Cold Hypersensitivity in Raynaud's Phenomenon

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SUMMARY
We have sought evidence that local cooling enhances the adrenergic neurotransmitter mechanism in resistance vessels in the hands of subjects with Raynaud's phenomenon. The method used was to examine the magnitude and time-course of the reflex vasoconstriction in the hand which follows application of ice to the neck. One hand of each subject was kept at 26°C and the other at 36°C, while the general thermal environment was varied. Enhancement was found in three groups of subjects: those with idiopathic, early age-onset, Raynaud's disease; those with Raynaud's phenomenon of late age-onset; and those with systemic scleroderma. It was absent in normal subjects. The effect could not be accounted for by structural abnormalities of resistance vessels, blood abnormalities, nor by interference with norepinephrine reuptake or dissipation at the neuro-effector junction.

Additional Indexing Words:
Blood viscosity  Fibrinogen  Plethysmography

The first systematic attempt to interpret the clinical features of Raynaud's phenomenon in terms of physiologic disturbance was made by Lewis and his colleagues over the period 1929 to 1938. Their conclusions were that in persons who suffer from this condition the precapillary resistance vessels of the fingers are hypersensitive to local cooling. Some of the bases for this conclusion were that nail-bed capillary pressure fell sharply on exposure of the finger to cold; the ulnar nerve (sympathetic) blockade did not prevent involvement of the ring and little fingers in a vasospastic attack nor did it abolish vasoconstriction in these fingers after an attack had commenced; and cervicothoracic ganglionectomy did not permanently abolish attacks.

Latterly, there have been sporadic observations that have suggested that enhancement of sympathetic reflex action, or an aberration of peripheral neurovascular transmission, may be implicated. Peacock compared a group of subjects suffering from primary Raynaud's disease with a group of normal subjects. In a neutral thermal environment the hand blood flow of the former group was abnormally low (although after sympathetic release by body-heating, hand blood flow was identical in the two groups). This suggests that there may be tonic sympathetic vasoconstrictor overactivity. He also described an increased concentration of catecholamines in venous blood from the hands of persons with Raynaud's phenomenon, although Kontos and Wasserman were subsequently unable to confirm this. Reserpine, administered orally or intraarterially, has been reported to diminish the frequency and severity of attacks of digital vasospasm suggesting that there may be an aberration of some aspect of adrenergic transmission in the fingers.

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RAYNAUD'S PHENOMENON

We have set out to examine this last hypothesis in particular, by testing the effect of local cooling on reflex vasoconstriction in the hands of subjects suffering from Raynaud's phenomenon. As a test, we have used the application of ice to the neck, which we have previously shown to have a reproducible and predictable reflex vasoconstrictor effect in the hands of normal individuals.12

Methods

Nineteen persons suffering from Raynaud's phenomenon were studied, together with seven normal control subjects. All subjects were free volunteers. Three sets of data were obtained for each person:

(1) As background, a full clinical interview was undertaken and a thorough physical examination conducted. Particular attention was paid to age, sex, age at onset of symptoms, exposure to vibrating tools, state of the skin of the hands and fingers, and pulses of the upper limbs. On the basis of these data, the subjects were classified into four groups (table 1):

(a) Normal control subjects, recruited from among staff members, nurses, and medical students (normal group).
(b) Subjects with classic, idiopathic, Raynaud's disease (early-onset group), recruited also from among nurses and medical students. The criteria were that the age of onset of symptoms was less than 20 years, that all fingers of both hands were symmetrically affected by episodes of painful pallor, that there was no blood abnormality detectable, and that there was no abnormality of the skin of the digits.
(c) Subjects in whom there was no clinical evidence of systemic scleroderma, but who suffered from episodes of painful pallor affecting one or more fingers, and in whom the age of onset of symptoms was greater than 40 years (late-onset group).
(d) Subjects confidently diagnosed as having systemic scleroderma on a basis of widespread and progressive characteristic skin changes, and who had episodes of pallor in one or more digits (scleroderma group).

(2) A comprehensive blood analysis was performed, including measurement of hemoglobin concentration, plasma protein electrophoresis, and plasma fibrinogen concentration. A search was made for the presence of cold agglutinins, cryoglobulins, and antinuclear antibody.

