The Effect of Local Application of Glyceryl Trinitrate (Nitroglycerine) on Raynaud’s Disease and Raynaud’s Phenomenon

Studies on Blood Flow and Clinical Manifestations

By Martin S. Kleckner, Jr., M.D., Edgar V. Allen, M.D., and Khalil G. Wakim, M.D.

The authors investigated the effect of repeated inunction with 2 per cent glyceryl trinitrate in lanolin on the blood flow and skin temperature of the extremities in 14 cases of Raynaud’s disease and in 8 cases in which Raynaud’s phenomenon was associated with such vascular diseases as atherosclerosis (3 cases), chronic occlusive disease of the arteries (3 cases), occupational disease of the arteries (1 case) and livedo reticularis (1 case). The inunction almost invariably caused an increase in the blood flow and in the skin temperature of the digits in the 14 cases of Raynaud’s disease.

Episodes of various combinations of pallor, cyanosis and rubor of the skin of the extremities resulting chiefly from exposure to cold constitute the syndrome recognized as Raynaud’s phenomenon and Raynaud’s disease. When these episodes of discoloration are secondary to organic disease, the correct designation is “Raynaud’s phenomenon”; in the absence of an organic disease to which such episodes are secondary, the designation should be “Raynaud’s disease.” The disease most commonly associated with Raynaud’s phenomenon, in our experience, has been atherosclerosis (scleroderma of the acral parts). However, this phenomenon may be associated with occlusive arterial disease, with cervical rib, with organic neurologic diseases and, infrequently, with a number of other pathologic conditions. Clinical investigators differ on the explanation of Raynaud’s disease. Some believe that it is the result of an abnormality of sympathetic innervation, while others believe that it is due to a fault in the digital arteries. Medical management has included residence in a warm environment, the use of a variety of drugs to relieve arteriolar spasm, abstinence from smoking, and treating associated conditions such as the menopause, anemia and anxiety neurosis. Our experience in the treatment of Raynaud’s disease with a variety of drugs has been unsatisfactory. Even residence in a warm climate may be ineffective because color changes may occur when the environmental temperature is relatively high. Some of the newer adrenergic and ganglion-blocking drugs have been reported to be useful in the treatment of Raynaud’s disease and Raynaud’s phenomenon, but the action of these drugs is uncertain and, in our experience, they are of little or no practical value.

So far, sympathectomy is the most satisfactory method of treatment of Raynaud’s disease. This operation cures Raynaud’s disease of the lower extremities, but interruption of the sympathetic nerve supply of the upper extremities produces results which range from good to unsatisfactory.

In general, what we have written about the treatment of Raynaud’s disease is applicable to Raynaud’s phenomenon except that the results of treatment, particularly when this phenomenon is associated with atherosclerosis, are even less satisfactory.

Recently, Lund has reported 30 cases of arteriosclerosis obliterans in which improvement occurred after about 0.5 to 1 Gm. of 1
per cent glyceryl trinitrate ointment had been rubbed repeatedly on the affected parts. Increased warmth, diminution of pain, improvement in consistency of the tissues, shedding of gangrenous tissue and improvement of ulcers of the affected extremity were noted. In addition, this treatment produced varying signs of improvement in 13 cases of intermittent claudication, in 3 cases of chilblains and in 17 cases of Raynaud’s disease. Lund said that this treatment deserves further consideration since sympathectomy fails to cure Raynaud’s disease of the fingers in a high percentage of cases. Fox and Leslie recently reported a case of Raynaud’s disease and a case of acrosclerosis in which the patients were successfully treated with topical application of 2 per cent glyceryl trinitrate in lanolin 3 times a day for long periods. There was not only persistent improvement in the subjective symptoms, but studies of the temperature of the skin and oscilometry demonstrated increased blood flow to the treated digits.

Our interest in the topical application of glyceryl trinitrate was stimulated by Dr. A. W. Adson, who suggested this treatment to Fox. We investigated the effect of repeated inunction with 2 per cent glyceryl trinitrate in lanolin on the blood flow and skin temperature of the extremities in 14 cases of Raynaud’s disease and in 8 cases in which Raynaud’s phenomenon was associated with such vascular diseases as acrosclerosis (3 cases), occlusive disease of the arteries (3 cases), occupational disease of the arteries (1 case), and livedo reticularis (1 case).

