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## OCCURRENCE OF URTICARIA (ERYTHEMA) DUE TO BOTH COLD AND HEAT

By

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Urticaria and/or erythema from cold or heat is a well-known phenomenon. However, cases of urticaria (erythema) from *both*, cold as well as heat are rare. At first *Hopkins, Kesten & Hazel* (1) described four women who developed generalized urticaria after warm and localized urticaria after cold stimuli. Their observations on persons with cold urticaria included the following: (a) One patient also reacted to acetylcholine; (b) another patient to psychic stimuli; (c) whealing occurred in such patients only when they entered a warm room; further (d) they became worse after warm stimuli. *Chmel & Hegyi* (2) reported on a woman aged 48 who had for 10 years suffered from urticaria due to cold *or* warm stimuli. Water or air of 3° C, or 12° C, water of 48° C, as well as infrared rays (44° C) induced urticaria. Sensitivity to histamine was observed. On the basis of the haemoclastic crisis test, which was difficult to evaluate, of negative passive transfers, and of the fact that urticaria could not be evoked until some time after the stimulation, the authors believed their case to be of non-allergic origin.

*Hellemans* (3) gave an account of two heat-allergic soldiers where those attacks could be reproduced by exposure to cold *or* hot showers. It was presumed that some disturbance in thermoregulation occurred with exercise or exposure to heat and cold, and that an abnormal histamine production followed

which produced the urticaria. *Herlitz* (4/a) described a case of cold sensitivity in which acetylcholine was capable of provoking the symptoms; atropine gave considerable improvement. As explanation it was suggested that perhaps cold blocked the acetylcholine-splitting enzyme systems.

It should be noted that in some similar cases presumably only one kind of thermal stimulus plays a rôle, and that the thermal difference, the sudden change of temperature elicits the wheals. In this connection the following observations should also be mentioned:

- (a) certain individuals react to cold only when they have recently been exposed to heat and vice versa (*Duke*, 5/a).
- (b) A sudden drop of temperature in warm weather may, the same temperature in cold weather, however, may not produce cold urticarial symptoms (6).

According to the literature, the pathomechanism of urticaria (erythema) due to both cold and heat is still obscure. In order to obtain a basis for discussion of the aetiology, we have investigated two cases which we will present:

*Case 1.* His urticarial eruptions had begun during the previous autumn in cold weather and had persisted during the winter. In spring there was a remission, but when hot weather began in summer, the hives recurred increasingly.

*Case 2.* Mechanic, aged 24, formerly in military service. History of external otitis and tonsillitis some years ago. Occasional gastric pain; diarrhoea after ingestion of lettuce or dill. In the contact with hot water had caused headaches; however, he was able to work under warm conditions. In 1951 he had done his military service during a hard inter. During the next winter his knees presented increased sensitivity to cold. In the winter of 1953 he observed erythematous patches on his body after having taken a cold bath. Since then there had been constant recurrences, especially when he felt exhausted or came in contact with cold air after having hurried or getting hot. The erythema remained for 1-3 hours.

#### EXPERIMENTAL

Factitial pressure stimuli were applied in the usual manner. Internal intake consisted of drinking hot tea.

Responses to psychic stimuli were noted in both cases following domestic quarrels.

Thermal stimuli: application of ice ( $0^{\circ}\text{C}$ ) for 3 minutes; stimuli ranging up till  $28^{\circ}\text{C}$  were applied with running water for 3 minutes, viz. from  $28^{\circ}\text{C}$  till  $41^{\circ}\text{C}$  with running water for 3 minutes or bathing for 5 minutes, respectively; stimuli of  $42^{\circ}\text{C}$  and  $44^{\circ}\text{C}$  by bathing for 3 minutes.

Water of  $20^{\circ}\text{C}$  was applied for 3 minutes by means of:

- (a) one Erlenmayer flask with a diameter of 4 cm.,
- (b) two Erlenmayer flasks, each with a diameter of 12 cm.

For provocation of symptoms the following solutions were used:

|                     |                           |
|---------------------|---------------------------|
| Acetylcholine ..... | 100 mg. (intramuscularly) |
| Histamine .....     | 1 mg. (subcutaneously)    |
| Pilocarpine .....   | 10 mg. (subcutaneously)   |

For intracutaneous injections, 0.05 ml. of the following solutions were used:

|                     |              |
|---------------------|--------------|
| Acetylcholine ..... | 1 per cent   |
| Histamine .....     | 0.1 per cent |
| Lactic acid .....   | 1 per cent   |

The results of intracutaneous histamine tests were compared with tests in controls.