(3) Hand blood flow measurements were made under laboratory conditions by a protocol which has been described in detail previously.12 Blood flow was measured simultaneously in both hands of each subject by venous occlusion plethysmography at 20-sec intervals, with water-filled plethysmographs. One hand was maintained at 26.0 ± 0.5°C (cool), the other at 36.0 ± 0.5°C (warm). Air temperature was neutral for our climate (21.0–22.5°C). The lightly clad subject was covered by one blanket during an initial set of recordings; then body-heating was induced by means of an electric blanket until sweating was just detectable. At irregular intervals throughout the experiment a cube of ice was applied to the neck of the subject for a period of 10 sec.

The vasoconstrictor response to application of ice was analyzed in terms of magnitude and time-course. Its magnitude for the cool and warm hands of each group of subjects was estimated from the slope of the regression line for the data relating blood flow before to blood flow after the application of ice. Blood flow before was taken as the mean of the five estimates of blood flow made during the 80 sec immediately preceding the application of ice. Blood flow after was taken as the first flow after removal of the ice, at which time it has fallen to a minimum.12 Analyses of covariance were used to compare the slopes of these regression lines, both within and between groups.12 Differences in the time-courses of the responses within and between groups were sought

Table 1

<table>
<thead>
<tr>
<th>Age, Sex, and Clinical Data for Groups of Subjects Studied</th>
<th>Subjects with Raynaud's phenomenon</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal subjects</td>
</tr>
<tr>
<td>No. of subjects</td>
<td>7</td>
</tr>
<tr>
<td>Male:female</td>
<td>2:5</td>
</tr>
<tr>
<td>Mean age at time of study (yrs)</td>
<td>44.6</td>
</tr>
<tr>
<td>Age range at time of study (yrs)</td>
<td>19–62</td>
</tr>
<tr>
<td>Evidence of organic finger changes</td>
<td>0/7</td>
</tr>
</tbody>
</table>

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by comparing the half-times for recovery to the control level of blood flow, and by visual comparison of averaged blood flows after application of ice. In some subjects hand blood flow was unrecordable in the cool hand when the thermal environment was neutral, so the magnitude of the response to the ice could not be measured. This accounts for the inequalities in the numbers of observations in cool and warm hands.

Unless otherwise indicated, Student’s t-test has been used to compare sets of data. Values for probability greater than 0.05 were regarded as not significant.

Results

Clinical Data (Table 1)

Among the four clinical groups the sex distributions of the subjects were comparable, as were the age distributions (with the exception of the late-onset group among whom the mean age was greater). None of the subjects had been exposed to vibrating tools or had suffered cold injury to the hands. Fifteen of the 19 subjects with Raynaud’s phenomenon in the hands had noticed similar symptoms in the feet. Two of the six subjects in the early-onset group, and one of the eight in the late-onset group had a positive family history.

Physical examination disclosed organic changes in the fingers (pulp atrophy, sclerodactyly, or pulp ulceration) in all five subjects with generalized scleroderma, and in three of the eight in the late-onset group. All subjects had palpable and equal wrist pulses, none was hypertensive, and none had inequality of blood pressure between the two arms.

Blood Analyses (Table 2)

There was no evidence that the subjects of any of the three groups with Raynaud’s phenomenon possessed a blood abnormality which would account for their symptoms. In particular, comparison with the group of normal subjects revealed no significant elevation of hemoglobin concentration, plasma globulins, or plasma fibrinogen. In none of the plasma samples were cold agglutinins or cryoglobulins detected. No platelet abnormalities were seen in routine blood films.

The test for the presence of antinuclear factor was positive in four of the five subjects with clinically evident scleroderma, and in two of the eight subjects in the late-onset group (who had no clinical evidence of this disease).

