

57th WEEKLY NEWSLETTER

USF INTERNAL MEDICINE & PEDIATRIC DIVISIONS OF ALLERGY AND IMMUNOLOGY

A key historical article which made a significant impact in the medical literature is “Exercise-Induced Anaphylactic Syndromes: Insights into Diagnostic and Pathophysiologic Features” by Casale TB, Keahey TM, and Kaliner M. It was published in the *Journal of American Medical Association (JAMA)* in 1986.

From Thomas Casale, MD:

This paper was the first description of mechanisms involved in cholinergic urticaria (CU) and exercise-induced anaphylaxis (EIA), both of which can be induced by exercise. Through a series of experiments, we found that passive heat challenges inducing increases in core body temperature > 0.7 °C can release histamine and lead to anaphylaxis only in CU patients. When core body temperatures were increased after administration of IV endotoxin, no anaphylaxis was observed since pyrogens result in an elevation in the central set point about which body core temperature is regulated, whereas the hyperthermia associated with exercise is not. Thus, only elevations in core temperature induced by either exercise or passive heating result in cholinergic compensatory responses to lower core body temperature (i.e., sweating and/or vasodilation), leading to mast cell degranulation. Prior to this paper, it was thought that patients with CU could have an urticaria episode with a fever. EIA is not related to core temperature and appears to be due to either an abnormal release of a mast cell degranulating factor or an exaggerated response to a factor ordinarily released during exercise that is capable of inducing mast cell degranulation (e.g., opioids).

Casale TB, Keahey TM, Kaliner M: Exercise-Induced Anaphylactic Syndromes: Insights into Diagnostic and Pathophysiologic Features. *JAMA* 1986; 255 (15):2049-2053.

With warm regards,

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Exercise-Induced Anaphylactic Syndromes

Insights Into Diagnostic and Pathophysiologic Features

Thomas B. Casale, MD; Thomas M. Keahey, MD; Michael Kaliner, MD

• To differentiate the diagnoses of exercise-induced anaphylaxis and cholinergic urticaria/anaphylaxis, we developed reproducible diagnostic provocative challenges. The data derived from the study of two representative patients, one with cholinergic urticaria and the other with exercise-induced anaphylaxis, suggest approaches to distinguishing these diagnoses. After specific exercise challenges, both patients developed symptoms consistent with anaphylaxis and had associated increases in plasma histamine levels. After passive heat challenges inducing increases in core body temperature more than 0.7 °C, only the patient with cholinergic urticaria developed anaphylactic symptoms and had a rise in the plasma histamine level. Neither patient developed symptoms of anaphylaxis when core body temperatures were increased after administration of intravenous endotoxin. Thus, passive heat challenges are extremely valuable in differentiating these two exercise-related syndromes. Although not important in exercise-induced anaphylaxis, specific thermoregulatory mechanisms appear to play an intricate part in the pathophysiology of cholinergic urticaria/anaphylaxis.

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EXERCISE is known to produce a spectrum of clinical symptoms in predisposed individuals, ranging from pruritus and urticaria to generalized anaphylactic reactions.¹⁻¹⁶ The term *exercise-induced anaphylaxis* has been used to describe a distinct form of physical allergy manifested by the sensation of cutaneous warmth and pruritus followed by erythema, urticaria, and often hypotension and/or

upper airway obstruction.^{1,2} Predisposing events in the form of ingesting either a specific food⁵ or any meal⁶ have been reported in a few such patients, and a family tendency is suggested in some reports.⁷

Cholinergic urticaria is another form of physical allergy that can be precipitated by exercise.⁸⁻¹⁶ The skin lesions are often distinctive and appear as 2- to 4-mm pruritic wheals surrounded by extensive areas of macular erythema.⁸⁻¹⁶ Systemic manifestations, including confluent urticaria, angioedema, hypotension, wheezing, and gastrointestinal complaints, have also been reported in patients with cholinergic urticaria after exercise.⁸⁻¹² Furthermore, in-

creases in plasma histamine levels have been demonstrated after exercise challenges for patients having either exercise-induced anaphylaxis or cholinergic urticaria.^{2,3,7-10} Thus, both these diseases are provoked by exercise and involve mast cell degranulation.

To differentiate these two forms of exercise-related syndromes, we developed reproducible diagnostic provocative challenges.

