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 acrosclerosis (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 acrosclerosis (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 acrosclerosis, 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. In-
creased warmth, diminution of pain, improve-
ment in consistency of the tissues, shedding of 
gangrenous tissue and improvement of ulcers 
of the affected extremity were noted. In addi-
tion, this treatment produced varying signs of 
 improvement in 13 cases of intermittent claudia-
cion, in 3 cases of chilblains and in 17 cases 
of Raynaud's disease. Lund said that this treat-
ment deserves further consideration since sym-
pathectomy fails to cure Raynaud's disease of 
the fingers in a high percentage of cases. Fox 
and Leslie\textsuperscript{11} recently reported a case of Ray-
naud's disease and a case of acrocyanosis 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 improve-
ment in the subjective symptoms, but studies 
of the temperature of the skin and ophthalmometry 
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 tempera-
ture 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 acrocyanosis (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 expen-
sive and cannot be prepared by most druggists 
and chemists, we also studied in a limited man-
ner the effects of inunction with ointments 
prepared with Priscoline (2-benzylimidazoline 
hydrochloride), Etamon chloride (tetraethyl-
ammonium chloride), Mecholyl chloride, histamine 
diphosphat, 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 vaso-
constrictor motor pathways, possibly at their 
termination in smooth muscle. It has been 
reported that the oral or parenteral admini-
stration of this drug improves the blood flow 
in the peripheral vessels. The results which 
other authors\textsuperscript{12, 13} 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.\textsuperscript{14, 15} When it is ad-
inistered 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, intramuscu-
larly, or by iontophoresis. It has been only 
partially effective in the treatment of Ray-
naud's disease, chronic occlusive disease of the 
arteries, and varicose ulcers. Histamine diphos-
phat dilates the capillaries, apparently in-
dependently 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 periph-
eral vessels. The most prominent effect of 
the nitrites is antispasmodic. This effect results 
in dilatation of the small blood vessels, par-
­ticularly the capillaries and venules.\textsuperscript{16} When 
glyceryl trinitrate is administered sublingually 
in the form of tablets, it causes vasodilation 
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 Ray-
naud'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 acrocyanosis (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 hand.

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. After inunction of the fingers with the glyceryl trinitrate ointment, there was an increase in the blood flow in the ipsilateral fore-
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>Temperature, degrees C.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Digits treated with 3% glyceryl trinitrate in lanolin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Before treatment</td>
<td>After treatment</td>
<td>Difference</td>
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<tr>
<td>1</td>
<td>Raynaud’s disease</td>
<td>Finger</td>
<td>27.0</td>
</tr>
<tr>
<td>2</td>
<td>Raynaud’s disease</td>
<td>Toe</td>
<td>26.4</td>
</tr>
<tr>
<td>3</td>
<td>Raynaud’s disease</td>
<td>Finger</td>
<td>31.2</td>
</tr>
<tr>
<td>4</td>
<td>Acrosclerosis with Raynaud’s phenomenon</td>
<td>Finger</td>
<td>29.7</td>
</tr>
<tr>
<td>5</td>
<td>Acrosclerosis with Raynaud’s phenomenon</td>
<td>Toe</td>
<td>25.1</td>
</tr>
<tr>
<td>6</td>
<td>Thromboangiitis obliterans with Raynaud’s phenomenon</td>
<td>Finger</td>
<td>32.4</td>
</tr>
<tr>
<td>7</td>
<td>Arteriosclerosis obliterans with Raynaud’s phenomenon</td>
<td>Toe</td>
<td>27.4</td>
</tr>
<tr>
<td>8</td>
<td>Livedo reticularis with Raynaud’s phenomenon</td>
<td>Finger</td>
<td>33.5</td>
</tr>
<tr>
<td>9</td>
<td>Occupational occlusive arterial disease with Raynaud’s phenomenon</td>
<td>Toe</td>
<td>27.1</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.

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<tr>
<td></td>
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<td>Difference</td>
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<tr>
<td>1</td>
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<td>Finger</td>
<td>27.0</td>
</tr>
<tr>
<td>2</td>
<td>Raynaud’s disease</td>
<td>Toe</td>
<td>26.4</td>
</tr>
<tr>
<td>3</td>
<td>Raynaud’s disease</td>
<td>Finger</td>
<td>31.2</td>
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<td>Finger</td>
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<td>Livedo reticularis with Raynaud’s phenomenon</td>
<td>Finger</td>
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<td>9</td>
<td>Occupational occlusive arterial disease with Raynaud’s phenomenon</td>
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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

176 per cent in the blood flow in the treated hand while inunction with lanolin alone was followed by an increase of 90 per cent in the blood flow of the treated hand. In all but one of these 11 cases (case 22), 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.

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

<table>
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<th>Case</th>
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<th>Blood flow, cc. per 100 cc. of tissue</th>
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<td></td>
<td></td>
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<td>10</td>
<td>Acrosclerosis with Raynaud’s phenomenon</td>
<td>3.0</td>
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<tr>
<td>11</td>
<td>Chronic occlusive arterial disease with Raynaud’s phenomenon</td>
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</tr>
<tr>
<td>12</td>
<td>Raynaud’s disease</td>
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<td>20</td>
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<td>3.2</td>
</tr>
<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).

The improvement of circulation of the treated digits was usually noted after inunction with glyceryl trinitrate or 2% lanolin ointment. 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 nitrate 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,

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**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>Before treatment</td>
<td>After treatment</td>
<td>Difference</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>
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<tr>
<td>12</td>
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<tr>
<td>13</td>
<td>Raynaud’s disease</td>
<td>27.7</td>
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<td>+5.9</td>
</tr>
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</tr>
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<td>33.6</td>
<td>+2.4</td>
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<td>21</td>
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<td>34.3</td>
<td>+6.9</td>
</tr>
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<td>22</td>
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<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
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-benzylimidazoline hydrochloride), 5 per cent of nicotine acid, 3.5 per cent of Mecholy chloride, 0.9 per cent of histamine diphosphate and 20 per cent of Etamon (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 38.** 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 46.** 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 became white, then red, and finally blue. The diagnosis was Raynaud’s disease. The patient also had hyperhidrosis, and the history was suggestive of hyperventilation and chronic nervous exhaustion. Pulsation was normal in the peripheral arteries, and there was no evidence of acrosclerosis 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 dyspneic on exertion, and had had episodes of discoloration of his fingers and feet for ten years. The episodes 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 hypertension, mild hypertensive heart disease and Raynaud’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 acrosclerosis (3 cases), chronic occlusive disease of the arteries (3 cases), occlusive 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 untreated 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 acrosclerosis, 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-
peared. With the exception of the headache, we have not observed any untoward effect of application of the ointment.

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