Resting Blood Flow Rates (Table 3)

Within each group, the blood flow in the 36°C (warm) hand was always greater than in the 26°C (cool) hand (P always <0.02), and in both hands the blood flow was greater after body-heating than before (P always <0.05). There were no significant differences among the groups with respect to blood flow in the warm hands when the general thermal environments were identical. With respect to the cool hands, when comparisons of blood flow were made with the normal group (either with the thermal environment neutral or after body-heating) no significant differences were revealed. However, when all flow data for the cool hands in each group of subjects were

Table 2

<table>
<thead>
<tr>
<th>Blood Screening Data*</th>
<th>Subjects with Raynaud’s phenomenon</th>
<th>Onset age</th>
<th>Onset age</th>
<th>Scleroderma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal subjects</td>
<td></td>
<td>&lt; 20 yr</td>
<td>&gt; 40 yr</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>13.7 ± 0.3</td>
<td>12.1 ± 0.5†</td>
<td>12.6 ± 0.4</td>
<td>12.9 ± 1.0</td>
</tr>
<tr>
<td>Total protein</td>
<td>7.64 ± 0.16</td>
<td>7.08 ± 0.30</td>
<td>7.38 ± 0.61</td>
<td>7.48 ± 0.31</td>
</tr>
<tr>
<td>Albumin</td>
<td>4.27 ± 0.20</td>
<td>3.95 ± 0.21</td>
<td>4.01 ± 0.14</td>
<td>3.60 ± 0.28</td>
</tr>
<tr>
<td>a1-globulin</td>
<td>0.43 ± 0.06</td>
<td>0.40 ± 0.05</td>
<td>0.45 ± 0.03</td>
<td>0.38 ± 0.04</td>
</tr>
<tr>
<td>a2-globulin</td>
<td>0.73 ± 0.07</td>
<td>0.60 ± 0.08</td>
<td>0.78 ± 0.05</td>
<td>0.82 ± 0.12</td>
</tr>
<tr>
<td>B2-globulin</td>
<td>1.04 ± 0.06</td>
<td>0.90 ± 0.11</td>
<td>0.99 ± 0.04</td>
<td>0.94 ± 0.09</td>
</tr>
<tr>
<td>g-globulin</td>
<td>1.17 ± 0.09</td>
<td>1.15 ± 0.11</td>
<td>1.18 ± 0.14</td>
<td>1.80 ± 0.48</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>0.43 ± 0.04</td>
<td>0.30 ± 0.03†</td>
<td>0.40 ± 0.04</td>
<td>0.26 ± 0.04†</td>
</tr>
</tbody>
</table>

*Mean values in g/100 ml ± standard error of mean, unless otherwise indicated.
†P < 0.05 for difference from normal subjects.
pooled, hand blood flow was significantly less than normal ($P < 0.05$) among those in the early-onset and late-onset groups.

In summary, flow in the cool hand of all groups was always less than that in the warm hand in the same general thermal environment; with the hand at constant temperature, body heating induced an increase in blood flow in all groups; and overall, flow was less than normal in the cool hands of the early-onset and late-onset groups.

**Magnitude of Blood Flow Responses to Ice Application (Table 4, Figures 1-4)**

In all groups, the plot of blood flow after the application of ice against that which obtained beforehand correlated well with a straight line, the correlation coefficients ranging from 0.884 to 0.652. The effects of the cool local environment compared with the warm one were tested by comparison of the slopes of these straight lines within each group. There was no difference between the behavior of cool and warm hands in normal subjects. However, a significantly greater flow depression resulted in the cool compared with the warm hands (for any given resting level of blood flow) in each of the three groups of subjects with Raynaud’s phenomenon.

**Table 4**

Analysis of Data Relating Hand Blood Flow Immediately After a 10-Second Period of Ice Application, $y$, to the Mean Flow During the Preceding 80-Second Control Period, $x$ (Plethysmograph Temperatures 26°C or 36°C)

