

CHRONIC URTICARIA

A clinical study with special reference to vascular reactions mediated by the kallikrein-kinin system

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The etiology of chronic urticaria is unknown in 70 to 90 % of the patients. The therapeutic response to antihistamines is moderate or poor. A number of reviews of chronic urticaria and factors influencing its course have been published (2, 4, 6).

Increased reactions to intradermal injection of kallikrein and a delayed abnormal reaction to bradykinin and histamine have recently been described in chronic urticaria and hereditary angioneurotic edema (9, 10). The pathological reactivity returned to normal after infusions of a kallikrein inhibitor. The patients became free from urticaria for one to twelve weeks (10). This indicates that the kallikrein-kinin system is probably an important mediator of the urticarial reaction.

These findings open the possibility of explaining some characteristic features of chronic urticaria as depending upon an induced disturbance in the kallikrein-kinin system. The aim of the present investigation was to answer the following questions: 1. How common is the abnormal reactivity to kallikrein in patients with chronic urticaria and is the reactivity normal or less abnormal during urticaria-free intervals? 2. Do patients with abnormal reactions to kallikrein differ from those with normal reactions with regard to medical history, clinical course, laboratory findings or therapeutic response? 3. How does the changed vascular reactivity influence other diagnostic skin tests?

Material and Methods

During one year the patients attending the dermatological clinic for treatment of

chronic urticaria were investigated with special regard to abnormal vascular reactions. For comparison a number of patients with factitious, cold, cholinergic and acute urticaria were also studied.

In the present study the urticaria was classified as chronic when there were frequent urticarial eruptions for more than four months. The term recidivating usually indicates that the urticaria-free periods are longer than those of the urticarial attacks. The borderline between chronic and recidivating urticaria is, however, somewhat diffuse and patients with chronic and those with recidivating urticaria were therefore regarded as one group. Factitious urticaria, cold urticaria and cholinergic urticaria are clinically well-defined urticarial conditions. Although they have a chronic course they were not included in the group of chronic urticaria.

Chronic and Recidivating Urticaria

Forty-three patients were studied in this group. Most of them were investigated in the wards because of frequent eruptions of urticaria. The age and sex distribution is indicated in Fig. 1 and shows that nineteen out of the twenty-eight women (68 %) were above 40 years of age. All patients had their urticaria for more than four months, and most of them for several years (Fig. 2). Thus twenty-nine patients had urticarial attacks for more than five years and eleven of them for more than ten years.

The frequency of urticarial eruptions varied from daily (18 patients, including 12 women above 40 years of age) to more irregular attacks (18 patients). Five pa-

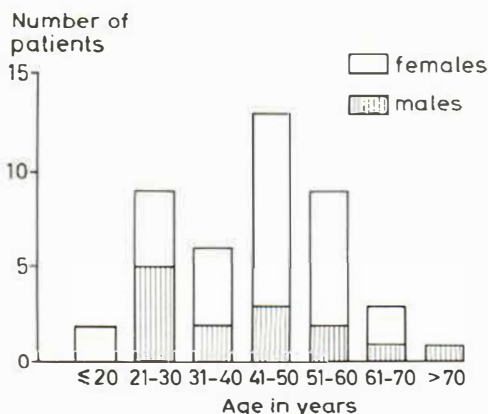


Fig. 1. Age distribution of 43 patients with chronic urticaria.

tients had no urticaria in the last three to four months and two patients had no urticaria in the last two years. Before then they had almost daily urticarial attacks for several years. Features in the medical history are listed in Table 1.

A family history of symptoms likely to be atopic (asthma, allergic rhinitis or atopic dermatitis) was found in eleven patients and a personal history of atopy in five patients. Five patients had a family history of chronic urticaria.

The initiating factor associated with the first urticarial eruption was usually obscure. Throat infection, cholecystitis, cholecystectomy, vaccination against smallpox, infections treated with penicillin, sulphonamides or aspirin were in some patients believed to have caused the first attack, but in thirty-two patients (74 %) no probable primary factor could be identified.

Incidence of cholecystectomy and cholecystopathy. Cholecystectomy had been performed in ten out of nineteen (52 %) women above 40 years of age and another two had a cholecystopathy with a non-functioning gall bladder. Thus 62 % had some abnormality in their biliary tract. Seven of them had experienced the urticaria before the cholecystectomy. In 100 other female patients aged 40 to 60 years and with various other dermatologic disorders a cholecystectomy had been performed in 12 %. Among seven men with chronic urticaria above 40 years of age in the present study, three had signs of chole-

