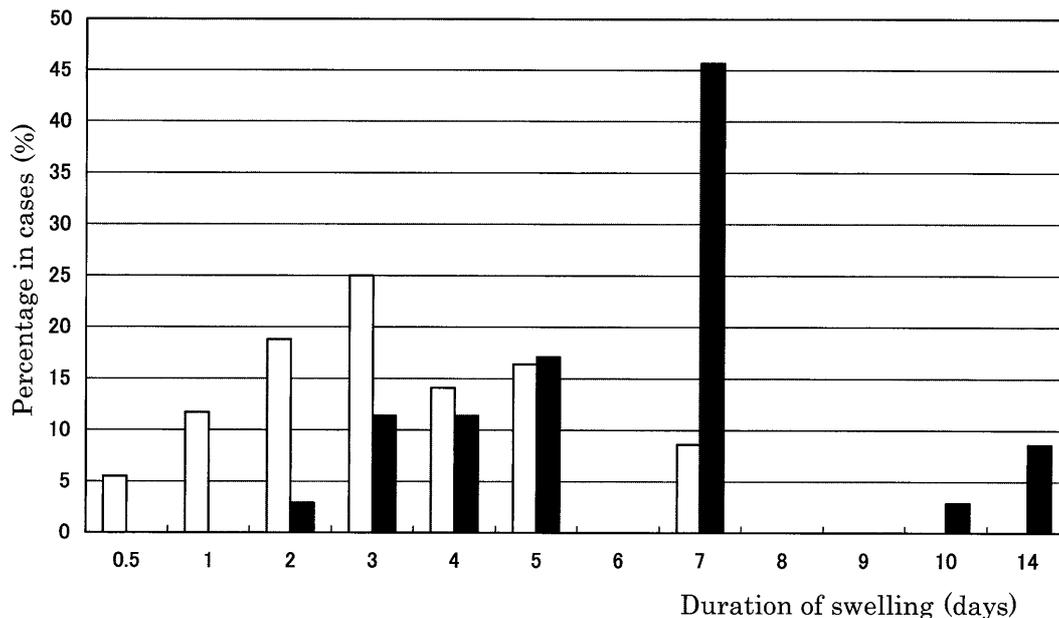


**Fig. 3** Distribution of maximum swelling diameter after mosquito bite

In most of the control cases (□), the diameter of swelling was around 1 cm, (the median 1.5 cm). In the cases with mosquito-bite-induced condition (■) it was 3 cm in most (the median 3 cm). The later tended to be greater than the former.

shown in Fig. 5. The control group shows smaller diameters and a shorter duration of swelling, while in the group with a mosquito-bite-induced condition, those individuals with smaller swelling diameters

tended to have the symptom for a longer time. The durations of almost all (20 of 35 cases) exceeded 7 days. Only three patients in this group showed swelling diameters of less than 3 cm and a duration



**Fig. 4** Distribution of duration of swelling after mosquito bite  
 In control cases (□), the median duration was 3 days. In cases with mosquito-bite-induced condition (■), it was 7 days. The later tended to be longer than the former.

of swelling within 7 days. These three patients exhibited lesions, such as blister formation and suppurative changes.

It was found that most of the cases with mosquito-bite-induced conditions showed a maximum swelling diameter of 3 cm or more that lasted at least 7 days, and lesions such as occasional blisters and suppurative changes.

### 3. Comparison of sequential responses following mosquito bites

For question 2 of questionnaire, sequential changes in the response to mosquito bites were recorded. The results are shown in Table.

For question 2a, "immediate swelling and complete recovery on the following day", a significantly large number of individuals met this condition in the control group ( $p < 0.05$ ).

For questions 2b, "swelling developing on the next day or later" and question 2c, "persistence of swelling", the number of cases meeting these conditions were significantly greater in the group with the mosquito-bite-induced condition ( $p < 0.05$ ).

In particular, "blister formation" described in question 2d and "oozing and suppurative changes" of question 2e were more prominent in the group

with the mosquito-bite-induced condition than the control group ( $p < 0.001$ ).

