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EXPERIMENTAL INVESTIGATIONS ON THE TRIGGER MECHANISM OF THE GENERALIZED TYPE OF HEAT AND COLD URTICARIA BY MEANS OF A CLIMATIC CHAMBER

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Abstract. The physical conditions of challenge were investigated in a climatic chamber on 8 patients with cholinergic urticaria and 10 patients with generalized cold urticaria. The cholinergic urticaria was induced by passive or active (physical exercise) heating and psychological stimulation; the generalized cold urticaria was induced by general cooling at rest and during physical effort. The ambient temperature was varied, and the mean body temperature was recorded continuously at different measuring points. The experiments revealed that in both types of urticaria the physical trigger mechanism seems to be strictly related to thermoregulatory processes; the crucial point is neither the actual temperature of the skin surface, the average skin temperature, nor even the 'core' temperature, but a rise or fall in the weighted *average body* temperature. In cholinergic urticaria it was not relevant whether skin lesions were provoked by *passive* heating of the body at rest (sauna-like conditions) or by *active* heating at low ambient temperature. A basically different challenge mechanism must be assumed therefore in the generalized type of heat and cold urticaria, in contrast to their localized contact types.

Key words: Cholinergic urticaria; Cold air/cold water urticaria; Physical trigger mechanism; Climatic chamber; Thermoregulation; Body temperature

The pathogenesis of the physically induced urticarias has long been a mystery. It is puzzling even today in many respects (8). Two problems are especially difficult to approach: In what manner and where does the transformation of physical effects (energy) into a chemical reaction take place? Where is the boundary of each situated? What are the acquired and pathologic hypersensitivities towards certain physical stimuli and what is this stimulus specificity based on? How, in cases with transferrable serum factor of type IgE and with a positive Prausnitz-Küstner reaction, does the related (auto) antigen originate? Is it a pre-existent substance released only by the physical trigger mechanism, or does it develop *de novo* under its influence?

Best known today is the third and last reaction phase of physical urticaria; as in hematogenic urticarias, the skin reaction in all acquired types of physical urticaria ends in a mast cell degranulation with histamine release which is the cause of all clinical symptoms. This also explains the similarity of skin lesions and of general anaphylactoid symptoms in physical and non-physical urticarias, as well as the suppression of symptoms by histamine (H_1-) antagonists in both cases (11).

In contrast to the hematogenic urticarias, physical urticarias show another special enigma: the existence of localized and generalized types (induced by heat or cold) in which the trigger mechanism must be localized in different places. In localized forms of the contact type, the trigger mechanism may be sought in the upper corium and dermal papillas, respectively. In generalized forms, however, it must be suspected of being at least partly extracutaneous.

Unlike cold contact urticaria, heat contact urticaria is extremely rare. The frequency of generalized cold and heat urticaria, however, is nearly the same. The basically different nature of heat contact urticaria and generalized cholinergic or cholinogenic heat urticaria has been known for some time (7). The special position of the so-called cold air/cold water urticaria has, however, scarcely been given any attention until the present (3).

We think though that the so-called cold air/cold water urticaria and the generalized heat urticaria must be considered together; the way in which both types of urticaria are challenged suggests to us that at least the physical part of the trigger mechanism must be sought at the level of the thermoregulatory processes. Most authors suppose, as a rule, that a rise in the so-called 'core temperature', following a thermoregulatory imbalance, could be crucial for cholinergic urticarial attacks. Patients with gener-

alized cold urticaria, on the other hand, regularly complain of 'freezing' or even 'shivering' before urticaria occurs, a remarkable clinical detail pointing to a thermoregulatory factor.

Our present investigation focuses especially on this suspected thermoregulatory component of the trigger mechanism which is methodologically difficult to approach and which has not been studied until now. As for the cholinergic urticaria, we refer to previous experimental studies dealing primarily with the role of sweating (9); here we were able to show that cholinergic urticaria also occurs in anhidrotic skin—which means without sweat secretion.