Since glyceryl trinitrate ointment is expensive and cannot be prepared by most druggists and chemists, we also studied in a limited manner the effects of inunction with ointments prepared with Priscoline (2-benzylimidazoline hydrochloride), Etamon chloride (tetraethylammonium chloride), Mecholyl chloride, histamine diphosphate, and nicotinic acid. These drugs are known or presumed to improve the blood flow in peripheral vessels. Priscoline is an adrenolytic drug. When it is administered in sufficient doses, it blocks the sympathetic vasoconstrictor motor pathways, possibly at their termination in smooth muscle. It has been reported that the oral or parenteral administration of this drug improves the blood flow in the peripheral vessels. The results which other authors have obtained with this drug in cases of Raynaud’s disease, chronic occlusive disease of the arteries and causalgia have been encouraging.

Etamon chloride acts on the ganglia of the autonomic nervous system. When it is administered intravenously or intramuscularly, it causes an increase in the blood flow in the peripheral vessels. Mecholyl chloride causes dilatation of the peripheral arterioles when it is administered subcutaneously, intramuscularly, or by iontophoresis. It has been only partially effective in the treatment of Raynaud’s disease, chronic occlusive disease of the arteries, and varicose ulcers. Histamine diphosphate dilates the capillaries, apparently independently of capillary innervation, and improves the blood flow. The administration of therapeutic doses of nicotinic acid to human beings causes general transient vasodilatation, probably by direct action on the blood vessels. It also causes a substantial increase in the skin temperature and in the blood flow in the peripheral vessels. The most prominent effect of the nitrites is antispasmodic. This effect results in dilatation of the small blood vessels, particularly the capillaries and venules. When glyceryl trinitrate is administered sublingually in the form of tablets, it causes vasodilatation which lasts for about 30 minutes.

After we had completed the pharmacologic phase of our study, we decided to investigate the therapeutic effect of repeated inunction with the glyceryl trinitrate ointment on the episodes of discoloration of the skin which are characteristic of Raynaud’s disease and Raynaud’s phenomenon. Accordingly the drug was administered in this manner in 15 cases of Raynaud’s disease and in 10 cases in which Raynaud’s phenomenon was associated with such vascular diseases as acrosclerosis (7 cases), occupational occlusive disease of the arteries (2 cases), and thromboangitis obliterans (1 case).
METHOD OF STUDY

In order to determine the effects of glyceryl trinitrate ointment on blood flow in the extremities, a plethysmograph with a compensating spirometer recorder was employed. The temperature of the fingers and toes was recorded galvanometrically. The patients omitted the meal prior to coming to the laboratory, where they lay quietly on a bed in a constant temperature room for at least half an hour after the plethysmographs were applied. For the determination of blood flow to the extremities, plethysmographs were applied to the legs and to the forearms. In selected cases in which it was desirable to determine blood flow in the hands only, special hand plethysmographs were used. After the period of adaptation to the environment, the control values for the blood flow and skin temperature were established. The plethysmographs were then opened and the thermocouples were removed. The fingers and toes of one side were rubbed with the glyceryl trinitrate ointment for about three minutes and the corresponding parts of the opposite extremities were rubbed simultaneously with the lanolin base only, for the same period. The ointment remained on the toes and fingers for 20 minutes, and it was then removed. Determinations of the blood flow were again made, 30, 45 and 60 minutes after the ointment was applied.

RESULTS OF STUDY OF BLOOD FLOW AND SKIN TEMPERATURE

Table 1 shows the effect of inunction of the fingers and toes with 2 per cent glyceryl trinitrate in lanolin on the blood flow in the forearm and leg in 3 cases of Raynaud’s disease and in 6 cases in which Raynaud’s phenomenon was associated with such vascular disturbances as acrosclerosis (2 cases), thromboangiitis obliterans (1 case), arteriosclerosis obliterans (1 case), livedo reticularis (1 case), and occupational occlusive disease of the arteries (1 case). As a control measure, the fingers and toes of the opposite extremities were anointed simultaneously with lanolin alone.