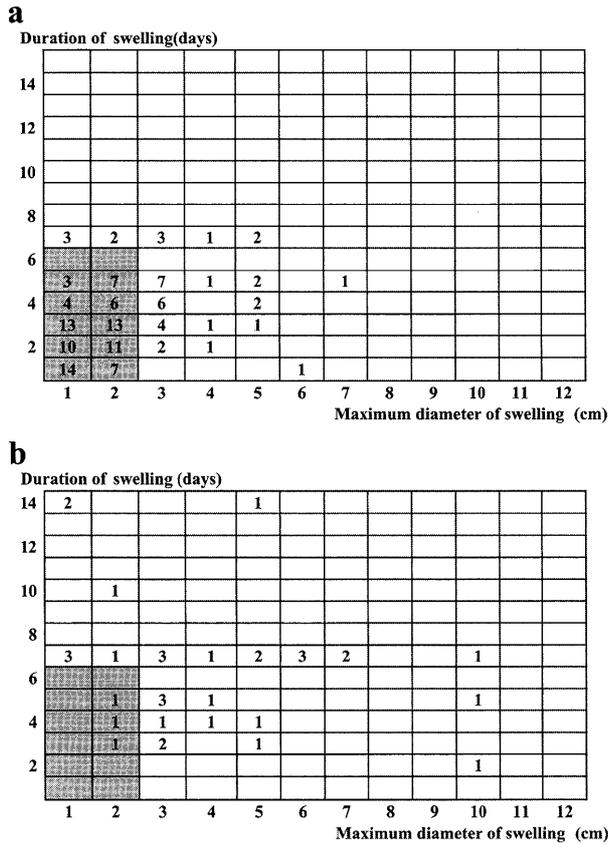
### 4. Comparison of the changes following preventive vaccination

The presence (or absence) of swelling, an adverse effect of vaccination, was asked in question 3 of the questionnaire.

A hard lump was felt for a number of days following vaccination in 13.3% of the control group and 22.9% of the group with the mosquito-bite-induced condition. No significant difference was found between the two groups. The use of the triple-vaccines was associated with the most frequent adverse effects: in both groups, more than half reported untoward effects.

### 5. Comparison of family histories

According to question 4, the incidence of similar symptoms in response to mosquito bites was investigated among relatives (including second-degree relatives). In the control group, 47 members (36.9%) were affected; and in the group with the mosquito-bite-induced condition, 20 cases (57.1%), the latter percentage being significantly higher ( $p < 0.05$ ).



**Fig. 5** Diameter and duration of swelling after mosquito bite

Numbers in figures were the number of cases.

a: control cases (n=128).

b: mosquito-bite-induced condition (n=35).

The control cases show smaller diameter and shorter duration, while in the cases with mosquito-bite-induced condition, it's diameter was almost 3 cm or more and it's lesion lasted for 7 days.

Dark backgrounds of figures were area in which the diameter was under 3 cm and the duration was under 7 days.

## 6. Comparison of treatment following mosquito bites

The kind of the treatment employed was investigated based on question 5. In the group with the mosquito-bite-induced condition, more than half of them were treated with anti-allergy agents in addition to anti-histaminics and steroid ointments.

Among the control group, 32 subjects (25%) were treated with ointments, such as antihistaminics and steroid preparations, at a dermatology department or another department. Eighty-three patients (64.8%) of this group had been treated with over-the-counter preparations, 5 were untreated, and 8 did not respond.

## 7. Evaluation of cases with the mosquito-bite-induced condition and treated with tranilast

1) Clinical backgrounds of patients with the mosquito-bite-induced condition who were treated with tranilast

Among those with the mosquito-bite-induced condition, 32 were available for observation following tranilast administration. More than one-half of them (19) had been receiving oral anti-allergy agents.

About one-half were treated with oxatamide (5) or ketotifen (4), which have antihistaminic actions, but their effects were not recognized.