SUBJECTS

Report of Cases

CASE 1.—A 28-year-old woman was referred to the National Institutes of Health (NIH) with a two-year history of multiple episodes of pruritus, urticaria, light-headedness, facial angioedema, and throat constriction after vigorous exercise. These episodes were not related to identifiable substances or to food intake. The patient had a history of mild allergic rhinitis due to house dust, and intradermal skin testing revealed positive reactions to dust and dust mite. The family history was negative for allergy, asthma, exercise-induced anaphylaxis, and cholinergic urticaria. Results of laboratory assessments (including blood chemistry values; complete blood cell count with differential cell analysis; sedimentation rate; IgG, IgM, IgA, and IgE levels; CH₅₀ [total hemolytic complement], C2, C3, and C4 levels; and urinalysis) and physical examination during an asymptomatic state were normal. The patient refrained from taking any medications for at least one week before any testing.

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Results of Provocative Challenges Performed on Subjects With Exercise-Induced Anaphylactic Syndromes

	Exercise			Passive Heating			Endotoxin			Methacholine Skin Test Results
	Increase in Core Temperature, °C	Increase in Plasma Histamine Level, %	Anaphylactic Symptoms	Increase in Core Temperature, °C	Increase in Plasma Histamine Level, %	Anaphylactic Symptoms	Increase in Core Temperature, °C	Increase in Plasma Histamine Level, %	Anaphylactic Symptoms	
Patient 1 (cholinergic urticaria/anaphylaxis)	1.5	3,350	Yes	1.2	1,417	Yes	1.8	0	No	Positive
Patient 2 (exercise-induced anaphylaxis)	1.1	9,952	Yes	1.3	0	No	2.0	420*	No	Negative
Normal volunteer	1.1	0	No	1.5	0	No	1.8	0	No	Negative

*Concurrent with violent rigors.

CASE 2.—A 40-year-old man was referred to the NIH with a five-year history of multiple episodes of diffuse pruritus, urticaria, angioedema, light-headedness, and nausea after vigorous exercise, including swimming. The severity of the episodes correlated with the degree of exercise and had no relationship to food intake. The patient did not have a personal history of atopy. The family history was also negative for asthma or atopy, as well as exercise-related anaphylactic events. Results of laboratory assessments (including blood chemistry values; complete blood cell count with differential cell analysis; sedimentation rate; IgG, IgM, IgA, and IgE levels; CH₅₀, C2, C3, and C4 levels; and urinalysis) and physical examination during an asymptomatic state were normal. Skin testing was negative to aeroallergens and food allergens. The patient refrained from taking medications for at least one week before any testing.

Normal Volunteers

The normal control subjects for these studies were selected from the normal volunteer program conducted at the NIH or were laboratory employees at the NIH. Their ages ranged from 20 to 30 years, and they had no histories of allergies, asthma, exercise-induced anaphylaxis, or cholinergic urticaria.

METHODS

Exercise Challenges

Exercise challenges consisted of having the subjects jog while dressed in sweat suits for 12 to 30 minutes in a gymnasium, with a rectal thermometer in place. The exercise was interrupted for short periods to draw blood for plasma histamine levels; monitor the pulse rate, blood pressure, and rectal temperature; and quickly examine the skin for erythema, urticaria, and/or angioedema. All of the above values were also recorded during a 15-minute period preceding exercise and at least 20 minutes after exercise challenge. The exercise was terminated when symptoms of anaphylaxis occurred or there was an increase in

core body (rectal) temperature of 1.1 °C or greater.

Passive Heat Challenges

Passive (exogenous) heat challenges were performed on subjects by raising core body temperature (as monitored by rectal thermometer) by 0.5 to 1.5 °C, using either hyperthermic blankets or by immersing one or more of the subjects' extremities in hot water (40 to 42 °C). Blood pressure, pulse rate, and rectal temperature were monitored continuously and blood was drawn periodically for determination of plasma histamine levels. The heat challenges were terminated when symptoms of anaphylaxis occurred, there was a rise in core body temperature of greater than 0.9 °C, or the challenge period exceeded 120 minutes.

Endotoxin Challenges

To simulate the pyretic response to infection, subjects received a single intravenous injection of *Escherichia coli* RE-2 endotoxin, 1.5 ng/kg of body weight. This endotoxin has been given at the NIH for more than 17 years, with reproducible results and no significant long-term side effects. Blood pressure, pulse rate, and core body temperature (as measured by rectal thermometer) were measured continuously, and blood was drawn periodically for determination of plasma histamine levels.