Table 2.—Effect of Inunction of Fingers and Toes with 2 Per Cent Glyceryl Trinitrate in Lanolin on Blood Flow in Whole Forearm and Leg in Cases of Disturbances of Peripheral Circulation

<table>
<thead>
<tr>
<th>Case</th>
<th>Diagnosis</th>
<th>Extremity</th>
<th>Blood flow, cc. per 100 cc. of tissue</th>
<th>Digits treated with 2% glyceryl trinitrate in lanolin</th>
<th>Digits treated with lanolin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Before treatment</td>
<td>After treatment*</td>
</tr>
<tr>
<td>1</td>
<td>Raynaud's disease</td>
<td>Upper</td>
<td>3.1</td>
<td>4.0</td>
<td>+29</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lower</td>
<td>3.2</td>
<td>2.8</td>
<td>-12</td>
</tr>
<tr>
<td>2</td>
<td>Raynaud's disease</td>
<td>Upper</td>
<td>6.1</td>
<td>9.1</td>
<td>+49</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lower</td>
<td>2.5</td>
<td>3.5</td>
<td>+40</td>
</tr>
<tr>
<td>3</td>
<td>Raynaud's disease</td>
<td>Upper</td>
<td>2.3</td>
<td>3.6</td>
<td>+57</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lower</td>
<td>1.9</td>
<td>1.9</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Acrosclerosis with Raynaud's disease</td>
<td>Upper</td>
<td>5.1</td>
<td>5.8</td>
<td>+14</td>
</tr>
<tr>
<td>5</td>
<td>Acrosclerosis with Raynaud's disease</td>
<td>Lower</td>
<td>3.5</td>
<td>5.2</td>
<td>+49</td>
</tr>
<tr>
<td>6</td>
<td>Thromboangiitis obliterans with Raynaud's phenomenon</td>
<td>Upper</td>
<td>8.9</td>
<td>11.6</td>
<td>+30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lower</td>
<td>3.5</td>
<td>5.6</td>
<td>+60</td>
</tr>
<tr>
<td>7</td>
<td>Arteriosclerosis obliterans with Raynaud's phenomenon</td>
<td>Upper</td>
<td>3.3</td>
<td>3.6</td>
<td>+9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lower</td>
<td>2.8</td>
<td>3.3</td>
<td>+18</td>
</tr>
<tr>
<td>8</td>
<td>Livedo reticularis with Raynaud's phenomenon</td>
<td>Upper</td>
<td>4.6</td>
<td>4.9</td>
<td>+7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lower</td>
<td>2.4</td>
<td>2.3</td>
<td>-4</td>
</tr>
<tr>
<td>9</td>
<td>Occupational occlusive arterial disease with lower Raynaud's phenomenon</td>
<td>Upper</td>
<td>8.5</td>
<td>17.8</td>
<td>+109</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lower</td>
<td>2.3</td>
<td>5.2</td>
<td>+126</td>
</tr>
</tbody>
</table>

* Maximum of 3 determinations.
arm in all of the 3 cases of Raynaud's disease (cases 1, 2 and 3). After inunction of the toes with this ointment, there was an increase in the blood flow in the ipsilateral leg in only one of these cases, namely, case 2. Inunction of the fingers and toes with lanolin alone was followed by an increase in the blood flow in the ipsilateral forearm and leg in all of these 3 cases. In the 6 cases in which Raynaud's phenomenon was associated with such vascular dis-

flow in the forearm and leg was observed after inunction with the glyceryl trinitrate ointment and after inunction with lanolin alone. In this case, the pulse in the toes which were anointed with lanolin could not be obtained before the lanolin was applied, and marked ischemia of one toe was apparent. In all of the 9 cases in table 1, the respective increases which occurred in the blood flow in the forearm and leg after inunction with glyceryl trinitrate ointment and

Table 2.—Effect of Inunction with 2 Per Cent Glyceryl Trinitrate in Lanolin on Skin Temperature of Fingers and Toes in Cases of Disturbances of Peripheral Circulation