2) The eosinophil count in those cases with the mosquito-bite-induced condition

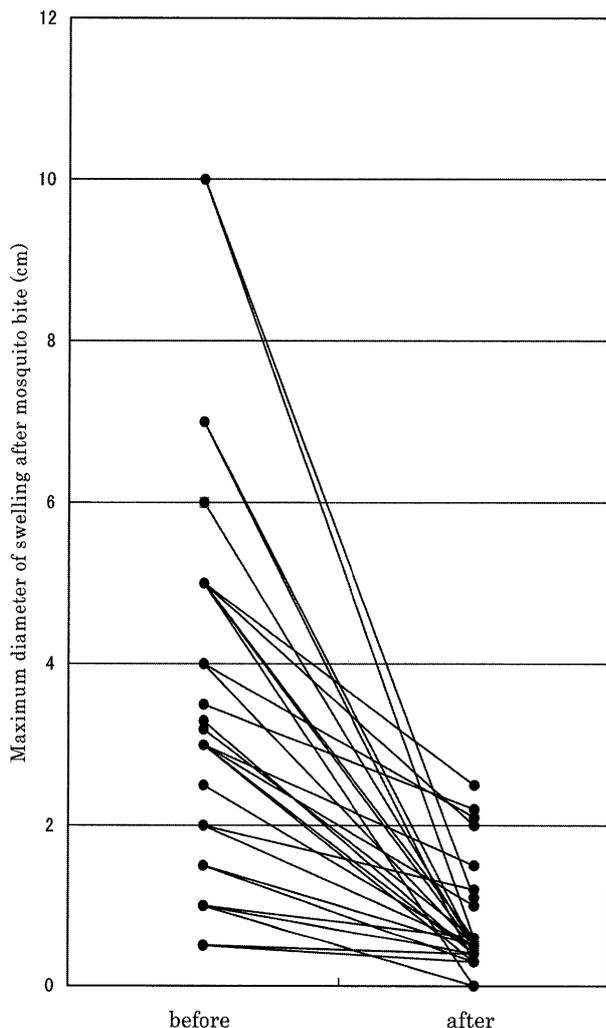
The mean eosinophil count of the patients with the mosquito-bite-induced condition was 391/ $\mu\text{l}$ . Only 5 (15%) exhibited an eosinophil count exceeding 500/ $\mu\text{l}$ .

3) Total IgE level of patients with the mosquito-bite-induced condition and their specific IgE anti-

**Table** Changes following mosquito bite

Responses	Cases (%)		p values
	mosquito-bite-induced condition	control	
a: Swelling within 30 min to 1 hr followed by amelioration on the next day	42 (32.8)	5 (14.3)	< 0.05
b: Swelling does not occur until the 2 day exacerbated thereafter	19 (14.8)	14 (40.0)	< 0.01
c: Immediate swelling followed by gradual exacerbation with prolonged recovery	43 (33.5)	20 (57.1)	< 0.05
d: Blister develops	11 ( 8.6)	13 (37.1)	< 0.001
e: The skin likely to be damaged through scratching, the lesion is often oozing and resists recovery	24 (18.8)	27 (77.1)	< 0.001

For question 2 of the questionnaire (Fig. 1), sequential changes in the response to mosquito bite were recorded.