Plasma Histamine Level Determinations

Histamine levels were measured by a radioisotopic-enzyme assay employing thin-layer chromatography, as described by Dyer et al.¹⁷

RESULTS

Both patients described symptoms of pruritus, urticaria, light-headedness, and angioedema after exercise, suggesting the diagnosis of exercise-induced anaphylaxis. To confirm this diagnosis, the subjects jogged under controlled conditions for 12 to 30

minutes. All subjects, including a normal volunteer, experienced an increase in core body temperature of greater than 1.1 °C during exercise (Fig 1 and Table). However, only the two patients developed anaphylactic-like symptoms and had associated increases in plasma histamine levels. The symptoms and rise in plasma histamine level in patient 1 correlated with increasing core body temperature (Fig 1, left). On physical examination, patient 1 developed confluent urticaria that initially appeared on the thorax as small punctate wheals surrounded by erythema. Patient 2, on the other hand, developed signs and symptoms of anaphylaxis after only 12 minutes of exercise, and his histamine level peaked at a time when his core body temperature was noted to have begun to decrease (Fig 1, right).

To separate exercise from increased core body temperature, passive heat challenges were performed on both subjects and a normal volunteer. Only patient 1 developed symptoms and had a parallel rise in the plasma histamine level with increasing core temperature (Fig 2 and Table). Patient 1 experienced diffuse pruritus, circumoral pallor, urticaria, angioedema, laryngeal edema, and light-headedness beginning at the point her temperature had risen 0.9 °C and continuing until she was treated with subcutaneous epinephrine. These observations suggested that patient 1 had cholinergic urticaria/anaphylaxis rather than true exercise-induced anaphylaxis. To confirm our hypothesis, patients 1 and 2 underwent several more heat and exercise challenges. Although both patients developed symptoms compatible with anaphylaxis and had concomitant increases in plasma histamine levels

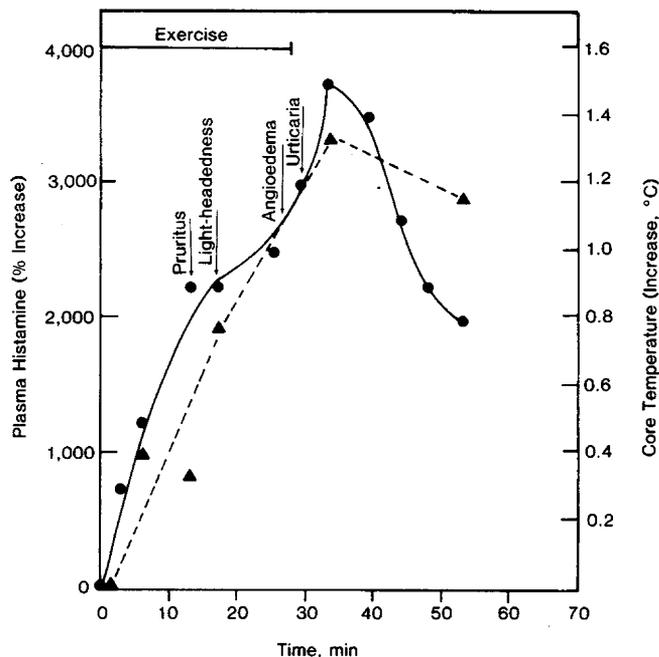
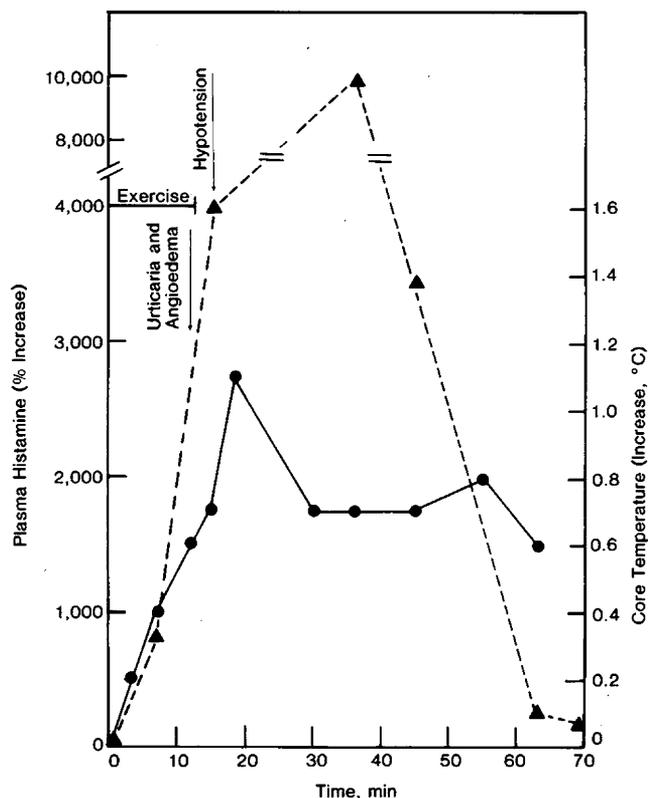


