Raynaud's Disease in Children

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SUMMARY
Six children with primary Raynaud's disease have been studied with plethysmography and multiple-site skin-temperature readings. All six were free of systemic disease. Each demonstrated the characteristic sequence of pallor, cyanosis, and rubor when subjected to generalized cold, but application of local cold produced only modest reduction in skin temperature and digital pulse. Only one child had a history of vasospastic symptoms associated with emotional stimuli, and she was the only one in whom an emotional challenge was able to produce Raynaud's phenomenon during the physiological studies. Tolazoline, in doses small enough to avoid generalized vasodilatation, was effective in substantially increasing flow to the affected digits.

The involvement of only one or two digits, next to completely uninvolved digits, is a conclusive argument for a primarily local sensitivity. However, the ability to precipitate vasospasm with generalized cold, versus local cold applications, and emotional stimuli indicates the importance of the nervous system in the manifestation of Raynaud's disease.

Additional Indexing Words:
Cold sensitivity  Emotional stimuli and vasospasm  Plethysmography
Reserpine  Skin temperature  Tolazoline
Vasospastic disorders

Raynaud described a vasopathic disorder in 1862 characterized by the sequence of pallor, cyanosis, and rubor. Allen and Brown proposed more rigid requirements for the diagnosis of Raynaud's disease, which have been widely accepted since 1932: "(1) episodes of change in color, of the vasospastic type, excited by cold or emotion; (2) bilaterality; (3) presence of normal pulsations in the palpable arteries; (4) absence of gangrene, or its limitation to the minimal grades of cutaneous gangrene; (5) absence of any primary disease which might be causal, such as cervical rib or organic disease of the nervous system, and (6) symptoms of two years or of longer duration." Allen and Brown attributed the first four criteria to Raynaud, but added the last two criteria in order to separate the primary disease from secondary vasomotor symptoms. Gifford and Hines in a very complete review of 756 female patients at the Mayo Clinic found these criteria very effective. (They actually used only five criteria; the third criterion is inherent in the fifth.) Additional characteristics of Raynaud's disease are predilection for young females and absence of severe pain. The sequence characteristic of Raynaud's disease but associated with other pathological states is usually called "secondary Raynaud's phenomenon."

The underlying mechanism of Raynaud's disease was thought to be hyperactive vasomotor nerves by Raynaud, but Lewis favored local hypersensitivity of the digital arteries. More recently, increased viscosity of the blood has been described in most patients as a major mechanism.

There have been no reports of Raynaud's disease in the pediatric literature, although occasionally a child has been discussed as part of a larger group of patients with the disorder.
Yet, children with the disorder present an unusual opportunity to study Raynaud’s disease in a pure form, since obstructive arterial disease is rare in children. We have studied six children with Raynaud’s disease with plethysmography and multiple-site skin-temperature recordings.

**Group Studied**

The six children ranged from 5 to 14 years of age. There were two males and four females. They all had had symptoms from several months up to 9 years. Underlying systemic disease was ruled out as far as possible. In particular, cardiopulmonary disease, fever, anemia, arthritis, and elevated sedimentation rate were excluded. None of the subjects had ever had frost bite or prolonged exposure to extreme cold.

**Methods**

The studies were performed with the subject in a supine position at an initial ambient temperature of 23 C (74 F); in two children, Raynaud’s phenomenon was present at a room temperature of 23 C, and for these, the room temperature was raised to 27 C initially. After a period of rest, control records were obtained. Then, an emotionally charged incident was staged in an attempt to provoke Raynaud’s phenomenon. The incident varied from patient to patient, such as confrontation with a 50-ml syringe attached to a spinal needle or searching questions about school performance. After a recovery period, the room temperature was gradually lowered to 0 to 5 C (32 to 41 F). If Raynaud’s phenomena were observed at more moderate temperatures, the room temperature was not lowered further, and the effect of a placebo and tolazoline (Priscoline) were investigated. A small gauge needle was inserted into an antecubital vein, and a slow drip of saline was begun. Records were taken during the insertion of the needle, and after a rest period, and during the administration of an amount of saline similar to the amount of tolazoline.

In the last three patients studied, the effects of local cold were measured by the repeated application of Turkish towels soaked in ice water to both hands, one at a time. To study the effects of generalized cold exposure, these patients were wheeled into a cold room at 5 C, instead of gradually lowering the room temperature. These subjects also were given a placebo and tolazoline subsequently.

