Evaluation of the Severity of Organic Occlusive Disease and Comparison of the Effectiveness of Various Procedures in Relaxing Peripheral Vasospasm.

Severity Evaluated by Determining Cutaneous Blood Flow in the Extremities from Records of Cutaneous Temperature during Maximum Vasodilation, Effectiveness of Spinal Anesthesia, Intravenous Tetraethyl Ammonium Ion (Etamon), Intravenous Benzylimidazoline (Priscoline) and Application of Heat to the Torso

By Harold D. Green, M.D., William Perkins, M.D. and Joseph Abernethy, M.D.

Both organic occlusion and vasospasm are usually present in peripheral arterial vascular diseases. The degree of occlusion and the probable effectiveness of treatment designed to relax vasospasm can both be determined by measurement of the maximum increase in cutaneous blood flow produced by suitable vasodilator procedures. These studies included warming the torso and/or injections of tetraethylammonium chloride or benzylimidazoline, and administration of spinal anesthetic. The effects obtained with all three methods were closely comparable. Cutaneous blood flow was estimated from recordings of skin, room and body temperatures.

In evaluating the status of the peripheral circulation in man, it is necessary to determine what maximum circulation is possible after all vasospasm has been abolished. By comparing the maximal flow in normal patients with that in patients with peripheral vascular disease after relaxation of all vasospasm, it is possible to determine quantitatively the amount of organic occlusion present in such conditions as thromboangitis obliterans and arteriosclerosis.

In an earlier paper¹ it was demonstrated that tetraethyl ammonium, TEAC (Etamon*) and benzylimidazoline (Priscoline†) possess good potentialities for relaxing vasospasm. This paper is a further study and comparison of the effectiveness of larger doses of these drugs with that of application of heat to the torso (body warming), that of body warming plus the above drugs, and that of spinal anesthesia in a series of normal subjects and in patients with demonstrated occlusive peripheral vascular disease.

Methods

Records of the cutaneous temperature were made with an 8-point Leeds and Northrup micromax using iron constantin thermocouples attached to the skin with a drop of collodion as was described in the previous report.¹ During the study, the subjects were placed in a room, the temperature of which was maintained at 19–20°C. The air was constantly circulated by a blower fan. The velocity of air circulation was approximately 25–50 feet per minute and the relative humidity was 50 per cent. The walls were cork insulated and had a surface temperature within ±1 degree of the air temperature. The cutaneous areas to be measured were exposed to the room air and care was taken to avoid all contact or close approximation of the mattress or blankets or other objects which might prevent rapid circulation of air past the exposed parts.

When, under the above conditions, the cutaneous temperature is stable thermal equilibrium may be assumed to be present between the rate of delivery of heat to the skin by the blood and the rate of loss of heat from the skin.² During equilibrium the rate of loss of heat to the environmental air may be represented by the equation:

\[ C_a(T_s - T_a) = \text{calories per minute} \]  

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Where $C_a$ equals the heat conductance of the air, i.e., the rate at which heat will be taken up by the air and walls per degree of temperature difference between the air and that of the surface of the skin; and where $T_s$ equals the surface temperature of the skin, and $T_a$ equals the air temperature.

The rate of transfer of heat from the subcutaneous tissue to the outer surface of the skin may be computed as:

$$C_s(T_{ab} - T_s) = \text{calories per minute} \tag{2}$$

Where $C_s$ is the heat conductance of the skin and $T_{ab}$ is the subcutaneous temperature, assumed equal to the venous blood temperature, and $T_s$ is the surface temperature of the skin.

The rate of delivery of heat to the subcutaneous tissues by the blood may be calculated as:

$$C_b(T_{ab} - T_s) = \text{calories per minute} \tag{3}$$

Where $C_b$ is the heat conductance of the blood, i.e., rate of delivery of heat by the blood per degree difference between arterial and venous blood temperatures; $T_{ab}$ is the arterial blood temperature; and $T_s$ is the venous blood temperature.