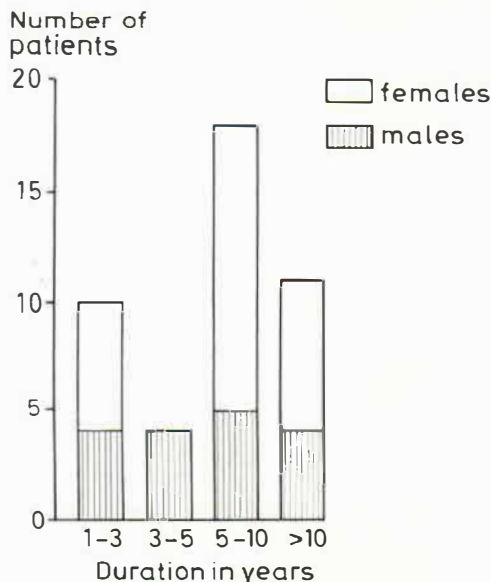


Fig. 2. Time from initial onset of urticaria.

cystopathy, but this was verified radiographically in only one of them.

Chronic infections were not prominent. In no case could a chronic infection be correlated with certainty to the onset of the urticaria. Six patients noticed exacerbation of their urticaria after upper respiratory tract infections.

Increased reaction to mosquito bites: Five patients had a history of large swellings in reaction to mosquito bites. On some occasions these had been followed by an urticarial reaction.

Increased reaction to tuberculin with pronounced edema of the skin around the test site had been observed in three patients several years before the first attack of urticaria. There was no history of tuberculous infections in these cases.

Influence of drugs. Acetylsalicylic acid was considered to be a main or predominating etiological factor in nine patients. In these patients the urticaria became worse after 0.5 g of aspirin. After avoidance of salicylates the condition improved. Another eight patients had noticed exacerbation of the urticaria after salicylates but were able to take aspirin without trouble during free intervals. Five patients had urticarial eruptions after penicillin, in two of them the skin test to penicillinoyl was positive, in the

Table 1. Features of the medical history of 43 patients with chronic urticaria

	Number of patients	%
Chronic urticaria—family history	5	12
Atopic disorders—family history	11	25
Atopic disorders—personal history	5	12
Cholecystectomy among 19 women above 40 years of age	10/19	52
Cholecystopathy among 19 women above 40 years of age	2/19	10
Chronic infection (dental infection, tonsillitis, sinusitis, urinary tract infection)	7	16
Increased reactions to mosquitoes	5	12
Increased reactions to tuberculin	3	7
Aggravation of urticaria		
after aspirin	17	37
after penicillin	5	12
after various other drugs (chloromycetin, nitrofurantoin, sulphonamides, nystatin, epsilonaminocaproic acid)	4	9
by psychogenic factors and fatigue	33	77
Seasonal variation	12	28
Response to antihistamines good	3	7
Response to antihistamines moderate	4	9
Response to antihistamines poor	34	83

others negative. In four patients the following drugs seemed to aggravate the urticaria: chloromycetin, nitrofurantoin, sulphonamides, nystatin and epsilonaminocaproic acid.

Psychogenic factors: Increased mental tension and fatigue were the main exacerbating or precipitating factors spontaneously reported by 77 % of the patients. Psychogenic factors were, however, never believed to have started the first attack of urticaria. The increased mental tension which aggravated the urticaria was usually said to be moderate, often consisting of seemingly normal tension-increasing reactions to ordinary daily events. Several of the patients had noticed an improvement with less or no urticaria during vacations. Only two patients had required medical help for nervous problems and in most of the patients there were no signs of increased nervous tension. Among the more extreme examples of psychogenic influences leading to urticarial eruptions were: a nurse who was involved in an anesthesia accident

leading to the death of the patient; a mother who was frightened each time she had to give her daughter driving lessons; a student who had urticaria each time he tried to pass an examination.

Response to antihistamines: The effect of various antihistamines was considered to be good in three patients, two of whom were sensitive to aspirin, and fair in four patients, also sensitive to aspirin. Otherwise the response to antihistamines was remarkably poor, at least in ordinary doses.

The *examination* of the patients generally revealed nothing abnormal except the urticarial lesions. These were often longstanding (10 to 24 hours), and sometimes tender to pressure, especially when located on the hands or feet. Sometimes they left a bluish discolouration similar to that occasionally occurring after intradermal tests with kallikrein. Another characteristic feature seen in patients with chronic urticaria was an erythematous and "glassy" swelling of the skin at the site of venipuncture, usually appearing 2 to 5 hours later. This tendency

varied, however, from time to time. It was observed in twelve of the forty-three patients (28%) with chronic or recidivating urticaria. Patients with aspirin as predominant etiological factor, however, usually had more superficial and less long-standing wheals than the other patients with chronic urticaria and they had no delayed reactions after venipuncture. Two women showed a marked tendency to flushing, probably menopausal. The urticarial lesions were most pronounced in the flushed skin and the flushing often preceded the eruption of hives.