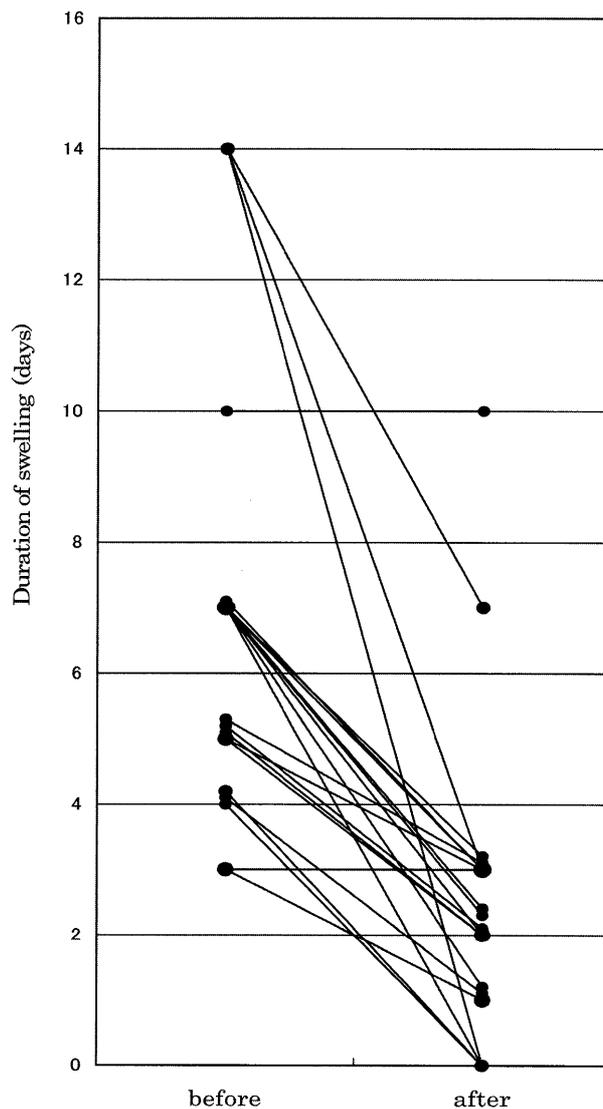
**Fig. 6** Changes in swelling diameter before and after tranilast administration

Investigation was done after 3 weeks of tranilast administration. According to the tranilast administration, the swelling diameter was 0.5 cm in after smaller than 3 cm in before.

body positivity

Because all had suffered from allergic diseases, the total IgE level was high among those with the mosquito-bite-induced condition (601.5 IU/ml). In fact, it was abnormally high (over 1,000 IU/ml) in 4 of them. However, for 5 of them, it was within the normal range in comparison with the total level for each age group. The specific IgE antibody content was negative for all items examined in 4 patients.

Because of a high incidence of allergic diseases among the patients with the mosquito-bite-induced condition, the positive reactions for specific IgE antibodies was high for house dust and mites. The



**Fig. 7** Changes in duration of swelling before and after tranilast administration

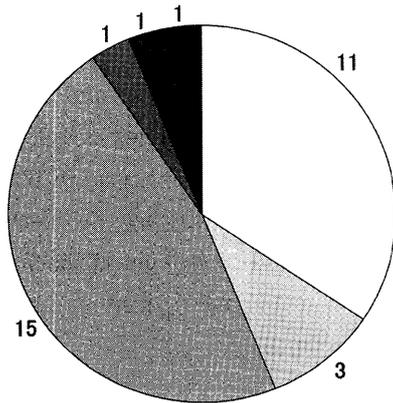
Investigation was done after 3 weeks of tranilast administration. According to the tranilast administration, the duration of swelling was 2 days in after shorter than 7 days in before.

group consisting of extremely young children ranging from 9 months to 6 years showed high incidence of positive reaction to eggs white.

Only one scored 1 in the radioallergosorbent test (RAST) for mosquitoes.

#### 8. Changes after a mosquito bite caused by tranilast administration

The median maximum diameter of the swelling caused by mosquito bites was 3 cm before tranilast administration. After tranilast administration, it tended to be reduced to a median of 0.5 cm (Fig. 6).



**Fig. 8** Evaluation of tranilast administration by guardian of 32 cases

Above numbers were the number of cases. Perfect point for drug efficacy at 5 was set. The mean point was 4.25. Most of points were over 4 points. These points were scored by guardians' observational judgment. 5 point was satisfied, 1 point was not effective.

□ : 5 points, ▒ : 4.5 points, ▒ : 4 points,  
 ▒ : 3.5 points, ■ : 3 points, ■ : 1 point.

The median duration of swelling after mosquito bites was 7 days but tranilast administration tended to reduce it to 2 days (Fig. 7).

### 9. Evaluation of tranilast administration by the patients' guardians

Setting a perfect point for drug efficacy at 5, a study was conducted on how the guardians of the patients rated the medication. These points were scored by guardians' observational judgment. The results are shown in Fig. 8. The mean was fairly high (4.25). A single point (not effective) was assigned by the guardian of one patient who also gave a RAST 1+ to mosquitoes.