<table>
<thead>
<tr>
<th>Case</th>
<th>Diagnosis</th>
<th>Digit</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>Difference</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Raynaud's disease</td>
<td>Finger</td>
<td>27.0</td>
<td>29.3</td>
<td>+2.3</td>
<td>28.6</td>
<td>27.3</td>
<td>+0.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Toe</td>
<td>26.4</td>
<td>27.2</td>
<td>+0.8</td>
<td>28.3</td>
<td>26.2</td>
<td>-0.1</td>
</tr>
<tr>
<td>2</td>
<td>Raynaud's disease</td>
<td>Finger</td>
<td>31.2</td>
<td>34.1</td>
<td>+2.9</td>
<td>29.5</td>
<td>34.2</td>
<td>+4.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Toe</td>
<td>24.1</td>
<td>28.2</td>
<td>+4.1</td>
<td>25.1</td>
<td>27.4</td>
<td>+2.3</td>
</tr>
<tr>
<td>3</td>
<td>Raynaud's disease</td>
<td>Finger</td>
<td>29.7</td>
<td>34.7</td>
<td>+5.0</td>
<td>34.7</td>
<td>35.7</td>
<td>+1.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Toe</td>
<td>25.1</td>
<td>26.3</td>
<td>+1.2</td>
<td>26.0</td>
<td>26.5</td>
<td>+0.5</td>
</tr>
<tr>
<td>4</td>
<td>Arteriosclerosis with Raynaud's phenomenon</td>
<td>Finger</td>
<td>28.0</td>
<td>21.0</td>
<td>-7.0</td>
<td>30.4</td>
<td>33.1</td>
<td>+2.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Toe</td>
<td>25.6</td>
<td>29.2</td>
<td>+3.6</td>
<td>23.1</td>
<td>26.9</td>
<td>+3.8</td>
</tr>
<tr>
<td>5</td>
<td>Arteriosclerosis with Raynaud's phenomenon</td>
<td>Finger</td>
<td>32.4</td>
<td>33.1</td>
<td>+0.7</td>
<td>30.5</td>
<td>32.1</td>
<td>+1.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Toe</td>
<td>27.4</td>
<td>30.4</td>
<td>+3.0</td>
<td>27.1</td>
<td>29.1</td>
<td>+2.0</td>
</tr>
<tr>
<td>6</td>
<td>Thromboangiitis obliterans with Raynaud's disease</td>
<td>Finger</td>
<td>33.5</td>
<td>35.1</td>
<td>+1.6</td>
<td>34.0</td>
<td>35.1</td>
<td>+0.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Toe</td>
<td>27.1</td>
<td>28.2</td>
<td>+1.1</td>
<td>26.9</td>
<td>28.1</td>
<td>+1.2</td>
</tr>
<tr>
<td>7</td>
<td>Arteriosclerosis obliterans with Raynaud's phenomenon</td>
<td>Finger</td>
<td>34.7</td>
<td>34.8</td>
<td>+0.1</td>
<td>34.0</td>
<td>34.7</td>
<td>+0.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Toe</td>
<td>30.2</td>
<td>30.6</td>
<td>+0.4</td>
<td>27.0</td>
<td>27.1</td>
<td>+0.1</td>
</tr>
<tr>
<td>8</td>
<td>Livedo reticularis with Raynaud's phenomenon</td>
<td>Finger</td>
<td>32.2</td>
<td>31.0</td>
<td>-1.0</td>
<td>33.4</td>
<td>30.2</td>
<td>-3.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Toe</td>
<td>29.6</td>
<td>29.9</td>
<td>+0.3</td>
<td>30.2</td>
<td>28.6</td>
<td>-1.6</td>
</tr>
<tr>
<td>9</td>
<td>Occupational occlusive arterial disease with Raynaud's phenomenon</td>
<td>Finger</td>
<td>35.4</td>
<td>36.7</td>
<td>+1.3</td>
<td>35.8</td>
<td>36.5</td>
<td>+0.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Toe</td>
<td>29.4</td>
<td>36.3</td>
<td>+6.9</td>
<td>29.9</td>
<td>35.2</td>
<td>+5.3</td>
</tr>
</tbody>
</table>

* Maximum of 3 determinations.
† The digits anointed with glyceryl trinitrate in lanolin had poor circulation owing to arterial occlusion while the digits anointed only with lanolin had normal circulation.