Dermographism of the ordinary immediate type was seen in two patients and one patient showed dermographism during the urticarial eruption, but not in the free intervals. Two patients had delayed dermographism with maximal intensity 3 to 6 hours later; one of them also showed immediate dermographism.

Dental infection was found in one patient, sinusitis in one and urinary infection in another. Systemic lupus erythematosus with a hemolytic anemia was diagnosed in one patient in whom chronic urticaria started the day after cholecystectomy. Discoid lupus erythematosus was found in one patient.

Laboratory findings: Routine laboratory examinations gave, as a rule, little useful information. The level of the immunoglobulins G, A, and M was determined in twelve patients. In six of them IgA was slightly increased. One patient with systemic lupus erythematosus had an increased level of IgG. The level of IgM was normal in all patients. The level of IgE was determined in seventeen patients. IgE was normal or lowered (8), except in two patients with both urticaria and asthmatic bronchitis, who had an elevated level of IgE.

The blood groups were determined in thirty-one of the patients (those seen in the later two-thirds of the study). Fourteen patients belonged to blood group A, four patients to blood group B, and thirteen to blood group O.

Other Types of Urticaria and Controls

Acute urticaria: Twenty patients, most of them above 30 years of age, had acute urticaria, mostly of unknown cause. Three patients had a severe generalized urticaria, induced by penicillin, in two patients aspirin was the probable cause and in three patients various other drugs. Often an upper respiratory tract infection was present. The patients were tested when they had their urticarial eruption, which usually lasted for two to ten days.

Factitious urticaria: Twelve patients, eight of them over 30 years, had marked dermographism and the urticarial lesions were referable to scratching or rubbing.

Cholinergic urticaria: Seven patients, aged 20 to 30 years, had typical cholinergic urticaria with small wheals surrounded by erythema appearing after exposure to heat or exercise.

Cold urticaria: Four patients had typical cold urticaria since seven to thirty years. Tests with ice cubes produced an urticarial reaction.

Delayed pressure urticaria: One patient, a woman, 39 years of age, with a history of atopic dermatitis, developed deep, painful, tense cutaneous infiltrates 4 to 6 hours after pressure. The symptoms first appeared one month after an operation for cervical carcinoma, type I.

Controls: Twenty-five apparently healthy men and women, mostly hospital personnel, aged 22 to 56 years, served as controls. Eleven of them were more than 30 years old.

Intradermal Tests

All patients were tested with intradermal injections of kallikrein, bradykinin and histamine as described elsewhere in detail (9). The drugs used were: Histamine hydrochloride, 0.1 mg/ml; Bradykinin,¹ 0.1 mg/ml; Kallikrein.² The dry powder containing 40 U kallikrein, 0.02 mg thiomersal-sodium and 3.44 mg sodium chloride was dissolved in 1 ml of saline. When tested the

¹ BRS, Bradykinin was kindly supplied by Sandoz, Stockholm, Sweden.

² Padutin®, Bayer AG, Leverkusen, Germany.

Table 2. Reaction to intradermal injection of kallikrein

	Number	Mean area of infiltration in mm ² ± SE of the mean				
		20 min	1h	2h	5h	24h
Controls 22-30 yrs	14	104 ± 11	119 ± 25	116 ± 25	316 ± 90	766 ± 158
Controls > 30 yrs	11	108 ± 16	126 ± 13	199 ± 21	342 ± 59	359 ± 89
Chronic urticaria	43	203 ± 27	520 ± 71**	889 ± 104***	1985 ± 261***	3154 ± 1086***
Acute urticaria	20	168 ± 22	278 ± 51**	339 ± 60	347 ± 56	233 ± 108
Factitious urticaria	12	109 ± 18	208 ± 53	446 ± 163	422 ± 128	533 ± 255
Cholinergic urticaria	7	118 ± 13	283 ± 99	255 ± 42	183 ± 33	101 ± 63
Cold urticaria	5	76 ± 6	157 ± 60	378 ± 267	541 ± 201	(942, 1375, 1570) ¹

¹ Only 3 patients checked at 24 hours.

** $p < 0.01$

*** $p < 0.001$ compared to controls > 30 years.

patients were receiving no internal therapy for their urticaria.

In forty-seven patients with various types of urticaria, routine skin testing with thirty-eight common allergens was also performed. The following types and numbers of antigens were used: dust (2), mold mixture (1), food (13), dander (6), pollen (7), plants (9). The test reactions were checked after 20 minutes and 1, 2, 3, and 5 hours by measuring the diameters of the wheals and the erythema and the results were evaluated according to the criteria suggested by Sheldon (20). The results were compared with those found in patients with other types of dermatological disorders.

In seventeen patients with chronic urticaria, the tuberculin reaction was checked using 2 TU of Purified Tuberculin Protein (Tuberculin Dept., The State Serum Institute, Copenhagen).