Passive transfer tests with the Prausnitz-Küstner method were performed with both cold and heat.

*Widal's* haemoclastic crisis test was carried out after the patient had exercised on a staircase.

Reflex inhibition: in the second patient a warm stimulus was applied to the one arm and simultaneously a cold stimulus to the other.

The therapeutic agents tried consisted of barbiturates as well as the following drugs: antihistaminic agents, atropine, ephedrine, chlorpromazine, and calcium preparations. On the first patient a vaccine prepared from the patient's tonsillar flora was also injected.

Continuous sleep was maintained for 5 days by administration of barbiturates and bromides in doses just sufficient to

keep the patient asleep. Sleep was interrupted three times daily for feeding etc. Physical stimuli were applied on the third day of "sleep" and 3 days after the course of treatment had been completed.

### RESULTS

The results of the investigations on the two patients sensitive to both cold and heat are summarized in table 1. Case 1 reacted to 20° C only with the method described under (b).

TABLE 1

|                                             | Case 1   | Case 2         |
|---------------------------------------------|----------|----------------|
| Factitial stimulus                          | Negative | Negative       |
| Pressure                                    | Negative | Negative       |
| Fatigue                                     | Urtica   | Erythema       |
| Internal intake                             | Urtica   | Erythema       |
| Psychic stimuli                             | Urtica   | Erythema       |
| Thermal stimuli:                            |          |                |
| Chloraethyl spray                           |          | Erythema       |
| 0 C°                                        | Negative | Erythema       |
| 0 C°-28 C°                                  | Urtica   | Erythema       |
| 28 C°-41 C°                                 | ?        | Negative       |
| 42 C°-44 C°                                 | Urtica   | Erythema       |
| General symptoms after local stimuli        | Lacking  | Lacking        |
| Refractory phases after test reactions      | Positive | Positive       |
| Provocation by acetylcholine                | Negative | Negative       |
| Provocation by histamine                    | Negative | Negative       |
| Provocation by pilocarpine                  |          | Erythema       |
| i.c. Skin reaction to histamine             | "Normal" | "Normal"       |
| i.c. Skin reaction to acetylcholine         | Negative | Negative       |
| i.c. Skin reaction to lactic acid           |          | Negative       |
| Passive transfers                           | Negative | Negative       |
| Hemoclastic crisis                          |          | Erythema       |
| Reflex inhibition                           |          | Positive       |
| Therapeutic results with barbiturates       | Negative | Positive       |
| Therapeutic results with other drugs        | Negative | Negative       |
| Eliciting of reactions to physical stimuli: |          |                |
| During a continuous sleep cure              |          | Diminished     |
| After a continuous sleep cure               |          | Not diminished |

TABLE 2  
*Haemoclastic crisis test (Widal).*

|            | Pulse rate | Blood Pressure | Axillary temperature | Sedimentation rate 1 hour | Bleeding time | Clotting time | Number of  |              | Colour of blood | Eosinophilia |
|------------|------------|----------------|----------------------|---------------------------|---------------|---------------|------------|--------------|-----------------|--------------|
|            |            |                |                      |                           |               |               | Leucocytes | Thrombocytes |                 |              |
| Before     |            |                |                      |                           |               |               |            |              |                 |              |
| crisis ... | 96         | 100/80         | 36.9 C°              | 2                         | 1'40"         | 5'            | 5000       | 290000       | Normal          | 4 %          |
| 30' after  |            |                |                      |                           |               |               |            |              |                 |              |
| crisis ... | 60         | 90/80          | 36.7 C°              | 1                         | 2'15"         | 8'            | 3700       | 116000       | Strawberry      | 1 %          |

The results of routine tests were not of special interest except for the data that both patients had a chronic tonsillar inflammation and both showed hypoacidity. The lymphocyte count in the peripheral blood picture was 50 % and 21 % respectively.

The results of *Widal's* haemoclastic crisis test are given in table 2.

#### DISCUSSION

In our cases—similarly to the findings of *Hopkins et al.*—a local contact type reaction to cold (e.g. with running water of 1 to 28° C) and a diffuse reflex-type reaction to heat and exercise were present. We found urticaria, respectively erythema in our patients under emotional influences. We will mention that a certain relationship was found between the size of the stimulated area and the appearance of the hives in case 1, viz. in so far as no hives could be evoked by stimulating a small area, while the hives appeared after a bigger site has been exposed to the thermal stimulus.