Under conditions of equilibrium, the right hand component of each of these equations must be equal. Therefore, we may say that:

$$C_s(T_a - T_s) = C_a(T_{ab} - T_s) = C_b(T_{ab} - T_s) \tag{4}$$

Animal experiments demonstrate that the heat conductance of the skin itself is quite rapid, i.e., under a variety of conditions the subcutaneous and outer surface temperatures proved to be practically identical. We may, therefore, by assuming $T_{ab}$ to be approximately equal to $T_s$, simplify Equation (4) to:

$$C_a(T_a - T_s) = C_b(T_{ab} - T_s) \tag{5}$$

and by rearranging we get:

$$\frac{C_b}{C_a} = \frac{T_s - T_a}{T_{ab} - T_s} \tag{6}$$

The quantity $C_b$ is equal to the flow of blood per minute through the skin ($F_b$) in cc. per minute times the heat capacity of blood ($K_b$) which is approximately one small calorie per cc. per degree centigrade change of temperature. $C_a$ is a term which expresses the rate of heat loss by the skin, per degree difference of temperature between the skin and the air and walls. It may be considered to be composed of a constant ($R$) representing the net radiation loss plus a variable representing the conductive heat loss. The latter is equal to the flow of air ($F_a$) past the skin area in cc. per minute times the heat capacity of the air ($K_a$), also expressible in calories per degree per unit volume of air. Substituting these terms in Equation (6) gives:

$$\frac{F_a K_a}{F_a K_a + R} = \frac{T_s - T_a}{T_{ab} - T_s} \tag{7}$$

$K_a$, $K_b$ and $R$ are constants and, under the conditions of our experiments, $F_a$ may be taken to be constant so that Equation (7) may be reduced to

$$F_a \cdot K = \frac{T_s - T_a}{T_{ab} - T_s} = r \tag{8}$$

Where:

$$K = \frac{K_b}{F_a K_a + R}$$

$F_a \cdot K$ is the ratio of the difference between skin and air temperatures to the difference between arterial blood and skin temperatures. If we could evaluate $K$ we could compute the blood flow per unit area of skin. This is not at the moment practical. However, since $K$ may be expected to remain relatively constant in a given experimental set up, we can use the expression $F_a \cdot K$ as a measure of the relative blood flow from time to time in the same subject; and if experimental conditions remain constant, from subject to subject. This expression is called the thermal circulation index ($r$) by Burton and we shall use this expression in this paper for the relative blood flow. Burton has prepared a nomogram for the rapid calculation of this index from the data on air, skin and arterial blood temperatures.

The relationship between cutaneous temperature and blood flow, as represented by the thermal circulation index, may be illustrated by computing the index for a few skin temperatures. Using 37 $C.$ for arterial blood temperature and 20 $C.$ for room temperature, we would obtain the following:

<table>
<thead>
<tr>
<th>Cutaneous Temperature</th>
<th>Thermal Circulation Index</th>
<th>Increment in Index</th>
<th>Percent Increase in index</th>
</tr>
</thead>
<tbody>
<tr>
<td>degrees $C.$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>0.06</td>
<td>0.15</td>
<td>250</td>
</tr>
<tr>
<td>22</td>
<td>0.21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>0.89</td>
<td>0.23</td>
<td>26</td>
</tr>
<tr>
<td>29</td>
<td>1.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>7.5</td>
<td>9.5</td>
<td>125</td>
</tr>
<tr>
<td>36</td>
<td>16.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Thus we see that at low skin temperatures a 1 degree rise represents a relatively small increase in flow; at medium temperatures 1 degree rise means a considerable increase in flow and at high temperatures 1 degree rise indicates a very marked increase in flow. Burton obtained similar changes in his computations, but because he expressed his results percentally, the important phenomena of the absolute increase of flow was masked. (See above column of percent increase.)

The normal subjects for this series of experiments were 16 medical students. Ten of the students served
as subjects for body warming, for Priscoline and for body warming plus Priscoline, and 10 served as subjects for body warming, for TEAC, and for body warming plus TEAC. Four of the subjects served for both groups of drugs studied. Two of the 3 subjects for spinal anesthesia also served as subjects for TEAC and one served for Priscoline. One or more of the types of study reported in this paper has been carried out on 85 patients. Three of these patients who received all the types of tests for comparative purposes are reported in this paper.

During the tests on the normal subjects, temperatures were recorded from the forehead, left little finger, left thigh, left shin, dorsum of the left foot and dorsum of the large and small toes. Blood pressure, measured with the sphygmomanometer cuff, and pulse rate were recorded prior to the administration of TEAC, Priscoline, or spinal anesthesia, and every four to five minutes for thirty to sixty minutes afterwards. Oral temperatures were taken at the beginning of each test and any subject with fever was omitted.