The following experiments are based on some newer concepts of thermoregulation, according to which cold and heat defence reactions such as shivering, sweat production and vasomotor responses are dependent on both core and skin temperature. The input signals generated in cutaneous thermoreceptors and internal thermoreceptive structures (hypothalamus, spinal cord) are processed in a central controller; the result determines the size of the output signals controlling the effector systems (skin blood flow, metabolic rate, sweating).

As a first approach, it is the mean body temperature, therefore, which determines the size of those thermoregulatory adjusting processes. From this fact the question arises of whether the generalized heat and cold urticarias could be described correspondingly as functions of the average body temperature.

MATERIAL AND METHODS

Eighteen patients were studied, 8 of whom were suffering from a typical generalized heat urticaria and 10 from a typical cold air/cold water urticaria. The investigations were performed in a climatic chamber (WEISS Company, Giessen). In the patients with cholinergic urticaria the following variables were recorded continuously: 1) Chamber (=ambient) temperature; 2) oesophageal and/or tympanic temperature (external auditory canal near the tympanon); 3) skin temperature of chest, upper arm, lower arm, thigh and lower leg; 4) local sweat rate at the thorax using a ventilated capsule 7 cm in diameter and an infrared vapour analyser; 5) heart rate; 6) in the effort test (see below) (O_2 uptake was recorded using an open system with a respiratory hood. (For details of methods see (5).)

Patient with cholinergic urticaria were subjected to the following four tests:

1. *'Sauna' test:* Preliminary period of rest seated comfortably in an armchair at neutral chamber temperature (27–28°C) to stabilize all values measured. Thereafter heat exposure by rapid increase of chamber temperature to 45°C (1.5°/min.).

2) *Effort test:* The patients had to work on a bicycle ergometer. They could read their heart rates from a meter fixed on the respirator hood and adjust the pedal revolutions to the extent that heart rate was maintained at a predetermined level. Chamber temperature was kept at 15–20°C.

3. *Carbachol test:* The study was performed at neutral chamber temperature. First a control injection of physiologic chloride solution was administered. Thereafter an injection of 1 ml carbachol 1 : 4000 s.c. was given.

4. *Gag reflex test:* The study was carried out at neutral chamber temperature. With all measuring probes in position the patients attempted to swallow the oesophageal probe with the thermo-element. In several cases a strong gag reflex occurred.

The 10 patients with cold air/cold water urticaria were studied in the following manner: After a preliminary period at neutral temperature (27–28°C) the chamber temperature was reduced by 0.75°/min until shivering and wheals appeared. This occurred at chamber temperatures between 20 and 5°C. In addition to the physiological variables 1, 2, 3, 5 and 6 (see above), the electrical muscle activity was recorded from the m. latissimus dorsi and the m. quadriceps femoris as a measure of shivering. An increasing slope of O_2 uptake and electrical activity as plotted against mean body temperature, $\bar{T}_b$, was taken as the shivering threshold.

In part of the studies the patients exercised on a bicycle ergometer.

Calculations

The mean skin temperature, $\bar{T}_s$, was determined arithmetically according to the following equation:

$$\bar{T}_s = (T_{\text{chest}} + T_{\text{upper arm}}) \cdot 0.3 + (T_{\text{thigh}} + T_{\text{lower leg}}) \cdot 0.2$$

The weighted mean body temperature, $\bar{T}_b$, was determined according to the equation:

$$\bar{T}_b = T_{\text{oesophagus}} \cdot 0.87 + \bar{T}_s \cdot 0.13$$

as in previous studies (5).

RESULTS

A. *Cholinergic heat urticaria*

1. *'Sauna' test.* Six patients were heat-exposed (one patient was double-exposed) at a chamber temperature increasing form 28 to 45–50°C. A typical example of a record is shown by Fig. 1. While skin and mean body temperature continuously increase from the beginning of heat exposure, oesophageal temperature is falling slightly due to the return of the cooled peripheral blood. Sweating as recorded by the capsular method which indicates sweating before sweat droplets are visible, begins at a mean body temperature of 36.9°C; 12 min after the onset of sweating, coin-sized erythema with itching and pinhead-sized wheals developed, mainly on the upper chest. After the development of urticaria the heat exposure test was terminated.