Fig. 1.—Time-dependent plasma histamine levels (triangles), core body temperatures (circles), and symptoms recorded during exercise challenges by running for patient 1 (left) and patient 2 (right). Onset of specific symptoms is denoted by arrows. Challenge period is indicated at top of each figure. Mean plasma histamine level for subjects before exercise was 300 ± 80 pg/mL.



during subsequent exercise challenges, only patient 1 developed a similar syndrome with exogenous heat challenges. Further, only patient 1 had a positive methacholine skin test. However, methacholine skin tests may be positive in only one third of patients with cholinergic urticaria.¹³ We would thus suggest that unless a methacholine skin test and specific heat challenges are done on patients presenting with symptoms of anaphylaxis after exercise, one might be unable to separate those individuals having true exercise-induced anaphylaxis from those having cholinergic urticaria/anaphylaxis.

Individuals having cholinergic urticaria have been reported^{9,13-15} to develop systemic symptoms after heating one or more extremities in hot water (40 to 42 °C), suggesting that a substance might be released into the bloodstream from the heated extremity that could ultimately result in mast cell degranulation. To test this hypothesis, we performed two additional challenges on patient 1 (Fig 3). In the first challenge, her forearm was immersed in 42 °C water for 40 minutes. This challenge resulted in a rise in core body temperature of 0.6 °C and the development of flush-

ing, facial angioedema, and confluent urticaria. In the second challenge, one forearm was placed in 42 °C water and the other in cold water maintained at 12 to 17 °C. At the end of a 70-minute challenge period, the patient's core temperature did not change significantly; she remained asymptomatic; and no increase in plasma histamine levels (baseline level, 170 pg/mL; level at 70 minutes, 180 pg/mL) was observed. Thus, the development of symptoms in patients having cholinergic urticaria does not appear to be dependent on the release of a factor from the heated body part, but rather on the development of an increase in core body temperature.

We wondered, therefore, whether a similar rise in core body temperature as seen in fevers accompanying infections might also lead to the development of anaphylactic symptoms with concomitant increases in plasma histamine levels. Therefore, to simulate the pyretic response to infection, we administered *E coli* RE-2 endotoxin (1.5 ng/kg of body weight) intravenously to both patients and three normal volunteers. All subjects responded with a rise in core body temperature of greater than 1.7 °C, but none developed symptoms of ana-

phylaxis (Table). Patient 2, however, did develop chills and shaking rigors and had two distinct rises in his plasma histamine level during the times that he was observed to have the most severe rigors. It is likely that the shaking rigors simulated an exercise challenge and resulted in histamine release. The amount of histamine measured, although significantly higher than baseline levels (fourfold), was only 3% as high as that measured during an exercise challenge (Fig 1, right), thus possibly accounting for the lack of associated anaphylactic symptoms. Furthermore, neither symptoms consistent with anaphylaxis nor elevated plasma histamine levels were observed in normal volunteers given endotoxin, despite the development of malaise, pyrexia, rigors, nausea, and vomiting.