In each study, on the normal subjects, a control period of one hour elapsed during which strong cutaneous vasoconstriction was induced by exposing the subject to the cool environment. Men were exposed only in shorts; women were clad in a slip. In order to obtain satisfactory vasoconstriction it was found necessary to have the subjects refrain from eating within two hours and not to exercise within one hour before the test. The degree of exposure was not sufficient to induce spontaneous shivering. When the subject had become sufficiently chilled so that strong vasoconstriction was present as indicated by the decline in the temperatures of the fingers and toes approximately to room temperature, one of five procedures was carried out:

1. TEAC was injected intravenously over a thirty-minute period in the amount of up to 20 mg./Kg. dissolved in 250 ml. of normal saline. Total amounts given varied from 900 to 1300 mg. in the normal subjects.

2. In 6 subjects, Priscoline was injected intravenously in amounts up to 2 mg./Kg. over a thirty-minute period dissolved in 250 ml. of normal saline. The total intravenous doses were 110 to 135 mg. In 4 subjects the Priscoline was given in four divided doses of 50 mg. each intramuscularly at ten-minute intervals. The Priscoline was preceded with one to two tablets of Trasentine with phenobarbital.

3. Body warming was induced by covering the torso and any portions of the extremities that were not being used for temperature studies with two woolen blankets and by applying electric heating pads to the back and front of the chest.

4. For the study of the effect of body warming plus TEAC or plus Priscoline, the period of heating was followed by an injection of the appropriate drug in the amount and at the rate indicated above for the drug alone while continuing the body warming.

5. Spinal anesthesia was induced by 75 to 100 mg. of procaine injected so as to produce complete anesthesia to T 11 or higher.

The registration of cutaneous temperatures, blood pressure, pulse, etc., were continued either until maximum skin temperature had been reached or until at least an hour had elapsed in those patients in whom no evidence of vasodilatation was noted. On any one study, only one drug was injected. The study was then discontinued and if a further study was made on this subject, it was carried out on a subsequent day after another control period of one hour of cooling to allow for maximal vasoconstriction.

**RESULTS**

**Effects of the Cool Environment.** The results of exposure to the cool environment in the various groups are summarized in columns (A) and (C) in table 1 and columns (A) and (D) in table 2, and in the first portions of all the figures. It should be noted that the lowest cutaneous temperatures reached and the most rapid rates of decline during the period of cooling were in the finger and the first and fifth toes; the next lowest were in the dorsum of the foot, the next in the shin, then in the thigh and finally in the forehead. The minimal thermal circulation indices for the first toe in the various experiments are summarized in table 4, column (A).

**The Effects of TEAC Alone.** The temperatures recorded in the first pair of columns of table 1; column (A) are those at the time TEAC was given and the readings found at the time of the maximum effect after TEAC was given are tabulated in the second pair of columns (B). Following the injection of TEAC, mild to moderate shivering was noted in all subjects. The time lag before the cutaneous temperatures began rising was less the faster the TEAC was given. The maximal thermal circulation indices corresponding to the large toe are summarized in table 4, column (B), where they may be compared with those of the subsequent experiments. The sequential changes in temperature in the finger and toes are illustrated in figure 1.

**Priscoline Alone.** The effects of Priscoline alone are summarized in column (D), table 1. No significant differences in the responses to 200 mg. of Priscoline given intramuscularly
and to 2 mg./Kg. of body weight given intravenously were noted and all results are pooled. Priscoline alone was significantly less efficient than alone, rather than with the trunk.

**Effects of Body Warming.** In 20 subjects, divided into two groups of 10 each, the torso was warmed, as described under "Methods."