Plethysmography was carried out in a supine position with the fingers and toes at approximate heart level. The instrumentation was a modified sonar system. Two small (5 mm in diameter) barium titanate crystals were placed across the anteroposterior dimension of the terminal phalanx, at the level of the nail bed. The velocity of transmission for 3 megacycle ultrasound through blood and most soft tissues is 1.5 mm per microsecond. The amplification of the system permits the recording of a pulse amplitude of less than a micron. The pulse can be expressed as a percentage of the diameter of the digit. In each patient, plethysmography was performed on an affected digit and a digit that was little affected according to history and examination. The method permits evaluation of rapid changes in pulse amplitude in a digit directly exposed to the ambient atmosphere, a distinct advantage in the study of Raynaud’s disease over the water-filled plethysmograph of the entire hand.

Slower changes of blood flow are reflected in skin temperature of digits, which was recorded by use of thermocouples constructed of 30-gauge copper-constantin wires held on the volar pads of the distal phalanx by a single layer of narrow adhesive tape. Up to eight sites were sampled sequentially on a Brown recording potentiometer by use of a telephone-type relay with automatic switching at 7-second intervals.

**Results**

**Clinical**

The six children were all native to Washington, and all but one came from the Puget Sound area where moderate, cool temperatures, associated with considerable dampness, prevail. In connection with the humidity as a contributing factor, one of the girls spent one winter in the eastern part of Washington, which enjoys a much colder but drier winter, and had no Raynaud’s phenomenon that year. Although her emotional milieu also changed that year, this patient had no history of Raynaud’s phenomenon precipitated or aggravated by emotional upsets.

The ages of onset were less than 3 years in two children (table 1). The boy, J.S., with onset at age 2½ years, had the most severe disease and demonstrated significant scars of previous ulcerations (fig. 1) and roentgenographic changes of the terminal phalanges of several fingers (fig. 2). He was examined by us at age 5½ years, and a thorough investigation was
Table 1

<table>
<thead>
<tr>
<th>Patients</th>
<th>Sex</th>
<th>Age (yr) at Onset</th>
<th>Involvement</th>
<th>Family history</th>
<th>Precipitated by Cold</th>
<th>Structural changes</th>
</tr>
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<tbody>
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<td>J.S.</td>
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<td>+</td>
<td>0</td>
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<td>S.C.</td>
<td>F</td>
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<td>+</td>
<td>0</td>
</tr>
<tr>
<td>S.S.</td>
<td>M</td>
<td>11</td>
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<td>+</td>
<td>0</td>
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<tr>
<td>T.B.</td>
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</tr>
<tr>
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<td>0</td>
</tr>
<tr>
<td>P.J.</td>
<td>F</td>
<td>14</td>
<td>Fingers &gt; toes</td>
<td>0</td>
<td>+</td>
<td>0</td>
</tr>
</tbody>
</table>

Figure 1

Fingers of J.S., a 5-year-old boy, with scars of previous ischemic ulcers. Onset of his symptoms occurred 3 years earlier. He has been followed for 4 years since this photograph was made and has been evaluated twice for evidence of scleroderma and other systemic disorders, with negative results. The thumbs, not well shown, were characteristically spared except for minimal scarring in one.

made to rule out other systemic diseases, particularly scleroderma, with negative results. Some 3 years later his case was worked up in California and skin biopsies were obtained; again no evidence of other disease was found.

Only one other patient (P.J.), a 14-year-old girl, had had ischemic ulcers. She had minimal cutaneous scarring but no bone changes.

Although hypesthesia was commonly associated with the pallid and cyanotic phases, and paresthesias with the subsequent rubor, severe pain was not described by any of the patients.

Family history for Raynaud's disease was positive in one half of the subjects, and in two of the families, there were multiple occurrences.

Emotional factors played a significant role in only one girl (S.L.), a 13-year-old. Her first episode of Raynaud's phenomenon occurred the same week she learned that her father had incurable carcinoma, and most of her subsequent attacks correlated with various crises in her school work and family relationships.

Although toes are reportedly less frequently involved than fingers, \(1^{2}\) they were involved in all of our patients and more severely involved than the fingers in half of them. Indeed, in one patient, the fingers were completely free of symptoms. Two of these patients with more severe involvement of the toes had no palpable dorsalis pedis pulses, although they had excellent posterior tibial pulses. (Approximately 3\% of normal subjects have no dorsalis pedis anatomically, and 12\% of normal subjects have no palpable pulse in that artery.)\(1^{4}\)

Experimental Results

In four of the six patients, there were no Raynaud's phenomena at the start of our observations, and in three of them, the finger temperatures were quite normal, above 28 C.\(1^{1}\) The toes were invariably 1 to 3 C cooler, a normal finding. Two patients upon arriving for the study demonstrated pale or blue fingers which persisted after an hour of supine rest at comfortable room temperatures (23 C). For these two patients, the room temperature was increased to 27 C, and they were allowed to warm their hands; in this manner, all subjects were free of vasospastic phenomenon at the beginning of the studies of local and general cold stress and emotional stress.
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Figure 2
The hands of J.S., a 5-year-old boy. The changes, although bilateral, are not symmetrical. The index and middle fingers are most severely affected, with greater bone destruction on the left. The severity of these changes are unique to this child, although the disease appears to be primary Raynaud's disease after thorough evaluation over several years.