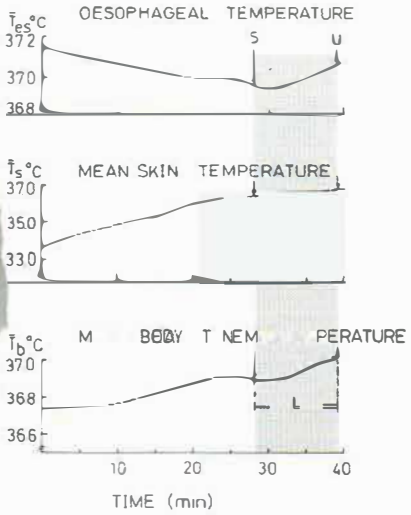

Fig. 1. Pat. G. W. ♂. Cholinergic urticaria, sauna test. Course of oesophageal (T_{es}), mean skin ($\bar{T}_s$) and mean body ($\bar{T}_b$) temperature during heat exposure. *S*, onset of sweating. *L*, latency between onset of sweating and appearance of urticaria (*U*).

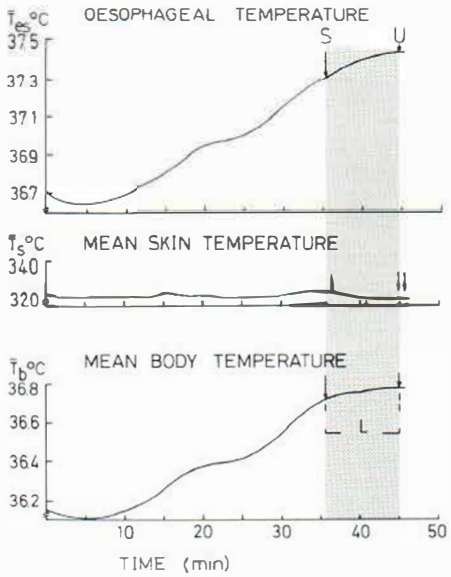

Fig. 2. Pat. N. H. ♂. Cholinergic urticaria, physical effort test. Course of oesophageal (T_{es}), mean skin ($\bar{T}_s$) and mean body ($\bar{T}_b$) temperature during physical effort *S*, onset of sweating. *L*, latency between onset of sweating and appearance of urticaria (*U*). Begin of physical exercise at time 0.

Similar results were obtained in 6 other patients. The results are given in Table I from which it can be seen that in 3 cases urticaria appeared before the oesophageal temperature had exceeded its initial value. Mean skin temperature, which is closely related to the ambient temperature, as well as mean body temperature were on the average increased by 3.69 and 0.45°C, respectively, when the urticaria appeared; the "core" temperature, on the other hand, was increased in only three patients at that time (mean + 0.1°C). Diffuse sweating began after 30–40 min; the time interval between sweating and urticaria was found to vary between 10 and 12 min.

2. *Physical effort test.* Six patients were examined at an ambient temperature of between 15 and 20°C. Body temperature was increased by physical exercise on a bicycle ergometer. As shown in Fig. 2, mean body temperature increased continuously as in the sauna test (Fig. 1); but in contrast to the latter, skin temperature remained constant while internal body temperature rose. Sweating began at a mean body temperature of 36.7°C. 9.5 min later the first signs of urticaria were seen. Accord-

Table I. *Cholinergic urticaria. Sauna test. Temperature deviations from initial values at onset of the skin lesions in 7 patients*

	Patient							
			G., P.					
	G., W	D., W	1st study	2nd study	W., R.	P., P.	N., H.	Median value
Oesophageal temperature, T_{es} (°C)	−0.10	±0	+0.10	+0.10	−0.05	+0.15	+0.35	+0.10
Mean skin temperature, $\bar{T}_s$ (°C)	+3.09	+2.90	+4.43	+3.12	+4.49	+3.69	+3.78	+3.69
Mean weighted body temperature, $\bar{T}$ (°C)	+0.27	+0.37	+0.66	+0.50	+0.54	+0.62	+0.80	+0.54