### Table 1. Changes in Cutaneous Temperatures Produced by Intravenous TEAC and Priscoline in Normal Subjects

<table>
<thead>
<tr>
<th></th>
<th>TEAC—10 subjects</th>
<th>Priscoline—10 subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Temperature at time TEAC given</td>
<td>Temperature at maximum effect after TEAC given</td>
</tr>
<tr>
<td>Range</td>
<td>Average</td>
<td>Range</td>
</tr>
<tr>
<td>Forehead</td>
<td>31.5-34.5</td>
<td>33.3</td>
</tr>
<tr>
<td>Finger</td>
<td>21.0-25.5</td>
<td>22.3</td>
</tr>
<tr>
<td>Thigh</td>
<td>28.5-33.5</td>
<td>30.5</td>
</tr>
<tr>
<td>Shin</td>
<td>27.5-30.0</td>
<td>29.0</td>
</tr>
<tr>
<td>Foot</td>
<td>25.0-28.5</td>
<td>26.9</td>
</tr>
<tr>
<td>1st toe</td>
<td>21.0-25.0</td>
<td>22.0</td>
</tr>
<tr>
<td>5th toe</td>
<td>21.0-25.0</td>
<td>22.1</td>
</tr>
</tbody>
</table>

### Table 2. Effects of Warming Torso plus TEAC and Priscoline on Cutaneous Temperatures in Normal Subjects

<table>
<thead>
<tr>
<th></th>
<th>TEAC—10 subjects*</th>
<th>Priscoline—10 subjects*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Temperature at time heat applied to the torso</td>
<td>Maximum temperature after heat applied but before TEAC given</td>
</tr>
<tr>
<td>Range</td>
<td>Average</td>
<td>Range</td>
</tr>
<tr>
<td>Forehead</td>
<td>32.0-35.0</td>
<td>33.0</td>
</tr>
<tr>
<td>Finger</td>
<td>18.0-30.0</td>
<td>21.7</td>
</tr>
<tr>
<td>Thigh</td>
<td>28.0-33.5</td>
<td>29.8</td>
</tr>
<tr>
<td>Shin</td>
<td>27.0-29.5</td>
<td>28.3</td>
</tr>
<tr>
<td>Foot</td>
<td>25.0-27.5</td>
<td>25.8</td>
</tr>
<tr>
<td>1st toe</td>
<td>20.0-24.0</td>
<td>21.0</td>
</tr>
<tr>
<td>5th toe</td>
<td>18.5-23.0</td>
<td>20.8</td>
</tr>
</tbody>
</table>

* These are the same subjects as those used for table 1, columns (A), (B), (C) and (D).

### Table 3. Effect of Spinal Anesthesia on Three Normal Subjects

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Temperature at time spinal anesthetic was given</td>
<td>Maximum temperature after spinal anesthetic was given</td>
</tr>
<tr>
<td>Range</td>
<td>Average</td>
<td>Range</td>
</tr>
<tr>
<td>Forehead</td>
<td>32.0-33.0</td>
<td>32.7</td>
</tr>
<tr>
<td>Finger</td>
<td>20.0-21.2</td>
<td>20.5</td>
</tr>
<tr>
<td>Thigh</td>
<td>28.2-29.0</td>
<td>28.6</td>
</tr>
<tr>
<td>Shin</td>
<td>27.2-29.0</td>
<td>28.1</td>
</tr>
<tr>
<td>Dorsum of foot</td>
<td>22.6-26.4</td>
<td>24.3</td>
</tr>
<tr>
<td>1st toe</td>
<td>20.0-21.5</td>
<td>20.7</td>
</tr>
<tr>
<td>5th toe</td>
<td>20.0-21.5</td>
<td>20.7</td>
</tr>
</tbody>
</table>
TABLE 4.—Summary of Thermal Circulation Indices for the Large Toe for All Experiments on Normal Subjects

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Minimum indices before application of heat or drug</td>
<td>Maximum indices after application of heat or drug</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>Average</td>
</tr>
<tr>
<td>TEAC alone</td>
<td>0.012-0.40</td>
<td>0.102</td>
</tr>
<tr>
<td>Priscoline alone</td>
<td>0.031-0.14</td>
<td>0.066</td>
</tr>
<tr>
<td>Heat to torso</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Priscoline group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Application of drug while heat being applied to torso</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEAC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Priscoline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spinal anesthesia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1.—Sequential changes in temperature in the finger, first and fifth toes in response to intravenous injection of TEAC (Etamon) in 10 normal subjects. Abscissal scale: time in minutes; ordinate scale: cutaneous temperature in degrees centigrade. Zero time is beginning of period of cooling of body to induce vasoconstriction. Arrow indicates start of intravenous injection of TEAC. The total doses administered are indicated in the figure. Average room temperature during the tests on the various subjects ranged between 19.0 and 20.6 C. (average of averages 19.9 C.). The extremes reached for brief moments, due to opening the door to the constant temperature room were 17.2 and 21.5 C.

after maximal vasoconstriction had been obtained by the initial period of approximately one hour of cooling. The results are summarized in columns (B) and (E) in table 2. The rates of change of temperature in the finger and toes are illustrated in figures 3–6 and the maximal
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thermal circulation indices in table 4, column (B).