Results

Kallikrein. The reaction to kallikrein in the various types of urticaria is shown in Table 2 where the mean area of infiltration is given in mm². Fig. 3 illustrates the individual areas of infiltration 5 hours after the injection of kallikrein in each patient with chronic, acute and factitious urticaria. The tendency to increased reactions to kallikrein described in a previous paper for patients with chronic urticaria when compared to the controls was also confirmed here. The same applies to significant differences observed when compared with other types of urticaria. Such differences were

found at 1, 2, 5, and 24 hours between acute and chronic urticaria ($p < 0.01$, 0.001 , 0.001 and 0.001 , respectively).

There were no significant differences between controls and patients with factitious, cholinergic or cold urticaria. The reaction to kallikrein in patients with acute urticaria was increased at one hour compared with the reaction in controls ($p < 0.01$), but did not differ at other times from the latter reaction. The reaction to kallikrein was usually within normal limits, with the exception of three patients with severe, generalized urticaria, in two of them induced by penicillin. The reactions returned to normal when they had been free from their urticaria for one week. Two other patients with acute urticaria had moderately increased reactions.

In patients with chronic urticaria and with aspirin as a predominant etiological factor the reaction to kallikrein was less ($p < 0.001$) than in the other patients with chronic urticaria, but it was still increased as compared to the reaction in healthy subjects ($p < 0.01$). Thus at 5 and 24 hours the values for nine patients with urticaria essentially caused by aspirin were 788 ± 105 and 281 ± 147 mm², respectively. The corresponding values for the rest of the group were 2393 ± 263 and 4234 ± 1225 mm², respectively.

Large, markedly voluminous reactions to kallikrein often seemed to be associated with blood group A. The mean values of the kallikrein reactions at 5 hours for patients belonging to groups A, B, and O are shown in Table 3. The reaction in the

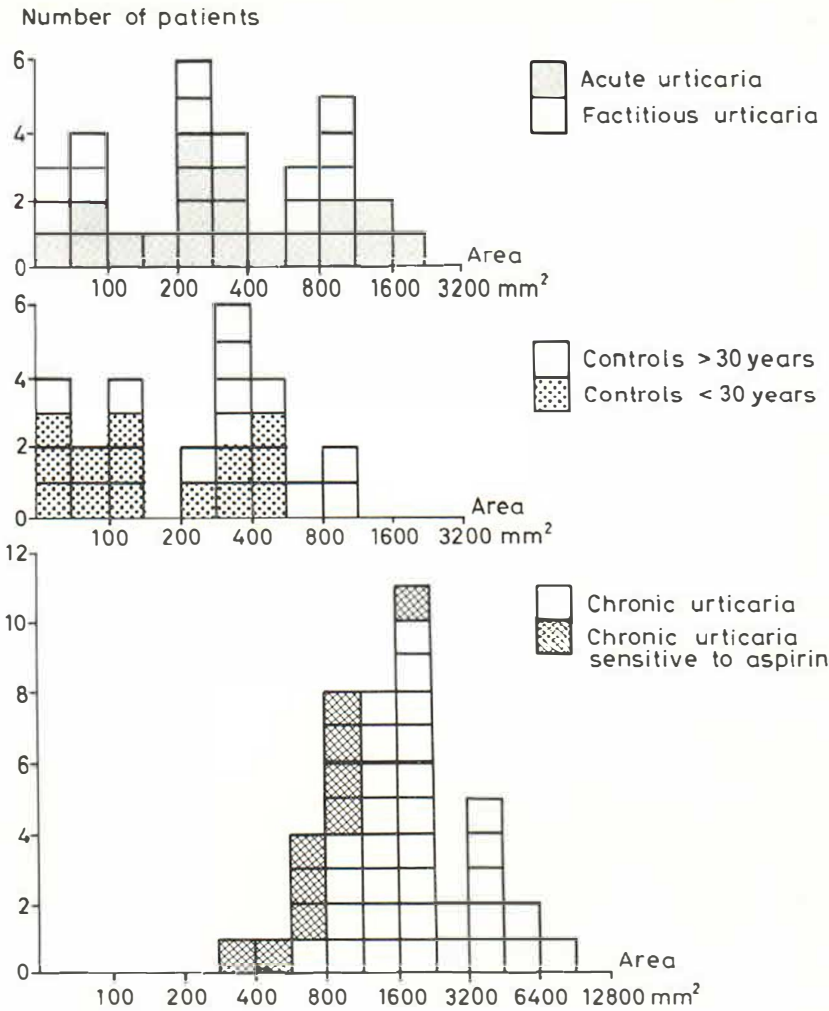


Fig. 3. Reaction to kallikrein in controls and in patients with acute, factitious and chronic urticaria. Area of infiltration 5 hours after injection of kallikrein.

patients with blood group A was significantly larger than in the patients with blood group O ($p < 0.01$). In one of the patients with blood group A the urticaria had been aggravated by aspirin, whereas those with blood group O included five who were sensitive to aspirin; in three of them aspirin was considered to be the main etiological factor.