COMMENT

Certain adverse responses to physical stimuli are termed "physical allergy" because the symptom complex appears to be caused by mediators released from mast cells.¹ Both exercise-induced anaphylaxis and cholinergic urticaria/anaphylaxis are physical allergies that can be precipitated

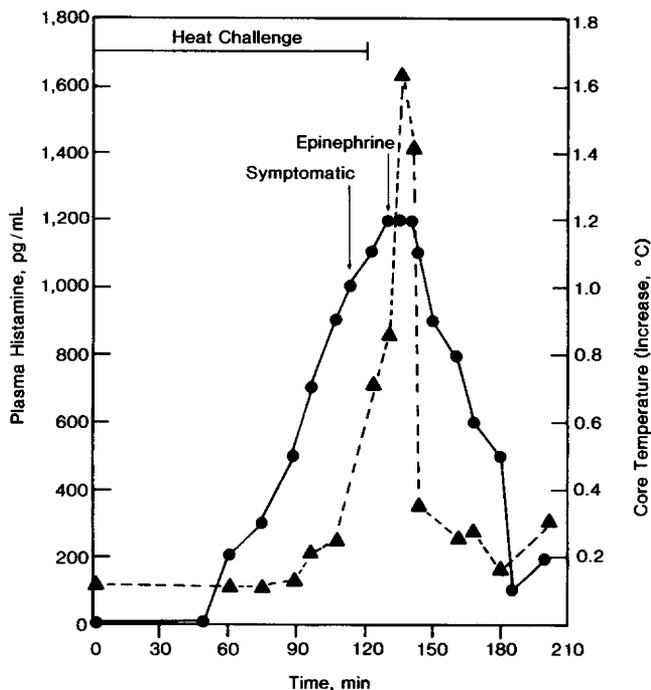


Fig 2.—Time-dependent plasma histamine levels (triangles) and core body temperatures (circles) during exogenous heat challenge with hyperthermic blankets for patient 1. Onset of symptoms incurred by patient 1 and time at which she was given epinephrine are denoted by arrows. Challenge period is indicated at top of figure.

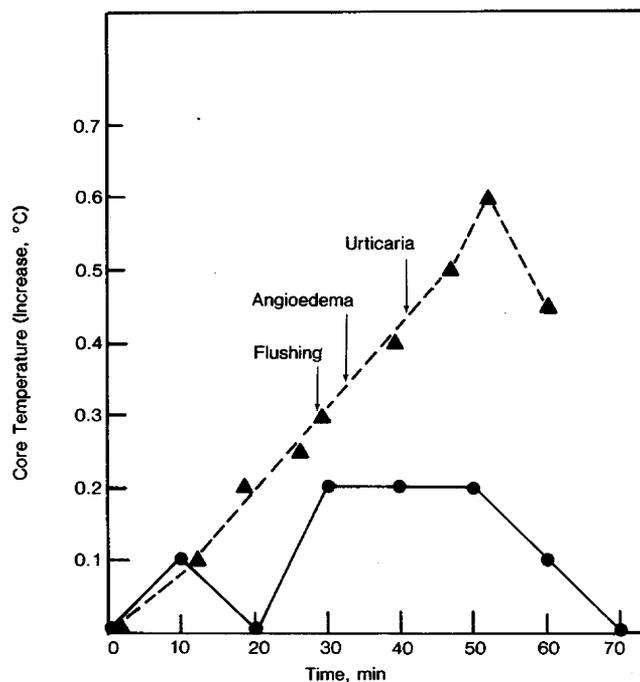


Fig 3.—Time-dependent changes in core body temperature during two different heat challenges for patient 1. In challenge 1 (dashed line), patient's forearm was immersed in 42 °C water for 40 minutes, and time of onset of symptoms is denoted by arrows. In challenge 2 (solid line), one forearm was placed in 42 °C water and the other in water at 12 to 17 °C for 70 minutes. No symptoms were noted during second challenge.

by exercise¹⁻¹⁶ and are associated with increases in plasma histamine levels during exercise challenges.^{2,3,7-10} It is difficult to distinguish between these two clinical entities by history. Although patients who have cholinergic urticaria/anaphylaxis classically have distinctive skin lesions (punctate wheals surrounded by large areas of erythema⁸⁻¹⁶), those tiny wheals may coalesce, making them difficult to differentiate from ordinary urticaria. Indeed, patient 1 initially denied having lesions consistent with cholinergic urticaria. Furthermore, small punctate wheals, giant urticaria, or angioedema without urticaria have all been described in association with exercise-induced anaphylactic reactions.¹⁻³ Thus, there is no "characteristic" skin lesion for exercise-induced anaphylaxis that allows the distinction between true exercise-induced anaphylaxis and cholinergic urticaria/anaphylaxis. One should, therefore, describe the skin lesions and not classify them unless definitive tests are done to establish a particular diagnosis (eg, heat challenge for cholinergic urticaria).