Effects of TEAC after Warming the Torso. In 10 subjects, after the maximal possible vasodilation had been obtained in response to warming the torso, TEAC was given in the same maximal temperatures were obtained in the toes but a significantly higher maximal temperature occurred in the fingers in response to body warming plus TEAC as compared with TEAC alone.

Effects of Priscoline after Warming the Torso.

![Graph](image)

**Fig. 2.**—Sequential changes in cutaneous temperature in the finger and toes in response to Priscoline alone. See figure 1 legend for further details. The average room temperatures ranged from 19.5 to 20.8°C (average of averages 20.2°C); extremes 18.5 and 21.0°C.

**Table 2, Column (F), table 4, column (B)**, and figures 5 and 6 illustrate the responses to intravenous Priscoline while warming the torso. The responses to warming the torso in this group of subjects was essentially the same as that for the subjects used for table 2, column (B). The response to Priscoline during body warming,

![Graph](image)

**Figs. 3 and 4.**—Sequential changes in temperature in the middle finger, and first toe in 10 normal subjects in response to warming the torso with blankets plus two 150 watt electric pads, followed by the intravenous injection of TEAC. Warming of the torso was begun at point indicated by the first arrow and continued throughout the remainder of the test. Injection of TEAC was begun at point indicated by the second arrow. The apparent break in the curves was necessitated by the fact that various intervals elapsed between the beginning of body warming and the starting of the injection of TEAC. For further explanation, see figure 1 legend. Average room temperature during these tests ranged from 19.0 to 20.6°C (average of averages 19.9°C); momentary extremes 17.2 and 21.5°C.
Fig. 5 and 6.—Sequential temperatures in the finger, and first toe in 10 normal subjects in response to warming of the torso followed by injection of Priscoline. For further explanation, see legend for figures 3 and 4. Average room temperature during these tests ranged from 19.5 to 20.0 C. (average of averages 19.9 C.), momentary changes 18.5 and 21.5 C.
however, was much more consistent and marked than it was with the subjects unwarmed.

Body warming plus Priscoline produced significantly higher temperatures in the finger, foot and toes than the use of Priscoline alone. The rate of rise of temperature was similar with body warming plus Priscoline, and body warming plus TEAC; the former produced a slightly higher thigh temperature, and the latter a slightly higher foot temperature. The thigh, shin and foot remained warmest during the period of development of vasoconstriction in response to cooling, but these portions did not warm to quite as high a temperature as the fingers and toes, after the application of heat to the torso and either TEAC or Priscoline.

Miscellaneous Observations in Regard to TEAC and Priscoline in Normal Subjects. It was noted that the subjects ceased perspiring after receiving TEAC. In all subjects both systolic and diastolic blood pressures tended to rise slightly. The maximum systolic rise was 14 mm. Hg and the maximum diastolic rise was 30 mm. No relationship between blood pressure rise and rapidity of or degree of rise in cutaneous temperatures was noted. In 5 subjects the increase in diastolic pressure was 12 mm. or less. The blood pressure changes with the use of TEAC alone or with body warming were comparable. Pulse rates increased in all subjects 28 to 54 beats per minute.

It was noted that Priscoline did not cause perspiration to cease as did TEAC, and did not seem to increase perspiration. Following the injection of Priscoline, systolic pressures remained the same or rose slightly, the maximum rise being 18 mm. Diastolic pressures tended to fall, the maximum fall being 18 mm. In general, the less the rise in systolic pressure the greater the fall in diastolic pressure, and vice versa. In either case the pulse pressure increased. The pulse rates increased in 9 subjects 8 to 68 beats per minute; no change occurred in one. These changes were essentially the same in the heated and unheated subjects.