From these results, one may expect that tranilast administration will be effective against the mosquito-bite-induced condition.

No other side-effects were recorded on tranilast.

### Discussion

It is believed that man's response to a mosquito bite is the skin response to the saliva that is manufactured in the salivary duct of a mosquito's anterior thoracic region. However, histamine in a quantity sufficient to provoke mosquito bite-related itching has not been isolated from this salivary duct substance<sup>1)2)</sup>.

The skin reaction caused by a mosquito bite changes with the frequency of bites, and it is believed to be an allergic response to the saliva that is injected intradermally through the bite<sup>2)</sup>.

The same reaction is generally divided into 2 groups according to the time sequence; an immediate and delayed reactions<sup>3)</sup>.

The immediate reaction develops within several minutes following the bite. Erythema and wheal accompanied by itching appear at the site where the bite has occurred; the symptoms reach a maximum 30 min later, then diminish and are eliminated within 2 hr. During this reaction, the presence of the IgE antibody specific to the mosquito salivary gland antigen can be proven, which leads to a conclusion that the process is a type I allergic reaction through the IgE antibody. It is classified as a Th2 type reaction. And the effect of antihistamines on this reaction was evaluated in children<sup>4)5)</sup>.

The delayed reaction develops several hours after the bite, reaches a maximum level in 24 to 48 hr, then lessens and becomes extinct about one week later. It closely resembles a type IV allergic reaction of hypersensitivity. The belief is that the reaction occurs through the induction of Th1. It has been reported that a lymphocyte stimulation test (LST), using a mosquito salivary gland antigen, produced a significant result<sup>6)</sup>.

These immediate and delayed reactions are combined differently in each individual. It is believed that the difference is due to the frequency of exposure to mosquito bites, one's age, and varied individual immune responses such as sensitization and desensitization<sup>7)</sup>.

In 1989, Ohtaki and Oka conducted a survey on responses to mosquito bites by 162 subjects aged 1 to 68 years, employing *hitosujishimaka* (*Aedes albopictus*. Skuse) that normally exists only in Japan<sup>6)7)</sup>.

In group 1, which was composed of young children between the ages of 1 to 6 years, no immediate reaction was noted in 12%; and the response course approximated delayed reactions. In groups 2 (7 to 10 years), 3 (11 to 20 years), and 4 (21 to 50 years), their responses were mainly regarded to fall into other reactions, where immediate and delayed

types were mixed; but the delayed reaction was absent in 47% of those in group 4, suggesting that their reaction was only immediate type. In group 5 composed of those at a more advanced age (51 to 68 years), many produced no responses. The investigators of this study reported no significant difference between genders or the presence (or absence) of an atopic history.

Although there were only 17 subjects in group 1 (composed of young children between 1 to 6 years) in the study by Ohtaki and Oka<sup>6(7)</sup>, the 128 nursery school children who made up the control group of our study were of the same age. The maximum diameter of the swelling after being bitten reported by the former was around 1 cm, which was comparable to the data from our study. However, around 30% of the subjects in our study produced a delayed type reaction after the bites: swelling or gradual exacerbation on the next day or later. This finding contradicted the report by Ohtaki and Oka<sup>7)</sup> (100% displaying a delayed reaction). Perhaps this discrepancy may be explained by the fact that many of the nursery school children in our study were older and had therefore been exposed to mosquito bites, thus producing only the immediate reaction. It was concluded from the results of our study that the median maximum diameter of swelling after the mosquito bites is 1.5 cm and the swelling lasts about 3 days in healthy infants.

As stated earlier, we came to the conclusion that the maximum diameter of swelling after the mosquito bites in the sensitive subjects exceeds 3 cm and the resultant swelling lasts over 7 days: in addition, many of these subjects characteristically developed blisters or experienced suppurative changes.