Table II. *Cholinergic urticaria. Physical effort test. Temperature deviations from initial values at onset of the skin lesions in 6 patients*

	Patient						Median value
	H., J.	G., W.	F., W.	G., P.	N., H.	W., R.	
Oesophageal temperature, T_{es} (°C)	+0.40	+0.35	+0.40	+0.67	+0.75	+0.67	+0.54
Mean skin temperature, $\bar{T}_s$ (°C)	−0.50	−0.09	−0.10	−0.64	−0.20	−0.16	−0.18
Mean weighted body temperature $\bar{T}_b$ (°C)	+0.28	+0.30	+0.34	+0.50	+0.62	+0.65	+0.42

ing to Table II, urticaria occurred in these physical exertion tests when mean body temperature had increased by 0.42°C, on average, a value very close to that found in the sauna test (Table I). The latency period between sweating and the appearance of skin lesions varied between 7 and 13 min.

3. *Carbachol test.* After all temperatures had stabilized at thermoneutral temperature the patient was given an s.c. injection of saline. Except for a slight increase in heart rate, no alterations occurred. No changes in temperature nor in the appearance of the skin were seen. Twenty-three minutes after the beginning of the study 1 ml carbachol was injected s.c. The patient eventually reported a flush of heat on the skin. Twelve minutes after the injection, sweating began at a barely measurable rate. Nine minutes later the first signs of urticaria occurred on the thorax. Tympanic and mean body temperature showed a slight fall throughout the experiment. At the onset of the urticaria, mean body temperature and tympanic temperature were lowered by 0.24 and 0.32°C, respectively, in comparison with the initial value.

4. "*Throat stimulation*". In a few patients an attempt to swallow the oesophageal probe was accompanied by an inclination to vomit (gag reflex) and a sudden onset of sweating which was followed by the appearance of urticaria. The body temperatures did not alter remarkably (Fig. 3). Sweating as well as urticaria occurred at a mean body temperature of 35.9°C—a relatively low value when compared with that found in the sauna test and the physical effort test (compare Figs. 1 and 2). Heart rate increased considerably in combination with the increase in sweat rate (Fig. 3). The latency between onset of sweating and the appearance of urticaria measured only 2–4 min in contrast to 10–12 min in the sauna test and 7–13 min in the physical effort test.

B. *Cold air/cold water urticaria*

1. *Examinations at resting conditions.* After a preliminary period at neutral temperature, the chamber temperature was reduced by 0.75°C per minute. After 10–20 min, shivering began. The latency between shivering and the appearance of urticaria measured between 15 and 82 min, with a median value of 28 min. The oesophageal temperature first increased due to vasoconstriction and eventually

Table III. *Cold air/cold water urticaria. Tests at rest. Temperature deviations from initial values at onset of the skin lesions in 10 patients*

	Patient										Median value
	B. A.	D. I.	K. I.	D. M.	M. S.	R. R.	B. S	W. K.	Sch. L.	L. E.	
Oesophageal temperature, T_{es} (°C)	+0.10	−0.17 (tymp.)	+0.10	−0.20 (oral!)	+0.10	−0.10	−0.25	+0.17	−0.06	+0.05	−0.005
Mean skin temperature, $\bar{T}_s$ (°C)	−5.30	−3.36	−7.20	−4.91	−7.75	−5.11	−4.73	−7.70	−7.54	−8.91	−6.25
Mean body temperature, $\bar{T}_b$ (°C)	−0.57	−0.59	−0.64	−0.68	−0.73	−0.75	−0.78	−0.86	−1.03	−1.12	−0.74

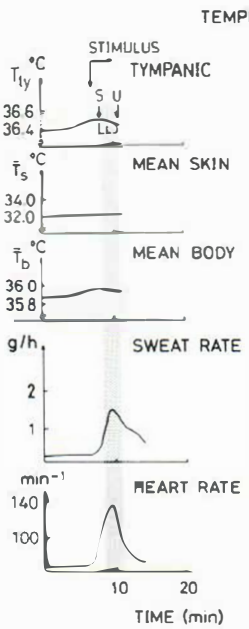

Fig. 3. Pat. F. W. ♂. Cholinergic urticaria following gagging caused by attempt to swallow oesophageal probe. Course of tympanic (T_{ty}), mean skin ($\bar{T}_s$) and mean body ($\bar{T}_b$) temperature; local sweat secretion and heart rate. *S*, onset of sweating. *L*, latency between onset of sweating and appearance of urticaria (*U*). Chamber temperature 27°C. Sweat rate in 10^{-1} g/h.