Turbances as artherosclerosis, thromboangiitis obliterans, arteriosclerosis obliterans, livedo reticularis, and occupational disease of the arteries (cases 4 to 9 inclusive), the effects of the inunction on the blood flow were very similar to those observed in the 3 cases of Raynaud's disease (cases 1, 2 and 3). In the case in which Raynaud's phenomenon was associated with thromboangiitis obliterans (case 6) and in the case in which this phenomenon was associated with arteriosclerosis obliterans (case 7), an increase in the blood with lanolin may be attributed to systemic absorption of the glyceryl trinitrate.

Table 2 shows the effect of inunction with 2 per cent glyceryl trinitrate in lanolin and with lanolin alone on the skin temperature of the fingers and toes in the same group of cases (cases 1 to 9 inclusive) listed in table 1. The effects on the skin temperature were variable. In all but one of the cases (case 8) there was an increase in the skin temperature of the fingers and toes that were anointed with 2 per cent glyceryl trinitrate in lanolin. The increase, how-
ever, was small and insignificant in most instances. Similarly, there was an increase in the skin temperature in all but 3 instances in 2 cases (cases 1 and 8) after inunction of the fingers and toes with lanolin alone. In all but 2 of the cases (cases 2 and 5) the increase in the skin temperature was greater in the digits treated with the glyceryl trinitrate ointment than it was in the digits treated with lanolin alone.

Because of the probability that the use of a plethysmograph enclosing the entire forearm

<table>
<thead>
<tr>
<th>Case</th>
<th>Diagnosis</th>
<th>Blood flow, cc. per 100 cc. of tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Acrosclerosis with Raynaud's phenomenon</td>
<td>Fingers treated with 2% glyceryl trinitrate in lanolin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Before treatment</td>
</tr>
<tr>
<td>11</td>
<td>Chronic occlusive arterial disease with Raynaud's phenomenon</td>
<td>8.2</td>
</tr>
<tr>
<td>12</td>
<td>Raynaud's disease</td>
<td>1.2</td>
</tr>
<tr>
<td>13</td>
<td>Raynaud's disease</td>
<td>4.0</td>
</tr>
<tr>
<td>14</td>
<td>Raynaud's disease</td>
<td>6.9</td>
</tr>
<tr>
<td>15</td>
<td>Raynaud's disease</td>
<td>5.0</td>
</tr>
<tr>
<td>16</td>
<td>Raynaud's disease</td>
<td>7.4</td>
</tr>
<tr>
<td>17</td>
<td>Raynaud's disease</td>
<td>6.5</td>
</tr>
<tr>
<td>18</td>
<td>Raynaud's disease</td>
<td>3.3</td>
</tr>
<tr>
<td>19</td>
<td>Raynaud's disease</td>
<td>3.4</td>
</tr>
<tr>
<td>20</td>
<td>Raynaud's disease</td>
<td>3.2</td>
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<tr>
<td>21</td>
<td>Raynaud's disease</td>
<td>4.2</td>
</tr>
<tr>
<td>22</td>
<td>Raynaud's disease</td>
<td>5.5</td>
</tr>
</tbody>
</table>

* Maximum of 3 determinations.

or leg might not indicate correctly the effects on the blood flow to the digits, we made additional studies by using a hand plethysmograph in 11 cases of Raynaud's disease and in 2 cases in which Raynaud's phenomenon was associated with such vascular disturbances as acrosclerosis (1 case) and chronic occlusive disease of the arteries (1 case). Table 3 shows the effects of inunction of the fingers with 2 per cent glyceryl trinitrate in lanolin and with lanolin alone on the blood flow in the hand. In the 11 cases of Raynaud's disease (cases 12 to 22 inclusive), inunction of the fingers with 2 per cent glyceryl trinitrate in lanolin was followed by an average increase of the arteries (case 11), the increase in the blood flow in the hand was greater after inunction with the glyceryl trinitrate ointment than it was after inunction with lanolin alone.

Table 4 shows the effect of inunction of the fingers with 2 per cent glyceryl trinitrate in lanolin and with lanolin alone on the skin temperature of the treated digits in the same cases listed in table 3. The results recorded in table 4 are similar to those recorded in table 3. Inunction of the fingers with the glyceryl trinitrate ointment and with lanolin alone was followed by an increase in the skin temperature of the treated digits in all but 2 of the 11 cases of Raynaud's disease (cases 12 and 17) while
inunction with lanolin alone was followed by an increase in the skin temperature in all but one of the 11 cases (case 12). The average increase in the skin temperature of the treated digits was 3.5 C. after inunction with the glyceryl trinitrate ointment and 2 C. after inunction with lanolin alone. Similar results were obtained in one case in which Raynaud's phenomenon was associated with acrosclerosis (case 10) and in another case in which this phenomenon was associated with chronic occlusive disease of the arteries (case 11).