Neither the duration nor the intensity of the chronic urticaria seemed to be correlated to the size of the kallikrein reaction. One patient who had been free from urticaria for two years, however, had a normal reaction. A marked increase in reactivity to kallikrein was seen in ten pa-

tients who had been free from urticaria for two to twenty-four months (mean area $2,430 \pm 290 \text{ mm}^2$ at 5 hours). Thus it is obvious that an abnormal kallikrein reaction can also be present during periods free from urticaria.

Histamine. The immediate reaction to histamine was within normal limits in all patients. In sixteen out of forty-three patients with chronic urticaria (37%) a wheal or infiltration was still present or reappeared 2 hours after an injection of histamine. The delayed urticarial wheal had its maximum after 5 to 10 hours in ten of the patients. Saline controls were negative. Except in one patient with a severe, peni-

Table 3. Comparison of reactions to kallikrein in patients with chronic urticaria—with regard to blood group A, B and O

	Number	Mean area of infiltration in mm ² ± SE of the mean
Patients blood group A	14	3042 ± 505
Patients blood group B	4	1897 ± 151
Patients blood group O	13	1233 ± 228

A > O: $p < 0.01$.

cillin-induced urticaria, patients with other forms of urticaria had no such delayed reactions.

Bradykinin. The initial reaction to bradykinin in patients with chronic urticaria did not differ from those seen in other types of urticaria. In twenty-one out of forty-three patients with chronic urticaria (48%) a reddish infiltration was still visible 2 hours after the injection. In fourteen of them it increased in size, with a maximum at 5 to 6 hours. Two patients with factitial and six with acute urticaria had a residual, usually skin-coloured infiltration at 2 hours. In two of the patients with acute urticaria (two of those with increased reactions to kallikrein) an infiltration was still present after 5 hours. The reactions returned to normal when the patients became free of urticaria. With these exceptions, no delayed reactions to bradykinin were seen in patients other than those with chronic urticaria.

The occurrence of delayed reactions to histamine and bradykinin showed no correlation to the duration, frequency or severity of the urticaria. They were not seen in chronic urticaria mainly induced by aspirin.

Intradermal tests with some common antigens mentioned on page 5 were performed in eighty patients with various diagnoses (Table 4). In chronic urticaria the immediate reactions were negative in nineteen patients and positive to one or several antigens in nine patients. The positive reactions were often small and without any known correlation to the medical history or to the clinical manifestations. With

the exception of two cases they were not followed by any delayed whealing. In nineteen out of the twenty-eight patients (68%) with chronic urticaria delayed whealing was found at several of the test sites. The control site was usually negative. The delayed reaction generally started 1 to 2 hours after injection with the formation of a wheal which reached its maximal size after 3 to 5 hours and disappeared after 8–10 hours. The diameters of the wheals were then usually about 15 to 20 mm (Fig. 4). A surrounding flare was often seen. The delayed whealing was most pronounced in patients with strongly increased reactions to kallikrein. At 5 hours the mean area of the kallikrein reaction in the group with a delayed reaction was 2519 ± 393 mm² and in the group without a delayed reaction 1211 ± 182 ($p < 0.01$). The delayed reactivity was most pronounced to spices, violet roots, pollens of reed, dandelion, and grass and horse epithelium. No delayed reactions were seen in other patients, except one single reaction to dandelion pollen in one patient with allergic rhinitis and one with atopic dermatitis.

Tuberculin reaction. Six out of seventeen patients with chronic urticaria (35%) had a very marked increase in the delayed response to tuberculin with an erythematous, tense and edematous infiltration, with a diameter 50 to 70 mm, in two cases with central necrosis. The increased reaction was first manifest at 24 hours and was pronounced after 48 to 72 hours. A subsequent tuberculin jelly patch test was negative in four of these patients. None of the seventeen patients had immediate reactions to tuberculin.