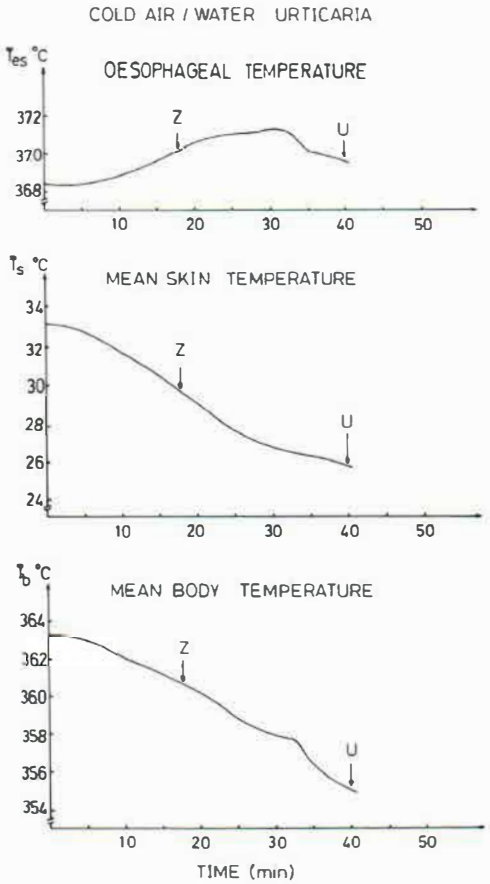

Fig. 4. Pat. K. J. ♀. Cold air/cold water urticaria. Course of oesophageal (T_{es}), mean skin ($\bar{T}_s$) and mean body ($\bar{T}_b$) temperature during cold exposure at rest. *Z*, onset of shivering. *U*, appearance of urticaria.

fell (Fig. 4). In 5 patients oesophageal temperature was still above the initial value when the urticaria appeared (Table III). Mean skin temperature as well as mean body temperature dropped continuously in all patients. Urticaria appeared when mean body temperature had fallen by 0.74°C, on average.

2. *Physical exertion test.* In five experiments we had the subjects work on a bicycle ergometer at low ambient temperatures (5–20°C) with the purpose of increasing internal temperature while skin temperature remained low. If mean body temperature rather than either deep body or skin temperature were the determining factor in causing urticaria, we would expect the appearance of cold urticaria to be delayed or even prevented by physical exertion. In one young male patient this was actually the case (Fig. 5). The moderate work rate in the first part of the test did not yield enough heat to prevent mean body temperature from falling, though the drop was delayed and hence the latency period up to the appearance of urticaria was prolonged. At the increased work rate in the middle of the test, the patient was able to increase mean body temperature; as anticipated, the urticaria disappeared. It was only with a drop in mean body temperature at the end of the strenuous exertion period that the urticaria reappeared. The remainder of the patients were not fit enough to exercise at a work rate sufficient to keep mean body temperature at the neutral level; hence, urticaria appeared. The corresponding temperature values are given in Table IV.

DISCUSSION

The results of our climatic chamber tests at rest and during exertion show that it is, in fact, necessary to distinguish between a generalized and a contact or localized type not only of heat urticaria but also of cold urticaria. In contrast to the contact type, provocation of the generalized type does not depend on

Table IV. *Cold air/cold water urticaria. Physical effort test. Temperature deviations from initial values at onset of the skin lesions in 4 patients*

	Patient						
	Sch. L.		D. I.				
	(U_1)	(U_2)	2nd study	3rd study	B. S.	M. S.	Median value
Tympanic temperature (°C)	−0.25	−0.35	−0.02	−0.02	+0.15	+0.22	−0.02
Mean skin temperature, T_s (°C)	−2.56	−3.48	−4.88	−2.13	−3.74	−7.46	−3.61
Mean body temperature, T_b (°C)	−0.55	−0.76	−0.68	−0.29	−0.36	−0.78	−0.62

the actual local skin temperature, the average weighted skin temperature, or on the so-called "core" temperature (the importance of which was formerly overestimated), but rather on the weighted *average body* temperature. The wheals occur, therefore, in accordance with a pattern of certain thermoregulatory adjusting processes.