The symptom of swelling did not abate in spite of repeated bites in some of those in the group with the mosquito-bite-induced conditions: some of those being treated at the outpatient clinic even experienced exacerbation of the symptoms in each season. Their courses appeared to differ from the common responses in which symptoms abate after repeated bites. The results of our study indicate that the patients with the mosquito-bite-induced condition do

not follow the clinical course that has been described previously; they exhibit a maximum diameter of swelling in excess of 3 cm and a duration of swelling lasted over 7 days. They developed abnormal conditions following the mosquito bites, which differ from mosquito-allergy in the narrow sense that is closely related to malignant diseases associated not only with dermal symptoms but also with systemic symptoms.

The administration of tranilast produced clinically satisfactory results in our patients. In analyzing the mechanism to explain this, the anti-keeloid and anti-scaring effects of this agent (which are not present in other anti-allergic agents) may play a role in manifesting its efficacy. In fact, in spite of a large number of children with allergic diseases in the present study, only one showed RAST 1 for the IgE antibody specific to mosquitoes. It suggests that the immediate reaction was not involved in the symptoms of the mosquito-bite-induced condition.

It has been reported that the effect of tranilast administration manifests mainly in fibroblasts by suppressing the release and production of TGF (transforming growth factor)- $\beta$ 1, a cytokine that is involved in enhancing collagen synthesis and matrix formation. It has also been reported that tranilast has an effect to suppress keloid formation or collagen synthesis by hypertrophic fibroblasts<sup>8)</sup>. Also one must not overlook its effect, like that of other anti-allergy agents, to suppress the release or production of histamine, prostaglandin E2, and active enzymes that are responsible for itching and other related symptoms. Almost all anti-allergic agents are equipped with a function to suppress type I hypersensitivity. It is believed that the unique efficacy recognized in the action of tranilast stems from its effects to inhibit TGF- $\beta$ 1 and suppress granulation, as expressed by inhibiting collagen synthesis.

In this study we focused on mosquito bites, because the children in both groups lived in an urban area, and there was little possibility of being bitten by horseflies or moths.

Some data on experimental mosquito bites on human have been reported in previous papers, but in

recent years such human experiments have not be permitted because of ethical issues. This was a retrospective study and relied on data obtained on the basis of guardians' memory, so some data may not be correct. For further assignment, it may be necessary to investigate a larger cohort or conduct a prospective trial.

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### 蚊刺症患児の臨床的背景と tranilast の効果

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一般小児科外来診療において、蚊刺により腫れて困っている患児がいることを多くの小児科医が経験しているが、これらの症状を呈する児の定義や治療は確立されていない。蚊によると考えられる虫刺症である蚊刺症の診断を考える上で、対象として保育園児の蚊刺後の反応を比較検討し、蚊刺症と判断する基準について調査した。更に、蚊刺症と判断した症例に対する tranilast 投与の効果についての評価を行った。当科および戸田中央総合病院小児アレルギー外来で蚊刺後の症状を主訴に蚊刺症として治療した児童 35 名を蚊刺症例群とし、荒川区内の 2 ヶ所の保育園児童 128 名を対照群とした。両群に蚊刺後の反応について、保護者に対しアンケート調査を行い比較検討した。また、蚊刺症例群には tranilast 投与の効果をも 5 点満点とする評価の調査も併せて行った。蚊刺後の最も大きく腫れた直径は、対照群では中央値 1.5cm に対し、蚊刺症例群では中央値 3cm と蚊刺症例群の反応が大きい傾向であった。蚊刺後の腫脹期間は、対照群では中央値 3 日に対し、蚊刺症例群では中央値 7 日と長くなっていた。従って、蚊刺症例群の特徴としては、最も大きく腫れた直径が 3cm 以上で腫脹期間が 7 日以上であると考えられる。tranilast 投与における蚊刺後の変化は、最も大きく腫れた直径の変化では、投与後は中央値 0.5cm と減少し、腫脹期間の変化でも投与後は中央値 2 日と短縮した。tranilast 投与の有効性の調査でも 5 点満点中 4.25 点と高い評価を認めた。このことから、蚊刺症に対する tranilast 投与の効果が期待される。