<table>
<thead>
<tr>
<th></th>
<th>No. of observations</th>
<th>Correlation coefficient</th>
<th>Line of best fit</th>
<th>Probability of difference in slope</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26°C</td>
<td>130</td>
<td>0.858</td>
<td>$y = 0.37x + 0.07$</td>
<td>$P &lt; 0.1$</td>
</tr>
<tr>
<td>36°C</td>
<td>141</td>
<td>0.839</td>
<td>$y = 0.42x + 0.63$</td>
<td></td>
</tr>
<tr>
<td>Early onset</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26°C</td>
<td>47</td>
<td>0.816</td>
<td>$y^* = 0.29x + 0.40$</td>
<td>$P &lt; 0.01$</td>
</tr>
<tr>
<td>36°C</td>
<td>70</td>
<td>0.891</td>
<td>$y = 0.54x + 0.14$</td>
<td></td>
</tr>
<tr>
<td>Late onset</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26°C</td>
<td>72</td>
<td>0.884</td>
<td>$y^† = 0.54x + 0.02$</td>
<td>$P &lt; 0.05$</td>
</tr>
<tr>
<td>36°C</td>
<td>98</td>
<td>0.808</td>
<td>$y^‡ = 0.66x - 0.76$</td>
<td></td>
</tr>
<tr>
<td>Scleroderma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26°C</td>
<td>43</td>
<td>0.652</td>
<td>$y = 0.41x + 0.79$</td>
<td>$P &lt; 0.01$</td>
</tr>
<tr>
<td>36°C</td>
<td>57</td>
<td>0.674</td>
<td>$y^§ = 0.80x - 1.43$</td>
<td></td>
</tr>
</tbody>
</table>

* $P < 0.01$ for difference from normal, 26°C.
† $P < 0.001$ for difference from normal, 26°C.
‡ $P < 0.001$ for difference from normal, 36°C.
§ $P < 0.01$ for difference from normal, 36°C.
Comparisons were then made among the different groups, with respect to the magnitude of the response to ice in the cool hands and in the warm hands. In the early-onset group the response to ice was greater for the cool hands than for the cool hands of normal subjects; in the late-onset group the response to ice was less than normal for both hands; and in the scleroderma group it was less than normal for the warm hand only.

In summary, within each of the groups of subjects with Raynaud's phenomenon local cooling of the hand enhanced the reflex vasoconstrictor response to distant ice application. Among the groups, by comparison with normal, the response to ice was exaggerated in the cool hand of the early-onset group, but was less than normal in both hands of the late-onset group and in the warm hand of the scleroderma group.
RAYNAUD'S PHENOMENON

Plot of hand blood flow immediately after a 10-sec period of application of ice against mean control flow over the preceding 80 sec. Data from eight subjects with late-onset Raynaud's phenomenon, with one hand at 26°C (72 observations) and one at 36°C (98 observations). Line of best fit at 26°C: y = 0.54x + 0.02. Line of best fit at 36°C: y = 0.66x - 0.76. Analysis of covariance for difference in slope: P < 0.05.

**Time-Courses of Blood Flow Responses to Ice Application**

These were examined visually by taking for each hand of each group the arithmetic average of all of the data for the five flows preceding and the five flows following the period of application of ice. The cool and warm hands were treated separately, and the averaged flows for each were normalized (with respect to the mean flow in the same hand preceding application of ice) and plotted against time (fig. 5).

The temperature of the hand did not appear to affect the rate of recovery of flow, except in the scleroderma group where there was an apparently slower recovery in the cool hand...
compared with the warm. When groups were compared, recovery appeared slower than normal among the subjects with late-onset symptoms and with scleroderma.

The asymptotic shapes of the recovery curves led us to compare the half-times for recovery from the first flow after removal of the ice to the mean control level of flow (table 5). The visual impressions described above were confirmed. In addition, among the normal subjects the half-time for recovery was shorter for the 36°C hand than for the 26°C hand.

**Discussion**

One of the difficulties in interpreting physiologic studies of persons suffering from Raynaud's phenomenon has been that the sufferers constitute a miscellaneous group in terms of underlying disease processes. In many reports it is not made clear whether the subjects studied suffered from organic abnormalities of the blood or blood vessels, and we have been at pains to take these variables into account when interpreting the hand flow data.

The commoner blood abnormalities that may be associated with a form of Raynaud's phenomenon are polycythemia and high plasma levels of cryoglobulins or cold agglutinins. None of the subjects we studied suffered from any of these blood disturbances. It is particularly noteworthy that in none of the groups of abnormal subjects was the plasma fibrinogen level elevated. There was no support for the report that blood viscosity and plasma fibrinogen were elevated in a similar group of subjects; nor is it clear why elevation of blood viscosity—unless it be by fibrinogen in a cryoprecipitable form—should be associated with cold-induced episodes of digital syncope, for the reported temperature coefficient for blood viscosity is small.