In generalized heat urticaria, wheals follow diffuse thermoregulatory eccrine perspiration after a relatively short latency period and with a remarkably low variability. In generalized cold urticaria, however, the latency period after thermoregulatory shivering appears not only to be longer but also shows a greater variability.

For this reason it is irrelevant for the development of cholinergic urticaria whether body temperature is increased by passive heating at rest (sauna conditions) or by physical exercise (active heating) at a low ambient temperature. In each case and independent of the regional skin temperature, diffuse eccrine transpiration (sweating) occurs and, after a certain latency period, cholinergic urticaria follows.

The urticarial lesions are not dependent on the actual temperature of the skin surface and may occur with rather cool skin; neither, in contrast to earlier conceptions (1, 2, 12) are they dependent on a rise in the so-called "core" temperature ("Kern"-Temperatur). The true provoking factor of cholinergic urticaria is the weighted average temperature of the whole body. The oesophageal temperature, as a measure of the "core" temperature, may even remain below the initial value when urticaria occurs. Mean body temperature, however, does increase under both experimental conditions: under sauna conditions due to an increase in skin temperature and during physical exercise due to an increase in the core temperature (14).

Cholinergic urticaria could also be provoked at neutral temperature, i.e. without any thermal stimulation, by the following measures: 1) By intramuscular injection of carbachol which, according to Illig & Heinicke (9), produces an urticarial attack by direct stimulation of eccrine sweat glands, and 2) by psychological stress, for example by the gag reflex which is accompanied by an increase in heart rate and an outbreak of cold sweating. This occurs in some patients when trying to swallow the oesophageal thermoprobe. During both situations temperature values remained practically unchanged. In these two special cases, therefore, we suggest a non-thermal stimulation of the neuroglandular junction of the eccrine sweat glands which, according to Illig & Heinicke (10), is a real "conditio sine qua non" for the provocation of any cholinergic rash.

These climatic chamber studies therefore support the hypothesis which is also upheld by the experimental data of Illig & Heinicke (9) that neither the diffuse eccrine sweating nor the sweat product itself can be the crucial challenging factor of cholinergic urticaria. It was observed that under different experimental conditions the latency period between sweating and the appearance of skin lesions was not the same as would be expected if the provoking factor were the sweating or the sweat product. Rather remarkable differences were seen depending on certain conditions of the challenge.

The longest interval was observed during thermal provocation by passive or active heating (7–13 min), and the shortest during psychological provocation by the gag reflex (2–4 min). After challenging by a needle prick (7), in all likelihood a psychological mechanism, the latency period between sweating and urticaria is also remarkably short. In the case of the gag reflex, the latency period between the out-