The Effects of Spinal Anesthesia in Normal Subjects. The results of spinal anesthesia on the various skin temperatures are summarized in table 3 and the sequential changes in temperature in the first toe in one of the subjects are reproduced in figure 7. The maximal thermal circulation indices are indicated in table 4, column (B). One subject received 100 mg. of procaine and 2 subjects 75 mg. One of the latter showed a 3 to 4 degree smaller response in the toes than with Priscoline or TEAC. All 3 subjects showed a slight fall in forehead temperature. One showed an increase in temperature of the finger to 31.5 C. In this subject the level of anesthesia was to and including T 5. The other 2 subjects showed no change in temperature of the finger with an anesthesia level to and including T 11. If the subject who showed a significantly lesser response to spinal anesthesia than to TEAC or Priscoline were omitted, the average final temperature levels in the toes and foot would be: first toe, 33.5; fifth toe, 33.3; foot 30.8 C. These values agree closely with those obtained by using heat plus TEAC or Priscoline or TEAC alone.

Comparison of Effects of TEAC, Priscoline and Spinal Anesthesia in Patients with Impaired Circulation. In patients with normal circulation in whom these agents produced rise in skin temperature approximating the maximum, large differences in blood flow would be necessary to produce significant differences in the recorded skin temperature in response to these agents. As a consequence, it is difficult to state precisely which of the three methods tested might be superior or whether they might be essentially equal in their capacity to relax vasospasm and thus unmask the degree of organic vascular occlusion in situations where there is only a very slight degree of organic occlusive disease. On the other hand, if the maximum possible circulation is small, relative to the normal, then small changes in blood flow will produce considerable alterations in the skin temperature, as indicated by the computations given under methods. Furthermore, it is precisely under these conditions that one wishes to know the relative effectiveness of various methods of relaxing vasospasm. We have, therefore, made comparisons of the three methods in 3 patients in whom there was demonstrated peripheral vascular disease. Plots of the sequential temperatures in these patients in response to TEAC, Priscoline and
spinal anesthesia are reproduced in figures 8, 9, and 10. Table 5 gives the maximal thermal circulation indices seen in these patients.

Figure 8 shows the temperature curves recorded on a 39 year old truck driver (K. D.) with a clinical diagnosis of Buerger's disease. He had a three year history of intermittent claudication and recently complained of pains in both feet at rest. The physical examination was negative except for absent dorsalis and posterior tibial pulses, and dependent rubor bilaterally. The normal value plotted is that of a typical normal subject. The results of the

![Graph showing temperature changes](image)

**Table 5.** Thermal Circulation Indices Corresponding to the Maximal Temperatures Reached in the Patients Illustrated in Figures 8, 9 and 10

<table>
<thead>
<tr>
<th>Test</th>
<th>KD (fig. 8)</th>
<th>WDM (fig. 9)</th>
<th>W (fig. 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left foot</td>
<td>Right foot</td>
<td>Left foot</td>
</tr>
<tr>
<td>Etamon plus body warming</td>
<td>0.23 0.29 0.51 0.43</td>
<td>0.67 0.21 0.12 0.14</td>
<td>0.75 0.80 0.04 0.04</td>
</tr>
<tr>
<td>Priscoline plus body warming</td>
<td>0.33 0.37 0.68 0.40</td>
<td>1.27 0.67 0.15 0.25</td>
<td>0.62 0.62 0.03 0.03</td>
</tr>
<tr>
<td>Spinal Anesthesia</td>
<td>0.58 0.45 0.55 0.17</td>
<td>1.35 1.07 0.15 0.31</td>
<td>1.66 1.28 0.05 0.04</td>
</tr>
</tbody>
</table>

Figure 9 shows the curves recorded during three different methods compare favorably with each other; all three indicate the presence of occlusive vascular disease. Spinal anesthesia was obtained through T 11.

Figure 8 shows the temperature curves...
studies on a 59 year old sheriff (W. D. M.) with a clinical diagnosis of arteriosclerotic occlusive disease in both feet. He complained of intermittent claudication of three months duration and of pains at rest in the right foot for three weeks. Physical examination revealed absent dorsalis pedis and posterior tibial pulses bilaterally. The right toes showed no temper-

ature increase following any of the vasodilating procedures. The poorer response to TEAC plus heat in the left toes was believed to be a result of a drop in blood pressure from 170/85 to 100/60 during that procedure.