Both patients 1 and 2 had histories compatible with life-threatening anaphylactic reactions after exercising that required emergent therapeutic intervention. At least three exercise challenges (free jogging or jogging on a treadmill) during an 18-month period were performed on each of the two patients, and all challenges provoked symptoms of anaphylaxis in both patients. The fact that there was a very strong correlation between the increase in core body temperature and plasma histamine level in patient 1, and that in the early stages of her rash, the lesions were consistent with those noted to occur in cholinergic urticaria,⁸⁻¹⁶ led us to believe that she may have actually had cholinergic urticaria/anaphylaxis and not true exercise-induced anaphylaxis. However, just by the clinical presentation of the two patients during their exercise challenges, it would have been difficult to make the diagnosis of cholinergic urticaria/anaphylaxis for patient 1 or, for that matter, to rule it out for patient 2.

As suggested by Grant and co-workers in 1936,¹⁴ and confirmed by more recent studies,^{9,13,15} cholinergic

urticaria is a disease in which symptoms can reproducibly be induced by warming the body. Patient 1 failed to correlate her symptom complex with passive heat intolerance (eg, hot showers or bathing). Similarly, patient 2 had no history of heat intolerance and also complained of symptoms when swimming, an activity that might not be expected to be associated with a significant rise in core body temperature. As shown in Fig 2, patient 1 developed symptoms when her core body temperature was elevated by passive heat provocation. Furthermore, the elevation in temperature was associated with a concomitant increase in plasma histamine levels. Therefore, we suggest that heat challenges may be necessary to differentiate those individuals having cholinergic urticaria/anaphylaxis from those having true exercise-induced anaphylaxis and that histories and exercise challenges, although helpful, are not sufficient.

It has previously been shown that if the circulation to a heated limb is occluded in a patient with cholinergic urticaria, no urticaria is provoked. However, after restoring the circula-

tion, a generalized urticarial reaction may occur.¹⁴ To help ascertain whether a factor might be released from the heated body part (ie, extremity) that might ultimately lead to mast cell degranulation, we performed the experiment outlined in Fig 3. If a factor is released from the heated extremity, one would expect that the second challenge detailed in Fig 3 would have also led to a rise in plasma histamine levels and the development of symptoms. However, maintaining a normal core body temperature prevented the symptoms ordinarily associated with heating an extremity, strongly militating against the release of a factor from the heated extremity.

To objectively determine if a rise in core body temperature by a fever might lead to the development of symptoms, we intravenously administered *E coli* RE-2 endotoxin to both of our patients and normal volunteers. All subjects developed elevations in core body temperature, and the rapidity with which the increases occurred was similar to that attained during the exogenous (passive) heat challenges. None of the subjects developed symptoms. With the exception of patient 2, who had histaminemia during violent rigors, none of the subjects had a change in their plasma histamine levels. One major difference between exercise or passive heating and pyrogen-induced fever is the lack of sweating associated with the latter. Although exercise and passively induced hyperthermia raised core temperature to the same point as pyrogen (Table), the provocations are qualitatively dissimilar.¹⁸ Febrile hyperthermia in response to pyrogen is the result of an actual elevation in the central set point about which body core temperature is regulated, whereas the hyperthermia associated with exercise is not.¹⁸⁻²⁰ Thus, only the elevations in core temperature induced

by either exercise or passive heating would be expected to result in compensatory responses to lower core body temperature (ie, sweating and/or vasodilation). Therefore, it is not unreasonable to find that passive heat challenges of patients with cholinergic urticaria might elicit symptoms, while endotoxin-induced hyperthermia might not, since they involve different mechanisms.

We postulate, therefore, that cholinergic urticaria is a disease related to the effector mechanisms involved in the compensatory responses in thermoregulation, either sweating and/or vasodilation. It seems likely that the abnormal methacholine skin test seen exclusively in cholinergic urticaria relates to specific hypersensitivity to the actions of cholinergic stimulation, and that this hypersensitivity is the mechanism responsible for mast cell degranulation. Exercise-induced anaphylaxis is not related to core temperature and appears to be due to either an abnormal release of a mast cell degranulating factor or an exaggerated response to a factor ordinarily released during exercise that is capable of inducing mast cell degranulation (eg, opioids²¹). Since the historical and clinical presentations of individuals having either of these two exercise-related syndromes are similar, specific diagnostic tests must be performed to distinguish those individuals having cholinergic urticaria/anaphylaxis from those with true exercise-induced anaphylaxis.

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