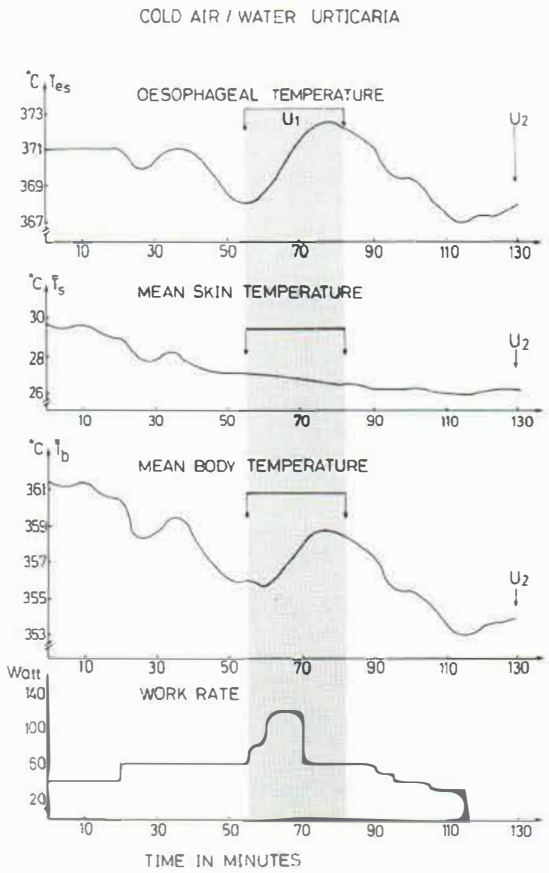

Fig. 5. Pat. S. L. ♂. Cold air/cold water urticaria. Simultaneous cold exposure and physical exercise. Course of oesophageal (T_{es}), mean skin ($\bar{T}_s$) and mean body ($\bar{T}_b$) temperature and work rate (on bicycle ergometer). The skin alterations which appeared after the first drop in mean body temperature (U_1) disappeared when body temperature was raised by increased work rate. After the second drop in mean body temperature the urticaria reappeared (U_2).

break of sweating and the appearance of wheals nearly coincides with that found in a simple histamine wheal following i.c. injection of the drug.

All circumstances therefore support our hypothesis that urticaria provocation is principally independent of the outbreak of sweating and is in no way caused by the sweat substance itself (for recent discussions of this idea see (15, 17)).

The name cholinergic (or generalized) "*heat*" urticaria is thus no longer quite appropriate because passive or active heating in cholinergic urticaria is not necessary for its provocation, in contrast to the crucial role cold plays in the generalized type of cold urticaria. As shown by our experiments with the climatic chamber, provocation is also possible at indifferent ambient temperatures (gag reflex). One of us has since additionally observed a special type of cholinergic urticaria which is provoked exclusively by physical effort (the so-called "Anstrengungsurticaria" or effort urticaria, cf. (8)). The simple name "cholinergic urticaria", already common in Anglo-American literature, should therefore be preferred.

As for the generalized type of cold urticaria, only one serious attempt to define more exactly the quality of the challenging stimulus and the provocation conditions has to our knowledge been published. Brehm (3) concluded from an experimental study on a patient with generalized cold urticaria that the true provoking factor was a *combined* action of cold *and* wind pressure (artificially produced by a wind machine). This concept cannot explain, however, either the need for generalized cooling or the fact that urticaria can be provoked by a cold bath.

The present climatic chamber studies show that the skin *surface* temperature cannot be the crucial challenging factor in generalized cold urticaria. A drop in mean body temperature must occur before urticaria breaks out. All patients complained of feeling cold before skin lesions occurred. No wheals appeared in the case of the young man, however, as long as his physical effort could prevent his mean body temperature from falling. This observation confirms the patients' assertion that by intermittent physical exercise they were able to make urticarial lesions stop or even disappear at a cool and challenging ambient temperature. A hot bath also accelerates the regression of urticarial lesions by apparently increasing mean body temperature by an increase in skin temperature.

Despite some unanswered questions, a comparison of the provoking situation in both types of generalized physical urticaria observed in the climatic chamber under controlled thermal conditions reveals a striking common feature: In both cases skin lesions are apparently induced by a change in the mean body temperature (not of the "core" temperature), in one by an increase thereof and in the other by a decrease.

In generalized cold urticaria no further components of the trigger mechanism are known as yet. In cholinergic urticaria, however, the already mentioned stimulation of the neuroglandular junction of the sweat glands is extensively discussed by Illig & Heinicke (9, 10).

In the generalized form of cold urticaria the same immune mechanism could act as a mediator between physical stimulation and mast cell degranulation as in the contact type. Nothing can be stated, however, about the boundary between the physical and chemical components of the trigger mechanism. In cold contact urticaria (localized type) an immune mechanism with a positive Prausnitz-Küstner reaction has already been proved but unfortunately in these experiments the two different types of cold urticaria were not exactly differentiated (9, 10). A similar immune mechanism in the generalized type of cold urticaria must therefore still be shown.

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