**Table 4.** Effect of Inunction with 2 Per Cent Glyceryl Trinitrate in Lanolin on Skin Temperature of Fingers in Cases of Raynaud's Disease and Raynaud's Phenomenon

<table>
<thead>
<tr>
<th>Case</th>
<th>Diagnosis</th>
<th>Temperature, degrees C.</th>
<th>Fingers treated with 2% glyceryl trinitrate in lanolin</th>
<th>Fingers treated with lanolin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Before treatment</td>
<td>After treatment*</td>
</tr>
<tr>
<td>10</td>
<td>Acrosclerosis with Raynaud's phenomenon</td>
<td>25.6</td>
<td>29.9</td>
<td>+4.3</td>
</tr>
<tr>
<td>11</td>
<td>Chronic occlusive arterial disease with Raynaud's phenomenon</td>
<td>32.0</td>
<td>34.5</td>
<td>+2.5</td>
</tr>
<tr>
<td>12</td>
<td>Raynaud's disease</td>
<td>26.6</td>
<td>26.5</td>
<td>-0.1</td>
</tr>
<tr>
<td>13</td>
<td>Raynaud's disease</td>
<td>27.7</td>
<td>33.6</td>
<td>+5.9</td>
</tr>
<tr>
<td>14</td>
<td>Raynaud's disease</td>
<td>32.4</td>
<td>35.4</td>
<td>+3.0</td>
</tr>
<tr>
<td>15</td>
<td>Raynaud's disease</td>
<td>30.7</td>
<td>34.9</td>
<td>+4.2</td>
</tr>
<tr>
<td>16</td>
<td>Raynaud's disease</td>
<td>33.4</td>
<td>35.6</td>
<td>+2.2</td>
</tr>
<tr>
<td>17</td>
<td>Raynaud's disease</td>
<td>32.2</td>
<td>32.1</td>
<td>-0.1</td>
</tr>
<tr>
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<td>Raynaud's disease</td>
<td>31.0</td>
<td>33.1</td>
<td>+2.1</td>
</tr>
<tr>
<td>19</td>
<td>Raynaud's disease</td>
<td>31.4</td>
<td>35.3</td>
<td>+3.9</td>
</tr>
<tr>
<td>20</td>
<td>Raynaud's disease</td>
<td>31.2</td>
<td>33.6</td>
<td>+2.4</td>
</tr>
<tr>
<td>21</td>
<td>Raynaud's disease</td>
<td>27.4</td>
<td>34.3</td>
<td>+6.9</td>
</tr>
<tr>
<td>22</td>
<td>Raynaud's disease</td>
<td>27.8</td>
<td>34.4</td>
<td>+6.6</td>
</tr>
</tbody>
</table>

* Maximum of 3 determinations.

The results of our study leave little doubt that the local application of 2 per cent glyceryl trinitrate in lanolin improves the circulation. The improvement was indicated by an increase in the blood flow and in the skin temperature in most instances, although the amount of the increase was variable. The increase in blood flow to the extremities treated with lanolin only was less in most instances than was the increase in the extremities treated with nitroglycerine ointment.

It appeared important to determine whether the act of rubbing or the systemic absorption of glyceryl trinitrate or both caused the apparent increase in blood flow and in the skin temperature. It had been noted that the improvement in circulation in the extremities to which lanolin alone had been applied invariably appeared in the final stage of the observation. No very significant changes were noted in the blood flow or in the skin temperature in cases in which one hand was rubbed with lanolin ointment alone while the other hand remained untreated. Therefore, it seemed to us that, on the basis of this evidence, whatever increase occurred in the circulation of the extremities treated with lanolin alone when the opposite part was rubbed with glyceryl trinitrate ointment could not be adequately explained on the basis of rubbing alone but was also attributable to the systemic absorption of glyceryl trinitrate. This was further substantiated by the fact that nitrite headache commonly occurred after inunction with the glyceryl trinitrate ointment.