### Table 5

**Times (in Seconds) for Half-Recovery of Hand Blood Flow to the Mean Control Level, Measured from the Time of Removal of Ice After a 10-Second Period of Application**

<table>
<thead>
<tr>
<th>Subjects with Raynaud's phenomenon</th>
<th>Normal subjects</th>
<th>Onset age &lt; 20 yr</th>
<th>Onset age &gt; 40 yr</th>
<th>Scleroderma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand at 26°C</td>
<td>23.4 ± 1.2</td>
<td>27.6 ± 2.2</td>
<td>30.0 ± 1.8†</td>
<td>35.6 ± 3.2†</td>
</tr>
<tr>
<td>Hand at 36°C</td>
<td>22.0 ± 0.8**</td>
<td>23.8 ± 1.6</td>
<td>32.4 ± 2.4‡</td>
<td>27.2 ± 2.2‡§</td>
</tr>
</tbody>
</table>

*Values as mean ± standard error.

†*P* < 0.05 for difference from normal subjects.

‡*P* < 0.01 for difference from normal subjects.

§*P* < 0.05 for difference between two hands.

**P* < 0.02 for difference between two hands.
On the other hand, it is overwhelmingly probable that our sclerodermatous subjects, and some of those whose symptoms were of late age-onset, had structural narrowing of their digital arteries and intimal proliferation and medial infiltration in the smaller resistance vessels. Such changes are a constant feature in the skin of patients with scleroderma and have been demonstrated both by arteriography and by microscopy. It is also likely that at least some of the patients in our late-onset group had similar structural changes in the digital vasculature. In two of these patients antinuclear factor was detected in the serum. Three others of the eight had atrophy or ulceration of the digital pulps. In similar groups of subjects arteriography and microscopy have revealed structural abnormalities of digital arteries, and the maximal hand blood flow attainable by body-heating has been reported as being less than normal.

Can the physiologic changes which we observed in the late-onset and sclerodermatous groups of subjects be entirely explained by structural disease of the digital vasculature? The transient episodes of digital syncope of which the patients complained are explicable on a basis of a normal pattern of tonic sympathetic constrictor discharge acting on vessels whose transmural pressure is reduced by narrowing of the proximal digital arteries. Likewise, our observation that the reflex constrictor response to application of ice was less in magnitude than normal (figs. 3 and 4) but of longer time-course (table 5, fig. 5) could be accounted for by increased "stiffness" of the resistance-vessel walls. Indeed, Willerson et al., who assessed digital blood flow in similar subjects with Raynaud's phenomenon by measuring digital heat loss, found a similar unresponsiveness to the more protracted stimulus of transfer from a neutral to a cold environment and offered a similar explanation. However, this does not explain our observation that local cooling enhanced the response to ice.

In the groups of subjects with early-onset Raynaud's disease it is extremely unlikely that there were structural changes in the digital vessels. The subjects were drawn from a "normal" population rather than from among hospital patients. None of the subjects had signs of persistent digital ischemia, even though some had suffered attacks of Raynaud's phenomenon for years. In similar groups of subjects the digital vessels have been shown to be structurally normal by arteriography or by microscopy, and the maximal hand blood flow response to body-heating is also normal. In the early-onset group (as in those of late-onset and with scleroderma) we have shown that the reflex vasoconstrictor response to application of ice is enhanced when the hand is cool (fig. 2), in circumstances that preclude this being other than a local effect and in contrast to normal control subjects (fig. 1) in whom this effect was not observed.