Figure 3
Plot of skin temperatures in S.S., an 11-year-old boy. There was mild pallor when the patient was initially examined, necessitating a higher room temperature 27 C (80 F). The patient was exposed to cold room temperatures twice, and after the second exposure, received 10 mg of tolazoline intravenously. At the bottom of the chart are six representative plethysmographic recordings from an affected finger. The timing of these recordings is indicated by the large numbers close to the finger temperature plot. The pulse dimension is expressed as a percentage of the finger diameter. Note the relatively slight changes in skin temperature and pulse magnitude when a Turkish towel soaked in ice water was applied to the other hand, or even the hand being studied, as compared to the exposure of the entire patient to roughly the same temperature in a cold room.

When the subjects were challenged with an unexpected emotional stimulus, there was invariably a transient diminution in pulse amplitude and the volume of the digit, of brief duration, unaccompanied by significant changes in skin temperature, a normal reaction. In only patient S.L. was there a marked and sustained reaction to emotional stimulation which produced definite Raynaud's phenomenon.

Local cold applications were surprisingly ineffective in producing vasospastic reactions. Although towels soaked in ice water produced a transient decrease in the skin temperature of the contralateral digits and a more sustained decrease with ipsilateral application, the changes were of much smaller magnitude than when the room temperature was low (fig. 3).
In every one of the six subjects, room temperatures below 10 C invoked white digits, succeeded by blueness. In all six subjects, at least one or more digits still demonstrated an abnormally small pulse on plethysmography and subnormal temperature after return to comfortable room temperatures. Injection of a small volume of normal saline intravenously produced no change in the vasospasm, but small amounts (10 mg or less) of tolazoline (Priscoline) produced a prompt improvement in skin temperature and digital pulses, even when amounts were used that produced no generalized vasodilatation. Of particular interest were the effects of tolazoline on the abnormal digit in contrast to the effects on a normal digit in the same individual. For example, in patient S.C., who had minimal involvement of her fingers and marked vasospastic involvement of her toes, 10 mg of tolazoline produced a 300% increase in pulse amplitude in the toes, only 50% increase in the fingers, and no change in blood pressure as determined by auscultation. These results were achieved with a dosage only one tenth of the dosage recommended for adrenergic blockade.

Tolazoline was given too rapidly intravenously to S.L., and the patient experienced generalized vasodilatation. She became very upset and cried; the digits involved in the Raynaud phenomenon showed a brief increase in pulse amplitude and then showed the most intense vasoconstriction that we had observed, which persisted for almost an hour. This patient was the only one in the series with a convincing history of precipitation of vasospasm by emotional stimuli.

Discussion
Although only one of the patients showed a close relationship between emotional stimuli and Raynaud’s phenomenon, the more potent effect of generalized cold versus local application of cold in the other subjects suggests that the mechanism operating in Raynaud’s disease is a combination of unique local hypersensitivity of the arterioles superimposed on a cardiovascular system with normal—and in some cases increased—reactivity. The occurrence of the vasospastic disorder in one digit of a limb and not in the next digit obviously militates against the hypothesis that Raynaud’s disease is due simply to alterations in viscosity, although blood will, of course, be more viscous at lower temperatures. If a primary disease state produces increased viscosity of the blood, and the patient has a tendency toward vasospasm, Raynaud’s phenomenon will likely occur. Similarly, anatomic variations which might be unimportant in a normal individual may contribute significantly to the severity of a vasospastic diathesis, a distinct possibility in two of our patients with absence of dorsalis pedis pulses.

The efficacy of tolazoline selectively to increase flow in the spastic arteries makes it an ideal agent for use in the milder cases. The boy with structural changes moved to a warmer, dry climate and enjoyed considerable improvement except for one unusually cold winter which produced a recurrence. Reserpine was prescribed in addition to tolazoline for S.L., whose attacks were precipitated by emotional stimuli; she did well thereafter, but it is not possible to state whether the addition of reserpine was beneficial.

All of the children have been followed for over 2 years, and none has developed evidence of systemic disease such as scleroderma. It is still possible that underlying disease may eventually appear, but all six children continue to fulfill the criteria for primary Raynaud’s disease.

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