A careful study of our records indicates that the following conclusions are valid. The local application of glyceryl trinitrate in lanolin to the digits of an extremity usually causes an improvement in the circulation of the extremity. There is usually improvement in the circulation of the companion extremity, which,
however, is ordinarily of smaller magnitude and is due to the absorption of glyceryl trinitrate into the general circulation.

**Action of Other Vasodilating Drugs**

In order to determine whether the local application of other vasodilating drugs would produce the same effects as those produced by similar application of glyceryl trinitrate in cases of Raynaud's disease, we applied ointments containing 10 per cent of Priscoline (2-benzyl-imidazoline hydrochloride), 5 per cent of nicotinic acid, 3.5 per cent of Mecholy chloride, 0.9 per cent of histamine diphasphate and 20 per cent of Etamon chloride (tetraethylammonium chloride), respectively, in a base of equal parts of petrolatum and lanolin. The method used in this part of our study was the same as that used in our investigation of glyceryl trinitrate. A hand plethysmograph was used to determine the effects of these drugs on the blood flow. Local application of these drugs failed to produce any significant alteration in the blood flow or in the skin temperature in cases of Raynaud’s disease.

**Clinical Observations**

Although the results of the pharmacologic part of our study seem to be of some importance, our main objective was to determine whether repeated local application of 2 per cent glyceryl trinitrate in lanolin would prevent the episodes of discoloration of the skin which are characteristic of Raynaud’s disease and Raynaud’s phenomenon. In order to obtain this information, the ointment was applied locally in 25 cases of Raynaud’s disease or Raynaud’s phenomenon. In all of these cases, the untreated hand was gloved while the ointment was being applied to the opposite hand. The pertinent data in 6 cases will be summarized briefly.

**Case 28.** A man, aged 24 years, had had Raynaud’s phenomenon of the second finger of the right hand for two weeks, apparently as a result of the use of a vibrating tool. Arteriography disclosed evidence of occlusive arterial disease. After glyceryl trinitrate ointment had been applied for three months, the affected finger appeared warmer and less numb than it had been previously. The color improved, but slight pallor occurred on cold days.

**Case 30.** A woman, aged 53 years, had noted sensitiveness of her hands and feet to cold since childhood. She had had episodes of discoloration of the fingers, characteristic of Raynaud’s disease, for 10 years. Sympathectomy had been performed four years previously but had not produced any benefit. Application of glyceryl trinitrate ointment four times daily for seven weeks did not have any effect on the episodes of discoloration.

**Case 32.** A woman, aged 38 years, had had advanced acrosclerosis of the hands, forearms, neck, face, and esophagus for six years. Examination disclosed bilateral trophic changes of the nails and Raynaud’s phenomenon of the fingers. She applied about 1 Gm. of glyceryl trinitrate ointment to the right hand four times daily while the contralateral hand was gloved. After seven days of inunction, no clinical improvement in her hands was noted.

**Case 42.** A man, aged 49 years, who did not smoke, had had episodes of pallor and rubor in the third and fourth fingers of his left hand upon exposure to cold or excitement for eight months. In addition, he had had three episodes of thrombophlebitis in his legs within the past four years, numerous instances of nocturnal cramps in his legs and often had had a dull ache associated with pallor in his fingers. Examination disclosed obliteration of pulsation in both ulnar arteries. The result of Allen’s test was positive. Pulsation was normal in the other peripheral arteries. Examination disclosed pallor, grade 2, of the right hand and pallor, grade 1, of the left hand upon elevation. The diagnosis was chronic occlusive arterial disease (probably thromboangiitis obliterans) associated with Raynaud’s phenomenon. The patient applied glyceryl trinitrate ointment to his left hand four times daily for several days but he was unable to notice any improvement.

**Case 48.** A housewife, aged 28 years, had had epi-
sodes of discoloration of both hands and all of the
toes for one year. The episodes had tended to occur
after exposure to cold but they also had occurred
without any apparent cause. In the course of the
episodes, the involved parts first had become white,
then red, and finally blue. The diagnosis was Ray-
naud’s disease. The patient also had hyperhidrosis,
and the history was suggestive of hyperventilation
and chronic nervous exhaustion. Pulsation was nor-
mal in the peripheral arteries, and there was no evi-
dence of atherosclerosis or any contributing vascular
disturbance. After the patient had applied glyceryl
trinitrate ointment to the right hand, the episodes of
discoloration disappeared in this hand.