Between 28° C and 41° C there was no reaction in case 2; in case 1, urticaria developed once spontaneously in hot weather when the temperature exceeded 30° C, but this observation was not reliable because other influences could not be ruled out. Reflex inhibition in sweating experiments has

TABLE 3

*Supposed mechanism of the cases due to sensitivity to heat and cold.*

| <i>Evidence for allergy (14):</i>                                                         | <i>Remarks:</i>                                                                                                                                      |
|-------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|
| Occurrence of sudden attacks                                                              |                                                                                                                                                      |
| Positive dermal and exposure tests                                                        |                                                                                                                                                      |
| Itching as accompanying symptom                                                           |                                                                                                                                                      |
| Refractory phases after the positive tests                                                |                                                                                                                                                      |
| Positive haemoclastic crisis test                                                         | It is now regarded as only accompanying phenomenon. However it was used before as argument for the allergic origin of e.g. cold haemoglobinuria (16) |
| <i>Evidence for non-allergic cold pathergy (9):</i>                                       |                                                                                                                                                      |
| Both cold and heat caused symptoms in our cases                                           |                                                                                                                                                      |
| Negative passive transfers to heat and cold                                               | This is negative in cold urticaria in 34 % (17)                                                                                                      |
| Diminished pathologic response to thermal stimuli during a continuous sleep cure (case 2) | It is questionable whether this indicates a <i>specific</i> inhibition                                                                               |
| Relative good therapeutic effect of barbiturates (case 2)                                 |                                                                                                                                                      |
| Absence of personal or family history of atopy (5/b)                                      | This is positive in only about $\frac{1}{3}$ of allergic cases (17)                                                                                  |
| Focal infection was present in our cases                                                  | According to <i>Urbach</i> these can be regarded as arguments for cold pathergy (9)                                                                  |
| Hypoaecidity was present in our cases                                                     |                                                                                                                                                      |
| Reflex inhibition phenomenon (see text)                                                   | When one forearm was exposed to cold, a contralateral reaction also appeared, which can be explained by vasoneurosis (4/b)                           |
| <i>Rôle of cholinogenic mechanism</i>                                                     |                                                                                                                                                      |
| Characteristic clinical picture (case 1): small wheals surrounded by a large flare (18)   |                                                                                                                                                      |
| Positive provocation after pilocarpine injection                                          | Found also by other workers (19, 20, 21, 9)                                                                                                          |
| Negative acetylcholine provocation                                                        | This is not of decisive value, mecholyl could not be tried                                                                                           |

been described (7). Thirty minutes after the haemoclastic crisis a collapse occurred in the second patient. The positive haemoclastic crisis test deserves attention, bearing in mind that in this case erythema was the only appreciable symptom. Observations on the lymphocyte counts, tonsillar inflammation, and gastric hypoacidity are reported elsewhere (8).

*Pathomechanism.* If the work done with the aim to make clear the mechanism of these cold/heat reactions is studied, it will be noted that *Urbach* in his book on allergy (9) discusses certain aetiologic possibilities which we quote together with the suggestions of some other authors:

- (a) based on specific antigen-antibody reactions;
- (b) secondary allergen (autogenous altered tissue protein) is suggested (10);
- (c) a liberation of histamine-like substances is suggested (11);
- (d) a cold specific vasomotor neuropathy (non-allergic cold pathergy). According to *Urbach* an "instability of the central and peripheral vasomotor mechanism may be responsible for the abnormal neurovascular response to local physical agents in some cases" (9);
- (e) central disturbance of the temperature regulating mechanism is assumed (5/a).

As a further mechanism (f), i.e. that acetylcholine acts as allergen, possibly combined with histamine (12), can be considered to occur in heat urticaria (13).

In our two cases the explanation of the pathomechanism is very difficult. In table 3 we present, as regards the possibilities mentioned above, some features corresponding to the points quoted under (a), (d), or (f), respectively.

As is pointed out by *E. Rajka Sr.* (14), the impossibilities of reagin demonstration does not definitely indicate a non-allergic pathergy, though there are undoubtedly cold urticarial cases of non-allergic origin. *Baer* states: "an allergic basis may be established clearly for some of those hypersensitivities, while in others, proof of specific immunologic mechanism may be weak or entirely lacking" (15).

After considering these conclusions and the collected arguments of table 3, the question whether the observed two cases based on an allergic (antigen-antibody reaction) or non-allergic mechanism (or in part on a cholinogenic mechanism) remains unsolved.

#### SUMMARY

A case responding with urticaria, and another responding with erythema to thermal stimuli ranging from 0° C to 28° C and beyond 42° C, i.e. combined abnormal thermal reactions due to both cold *and* heat are reported.

Some findings suggest an allergic origin; others the existence of a cold pathergy and certain cholinogenic features were also found. These patho-mechanistic possibilities are discussed.

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