Discussion

Reactions to kallikrein

The increased reactivity to kallikrein in patients with chronic urticaria has been confirmed further in this study. The increase was less pronounced in those who always had urticaria when exposed to aspirin. Why they react differently is uncertain, but one possibility is that they are repeatedly exposed to small amounts of salicylates present in food, etc. Their urti-

Table 4. Immediate and delayed reactions to "routine" intradermal allergy tests correlated to the kallikrein reaction in patients with different types of urticaria and in patients with various other dermatoses

Diagnoses	Number of patients	Reaction to kallikrein		Intradermal allergy test			
		Neg.	Pos.	Immediate reaction		Delayed reaction	
				Neg.	pos.	Neg.	Pos.
Eczema	13	13		10	3	12	(1)
Psoriasis	3	3	*	3		3	
Various disorders ¹	6	3	1	5	1	6	
Allergic rhinitis	4	1 ²	1		4	3	(1)
Atopic dermatitis	7	7		4	3	6	(1)
Chron. urticaria	28	1	27	19	9	9	19
Acute urticaria	3	3		3		3	
Cold urticaria	3	3		2	1	3	
Cholinergic urticaria	4	3	1 ³	4		4	
Factitious urticaria	8	8		6	2	8	
Delayed pressure urticaria	1	1		1		1	

¹ Diagnoses: discoid lupus erythematosus, vasculitis, stomatitis, hypostatis dermatitis.

² The kallikrein test not performed in two of the patients.

³ This patient had previous chronic urticaria for several years.

All figures represent number of patients. Positive reaction to kallikrein = size of infiltration area at 5 hours > mean area + 3 SD of the value in control subjects. For mean area, see Table 2.

caria might, therefore, be closer to the acute type where the reactions to kallikrein are normal.

It is essential to separate this group of patients from those who found that an already existing urticaria was worsened by aspirin, but that, in free intervals urticaria could not be induced even with large doses of aspirin. This group of patients had the same increased reactions to kallikrein as other patients with chronic urticaria. The worsening of their urticaria by aspirin was usually dose-dependent, which was not the case in those with a real hypersensitivity to aspirin.

With the exception of those sensitive to aspirin, patients with chronic urticaria showed strongly increased reactions to kallikrein. It is not known when they first develop the abnormal reactivity to kallikrein or for how long it will persist. Abnormal reactions were found in several patients tested for the first time when they had been free from urticaria for periods of four to twenty-four months. Six patients had approximately the same size of abnormal

reactions in the free interval as in a period with urticaria. A disturbance of the kallikrein-kinin system might therefore be present before onset of the urticaria, pointing to the possibility that it is induced by non-specific stimuli. Such a pathological function of the kallikrein-kinin system might also explain the increased reactions to mosquito bites and to tuberculin noted in some of the patients. How the abnormality in the kallikrein system is induced is unknown. Winkelmann states that "all urticaria begins as acute urticaria" (25) and Calnan finds it probable that "after one or more attacks the patient's condition no longer reverts to normal when the evident cause is removed. The abnormality of function appears to become a habit—a chronic state" (4).

In acute urticaria the reactions to kallikrein are normal. If it is correct that all chronic urticaria begins as the acute type, it could be the repeated stimulation of antigen that initiates the abnormal kallikrein response. The normal reactions found in patients with repeated attacks of acute

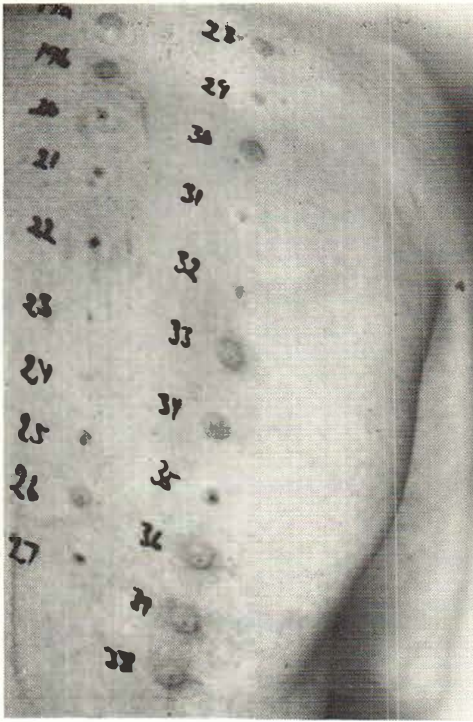


Fig. 4. Delayed whealing 5 hours after intradermal allergen test.

urticaria to a known antigen provide no support, however, for such an assumption.

Intradermal tests and the kallikrein-kinin system

Delayed reactions to bradykinin and to histamine, as well as delayed reactions after venipuncture were seen in several patients with chronic urticaria. These patients also often had delayed reactions to various antigens in the routine allergen-skin test, which were not seen in other patients. Ryan *et al.* (19) mention the occurrence of delayed histamine reactions in five and delayed reactions to ordinary allergen-skin tests in three of fifteen patients with delayed pressure urticaria. These reactions obviously are even more common in chronic urticaria. They found delayed dermographism in three patients and considered this as a feature of the disorder. Delayed reactions to histamine and bradykinin in our patients were usually not associated with the presence of delayed dermographism. In the

cases with delayed dermographism described by Baughmann and Jillson (1), molds were found to be the prime cause. But neither in our patients with chronic urticaria nor in the patients of Ryan *et al.* with delayed pressure urticaria did this seem to be an etiological factor.