Case 47. A retired salesman, aged 66 years, had
become fatigued easily, had become unusually dysp-
eic on exertion, and had had episodes of discolora-
tion of his fingers and feet for ten years. The epi-
sodes of discoloration had been characteristic of
Raynaud’s disease. The blood pressure was 180/106.
Examination disclosed benign hypertrophy of the
prostate gland and some narrowing and sclerosis of
the retinal arteries. The value for the blood urea was
52 mg. per 100 cc. The diagnosis was essential hyper-
tension, mild hypertensive heart disease and Ray-
naud’s disease. After the patient had applied glyceryl
trinitrate ointment to his hands and feet for three
days, his hands became warm for the first time in 10
years and failed to become discolored on exposure
to cold.

SUMMARY

We have investigated the effect of repeated inunction with 2 per cent glyceryl trinitrate in
lanolin on the blood flow and skin temperature of the extremities in 14 cases of Raynaud’s
disease and in 8 cases in which Raynaud’s phenomenon was associated with such vascular
diseases as atherosclerosis (3 cases), chronic occlusive disease of the arteries (3 cases), occu-
pational disease of the arteries (1 case) and livedo reticularis (1 case). The inunction almost
invariably caused an increase in the blood flow and in the skin temperature of the digits in the
14 cases of Raynaud’s disease. The increase which occurred in the circulation of the un-
treated extremity was attributed to the systemic absorption of glyceryl trinitrate. In the 8 cases in which Raynaud’s phenomenon was associated with such vascular diseases as atherosclerosis, chronic occlusive disease of the arteries, occupational disease of the arteries and livedo reticularis, the inunction produced an inconsistent increase in the blood flow and in the skin temperature of the extremity. Ap-
plications of lanolin alone and of 10 per cent
Priscoline (2-benzylimidazoline hydrochloride),
5 per cent nicotinic acid, 3.5 per cent Mecholyl
chloride, 0.9 per cent histamine diphasphate
and 20 per cent Etamon chloride (tetraethyl-
ammonium chloride), respectively, in a base of
equal parts of petrolatum and lanolin did not
produce any significant increase in the circula-
tion in the cases of Raynaud’s disease in which
they were used.

After we had completed the pharmacologic
phase of our study, we investigated the thera-
peutic effect of repeated inunction with the
glyceryl trinitrate ointment on the episodes of
discoloration which are characteristic of Ray-
naud’s disease and Raynaud’s phenomenon.
The ointment was applied in 15 cases of Ray-
naud’s disease and in 10 cases in which Ray-
naud’s phenomenon was associated with such
vascular diseases as atherosclerosis (7 cases), occu-
pational occlusive disease of the arteries (2
cases), and thromboangiitis obliterans (1 case).
In the 15 cases of Raynaud’s disease, the re-
ults were variable. Great improvement oc-
curred in 3 cases, moderate improvement oc-
curred in 5 cases, but little if any improvement
was observed in the 7 remaining cases. The
results also were variable in the 7 cases in
which Raynaud’s phenomenon was associated
with atherosclerosis. Moderate improvement
occurred in 1 case, but little if any improvement
was observed in the 6 remaining cases. In one
of the cases in which Raynaud’s phenomenon was associated with occupational occlusive dis-
ease of the arteries, great improvement oc-
curred; in the other case, only moderate im-
provement was observed. No improvement
occurred in the case in which Raynaud’s phe-
nomenon was associated with thromboangiitis
obliterans (table 5).

In the cases of Raynaud’s disease, as well
as in the cases of Raynaud’s phenomenon, the
improvement produced by glyceryl trinitrate
ointment was only temporary. This treatment,
therefore, is only palliative.

In practically all of the 25 cases, a transient
dull headache developed within from a half
hour to two hours after the ointment had been
applied. After the ointment had been applied
for several days, the headache usually disap-
peared. With the exception of the headache, we have not observed any untoward effect of application of the ointment.

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Manifestations of Raynaud's Disease and Raynaud's Phenomenon: Studies on Blood Flow and Clinical Manifestations

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