There have been other reports of an exaggerated effect of local cooling on hand blood flow in subjects with primary Raynaud's disease, though by comparisons between individuals so that differences in reflex sympathetic constrictor discharge rate could not be entirely excluded. Peacock has compared hand blood flow in a group of subjects with Raynaud's disease with that in normal control subjects, varying local hand temperature while maintaining the general thermal environment constant. He found that when hand temperature was less than 34°C, blood flow was lower than normal among the subjects with Raynaud's disease. Hillestad compared hand blood flow in two subjects with early-onset Raynaud's disease with that in three normal subjects, with various combinations of room temperature (10 to 32°C) and of hand temperature (6 to 40°C). He found that over the whole range of hand temperatures flow was lower than normal in the subjects with Raynaud's disease, and that the discrepancy reached a maximum at between 20 and 30°C.

It seems impossible to explain these observations by other than a cold-induced aberration of the peripheral adrenergic transmitter mechanism. One possible mechanism is that cooling inhibits norepinephrine reuptake or dissipation. However, the identity of the
time-courses of the response to ice in normal subjects and in those with early-onset symptoms (fig. 5, table 5) makes this improbable. Release of a greater quantity of norepinephrine per nerve impulse is also a plausible explanation. However this would not fit the clinical observation of recurrence of symptoms following demonstrably complete sympathetic denervation. Nor does it follow that, because reserpine ameliorates the symptoms, the primary abnormality is one of cold-induced excessive norepinephrine release.

A more likely explanation is that cold sensitizes the \( \alpha \)-receptor mechanism of the vascular smooth muscle, excitation-contraction coupling, or the contractile elements themselves. The first possibility is susceptible to testing by constructing dose-response curves for intraarterial norepinephrine, as has been done for normal subjects.\textsuperscript{30} The last possibility is not consistent with the known effects of cold on smooth muscle contractility.\textsuperscript{31}

It is interesting that a similar enhancement by cold of adrenergic transmission and of norepinephrine infusion has been reported in animal preparations. Webb-Peploe and Shepherd\textsuperscript{82} have demonstrated both these effects in the subcutaneous veins of the limbs of the dog, and Glover, Strangeways, and Wallace\textsuperscript{83} in the response of the artery of the rabbit ear to norepinephrine. Both sets of workers have suggested that this is a normal thermoregulatory mechanism in these species, and both have convincingly excluded inhibition of norepinephrine reuptake as the explanation.\textsuperscript{34-36} However, it seems from our present work that an analogous thermoregulatory mechanism does not obtain in hand resistance vessels of normal humans (fig. 1). Nor do we believe that the enhancement by cooling of the response to ice in the hands of subjects with Raynaud's phenomenon is explicable as an effect on venous resistance, for the reported time-course of constriction of human veins in response to a remote cold stimulus is much slower than the blood-flow response that we have observed.\textsuperscript{37-39}

Before one can accept enhancement of adrenergic transmission by local cooling as a principal cause for the symptoms of primary Raynaud's disease, the failure of cervicothoracic ganglionectomy to regularly cure the condition\textsuperscript{3, 4, 28, 29} must be explained. However, there is proof that in man hypersensitivity of the hand resistance vessels to intraarterial adrenaline and noradrenaline occurs after sympathectomy,\textsuperscript{40} and it is at least plausible that this effect, combined with emotion- or cold-induced release of catecholamines from the adrenal medulla, will account for the perpetuation of symptoms. We can find no report of persistence of symptoms in face of a combination of ganglionectomy and bilateral adrenalectomy.

There is one further form of Raynaud's phenomenon that occurs in subjects with structurally normal digital vessels: that which follows the use of vibrating tools. We have not had the opportunity of studying such subjects, but clinical evidence of a purely local hypersensitivity to cold is persuasive,\textsuperscript{41} and the disorder may have the same basis as we have suggested for early-onset primary Raynaud's disease.

If our thesis is correct, there are certain therapeutic implications. These are that, in idiopathic, early age-onset, Raynaud's disease, measures that reduce the concentration of norepinephrine at the \( \alpha \)-receptors of the digital vasculature will tend to ameliorate the symptoms in a nonspecific fashion but will not correct the underlying abnormality. On the other hand, it appears that in those with structural disease of the digital vasculature there is a double cause for symptoms: the action of normal sympathetic pressure and a vessels with a low transmural pressure and a hypersensitivity to local cold. Pharmacologic or surgical removal of sympathetic action will also tend to ameliorate, though not correct, both abnormalities.

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