As a rule there were several delayed reactions in each patient. Those to pollens were most common—dandelion pollen inducing the reaction most frequently. Pollens are known to be rich in enzymes, some of them proteolytic (12). Kind *et al.* (11) demonstrated the existence of factors in pollen which increased vascular permeability in mice. It is possible that they might activate kallikrein and thus explain the delayed reactions found in the present investigation. Antibodies of the reaginic type are probably not involved in the delayed reactions found since the radioallergosorbent test (RAST) was negative in three patients with pronounced delayed reactions to pollens (23) and since most of the patients had very low levels of immunoglobulin E (8).

Abnormally increased reactions to tuberculin (2 TU) were found in six out of seventeen patients with strong reactions to kallikrein. None of the seventeen patients had positive, immediate reactions. The enlarged erythematous infiltration first appeared after 24 hours and was maximal after 48 to 72 hours. In two patients central necrosis occurred. Such reactions from a low dose of tuberculin usually indicate the presence of active tuberculosis. These patients, however, had no signs of tuberculosis and they had a negative reaction to the tuberculin jelly patch test which is supposed to reveal high levels of sensitivity (18). The incidence of false, positive reactions to tuberculin is said to be low (24). The strong reactions may be interpreted rather as a non-specific increase of a moderately positive tuberculin reaction, resulting from a disturbance of the kallikrein-kinin system in this category of patients. If this assumption is correct, it would indicate that the kallikrein-kinin system might be involved in any inflammatory reaction of delayed hypersensitivity.

Blood groups A, B, and O and reactions to kallikrein

The significantly increased reactions to kallikrein in patients belonging to blood group A compared to those with group O are surprising. Little is known about the physiological differences between the various blood groups. A positive correlation has been found between blood group A and the incidence of gastric carcinoma and between blood group O and peptic ulcer (3). These findings are interpreted as indicating the existence of a genetic predisposition to certain disorders linked to certain blood groups. This might also be true with regard to some types of chronic urticaria.

Kallikrein reaction and the clinical course

It has not been possible to show if there are differences in the medical history and the clinical course between patients with strongly increased reactions to kallikrein and those with a moderate increase. It should be pointed out that the majority of the patients with large reactions to kallikrein had their first period of urticaria several years before the present investigation and 25% had a history of urticaria for more than ten years. They had irregular remissions and exacerbations with periods of urticaria varying from months to decades. The most pronounced manifestations of urticaria and the strongest reactions to kallikrein were seen in women over 40 years of age who also often were notably resistant to therapeutic efforts.

Incidence of associated disorders in chronic urticaria

A family history of atopic disorders in patients with urticaria is said to be common. In Green's statistical survey of chronic urticaria 30% had a family history of allergic diseases and 27% a personal history of associated "allergic" diseases (6), whereas Uhrbach (21) found a family history of atopy in only 15% of his cases. In the present study the association with atopic disorders could not be confirmed since only 10% had a personal history of atopy. Patients with asthma, allergic rhinitis, or

atopic dermatitis usually have an elevated level of IgE, but patients with chronic urticaria have normal or low levels (8). This strengthens the assumption that this type of chronic urticaria is not related to the atopic disorders.

The literature about hereditary factors in chronic urticaria is scanty. Moore and Warin found four families with this condition in successive generations (15). In the present study five out of forty-three patients (12%) had a family history of chronic urticaria. One of them had a family history but no personal history of atopy.

Chronic urticaria is occasionally said to be associated with other conditions such as focal infections or gastrointestinal disorders (4). Wernsdörfer found disorders of the gastrointestinal tract in 19% and diseases of the liver and gall bladder in 4% of his patients (22). In most of our patients no close association with other diseases was found. Infections, mental stress, various drugs and foods sometimes aggravated the urticaria and could be considered as secondary, non-specific factors.

Cholecystectomies in chronic urticaria

No reports on the frequency of cholecystectomy in patients with chronic urticaria have been found. The present study reveals, however, that cholecystectomy had been performed in 52% of the women over 40 years of age and an additional 10% had a cholecystopathy. Only 12% of other female patients in this age group (but with other dermatologic disorders) had a history of cholecystectomy. One possible explanation for the high frequency of gallbladder involvement in chronic urticaria might be that the urticarial process affects the mucosa of the gallbladder and its ducts, thus precipitating a gallbladder disease. A predisposition both to gallbladder disease and chronic urticaria may be another possible reason. The intestinal mucosa contains significant amounts and the pancreas large amounts of kallikreinogen, but whether and in what way—a cholecystopathy or cholecystectomy might influence the activity of these or other kallikreins is not known. The importance of the histamine-releasing abil-

ity of bile salts (17) as well as a tendency to urticaria in obstructive jaundice (25) should also be mentioned as factors of potential significance in this connection.

Psychogenic factors

The importance of psychogenic influence is stressed in all discussions on the etiology of chronic urticaria. The connection between emotionally induced vasodilation and urticaria was studied by Graham and Wolf (5). An obvious connection was observed only in two of our patients between flushing, which seemed to be menopausal, and urticaria. Certain types of psychogenic influence and fatigue aggravated the urticaria or produced new attacks in 77 % of our patients, but they had no signs of primary nervous disturbances. The combination of being under pressure and, at the same time, exhausted often worsened the urticaria while spontaneous improvement often came about during vacations. Nothing is known about the kallikrein activity in these situations. It is known, however, that norepinephrine perfusions leads to kallikrein release from the salivary gland (7) and kallikrein is also released from carcinoid tumours by epinephrine (16). It cannot be excluded that the same mechanism is present in situations with increased mental tension, and that the amount of released kallikrein in these patients with their high sensitivity to kallikrein is enough to worsen the condition. A pronounced worsening of the urticaria observed in three patients 5 hours after the first test with kallikrein, could illustrate that small amounts of kallikrein may induce or worsen the urticaria in these patients.

Therapy

Green *et al.* claimed that antihistamines are effective in most cases and 91 % of their patients had at least some relief from antihistamine treatment. This is in contrast to the findings of Mitchell *et al.* (14) who reported that only 26 % of their patients had any benefit from antihistamines. In the present study only 16 % improved after antihistamines. These discrepancies might be explained in several ways, such as dif-

ferences in the selection of patients, diagnostic criteria, severity of the urticaria, differences in ways of evaluating the effect, etc. It is interesting that the response to antihistamines seemed to be better in the group with aspirin hypersensitive patients with chronic urticaria. As mentioned above they showed reactions to kallikrein which were in between acute and chronic urticaria. That they, like patients with acute urticaria responded to antihistamine strengthens the possibility of a relationship to the acute type where histamine is probably the principal mediator. The poor response in the other patients with chronic urticaria might be explained by the probability that this condition is induced by other mediators, such as the kallikrein-kinin system. Some relief from antihistamines should, however, be expected as the reaction to intradermally injected kallikrein is diminished but not normalized after antihistamines (13). Infusion of a kallikrein inhibitor normalized the abnormal vascular reactions and relieved the patients of urticaria for one to twelve weeks (10). Such therapy cannot, however, be recommended at present for repeated use because of the risk of allergic reactions. Other effective drugs without side effects and capable of blocking or inhibiting the effects of the kallikrein-kinin system are needed for symptomatic therapy in these patients. The main problem is, however, to find the cause of the disturbance of the kallikrein-kinin system.

SUMMARY

Increased reactions to intradermally injected kallikrein and delayed reactions to bradykinin and histamine have been found in patients with chronic urticaria. The possibility of explaining some characteristic features of chronic urticaria as depending upon an induced disturbance in the kallikrein-kinin system is discussed on the basis of the present clinical study.

Pathological reactions were found also in patients free from urticaria for periods varying from some months to several years. The size of the reaction to kallikrein did not seem to be associated with the intensity of the urticarial symptoms. The size was found

to be approximately the same in free intervals as in the urticarial periods. When and in what way the increased reactivity to kallikrein is induced is not known. The possibility that a disturbance in the kallikrein-kinin system is the primary factor of importance in chronic urticaria cannot be excluded. This may explain why various non-specific stimuli induce an urticarial attack.

Among the patients with chronic urticaria the size of the kallikrein reactions was significantly larger in patients with blood group A than in those with blood group O.

Patients with chronic urticaria and sensitive to aspirin had only a small increase in their reactions to kallikrein as compared with the pronounced increase in other patients with chronic urticaria. It is suggested that the so-called chronic urticaria of some patients sensitive to aspirin may be closer to the acute than the chronic type.

In other types of urticaria normal reactions to kallikrein were found.

Delayed reactions to histamine showing a maximum after 5 hours were found in 23 % of patients with chronic urticaria and to bradykinin in 32 %. The presence of the pathological kallikrein reaction was associated with delayed whealing 3 to 5 hours after venipuncture and delayed reactions to routine allergen skin tests. Strongly increased delayed reactions to tuberculin with a maximum after 48 to 72 hours were seen in six of seventeen patients (35 %); in two of them there was central necrosis.

The most severe and therapy-resistant type of urticaria was present in female patients older than 40 years. Of these women 52 % had been cholecystomized and an additional 10 % had a cholecystopathy. Non-specific stimuli such as infections, drugs, and especially psychogenic influences were important secondary causative factors in many patients. The majority of the patients with chronic urticaria had a poor response to antihistamines.

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