Figure 10 reproduces the temperature changes in response to the three methods of testing in J. A. W., a 58 year old man. For several years he had noted tiredness in his right foot and calf muscles when he walked two to three blocks. One month prior to the tests he had noted coldness, pallor and numbness of the entire right foot which lasted two hours. Examination revealed the distal half of the right foot to be cold and blue. The popliteal pulses were present bilaterally; the dorsalis pedis, and posterior tibial pulses were present, though weak in the left foot, but were absent in the right foot.

The thermal circulation indices for these 3 patients are summarized in table 5. The slightly higher temperatures and thermal circulation indices obtained in the left toes in these patients in response to spinal anesthesia, as compared with TEAC or Priscoline plus heat, is believed to be due principally to an artefact

FIGS. 8, 9 AND 10.—Superimposed temperature responses in 3 patients with demonstrated peripheral vascular disease in response to spinal anesthesia, to body warming plus TEAC and body warming plus Priscoline. See text for description of patients. Period of cooling to induce vasoconstriction, and period of warming torso omitted. Zero time-start of injection of drug. Heat plus Priscoline and heat plus TEAC indicate that these drugs were given after a period of one hour had elapsed during which the torso was warmed as indicated in the legend for figures 3 and 4. See text and legends for previous figures for further explanation.

Fig. 8 (Mr. K. D.)—1500 mg. TEAC; 150 mg. Priscoline; 75 mg. procaine, anesthesia through T 11; room temperature ranged from 20.0 to 22.0 C. (average 20.6 C.).
caused by the circumstance that for the spinal anesthesia the patients had to be placed in a different position in the room in which the air flow past the left foot was less than with the studies using TEAC or Priscoline.

**Discussion**

In view of the fact that approximately the same average maximal cutaneous temperature 34 C. (thermal index 4.7) was reached in the thermal equilibrium could be maintained with an average cutaneous temperature of 34 C., then under the conditions of our experiments the cutaneous blood flow would be

\[
\frac{40 \text{ Cal.}}{M^2 \cdot \text{hr.}} \times \frac{4}{(37^\circ - 34^\circ)} \times \frac{60 \text{ min.}}{\text{hr.}} \times \frac{1 \text{ Cal.}}{L \cdot ^\circ\text{C}} = 0.87 \text{ L/min./}M^2 = 8.7 \text{ ml./min./100 cm}^2
\]

Fingers, toes and forehead with body warming plus TEAC, or Priscoline, and for the toes with spinal anesthesia, it seems reasonable to assume that these values represent the average maximum possible rate of cutaneous circulation in normal subjects. Similarly, the average minimum temperature of 21 to 22 C. (thermal indices 0.06 to 0.21) may represent the normal maximal degree of vasoconstriction.

If we assume maximum metabolic activity of about four times basal, and assume that and if we assume the cardiac output to be elevated to four times basal this would mean that approximately 7 per cent of the cardiac output would be passing through the skin. Since, however, the distal portions show the higher temperature rise these areas may have higher rates of flow. As a first approximation we might, therefore, assume a thermal index of 4.7 (equal to a cutaneous temperature of 34 C.) to be equivalent to a blood flow of approximately 8.7 ml./min./100 cm².
Conversely, if we assume maintenance of thermal equilibrium at basal metabolism with an average cutaneous temperature of 21°C, the cutaneous blood flow would be

\[
\frac{40 \text{ Cal.}}{M^2 \cdot \text{hr.}} \times 24 \times \frac{60 \text{ min.}}{\text{hr.}} \times \frac{1 \text{ Cal.}}{L \cdot ^\circ \text{C}}
\]

\[= 0.086 \text{ L/min.}/M^2 = 0.36 \text{ ml./min.}/100 \text{ cm}^2\]
equivalent to a thermal index of 0.06, and equal ml./100 ml./min. in the feet. A rough approximation gives the cutaneous area of the foot as equal to 55 cm²/100 ml. This would suggest average minimum flows of 3.7 ml./100 cm²/min., and average maximum flows of 18 ml./100 cm²/min. Their smallest flow (0.5 ml./100 ml./min.) would be approximately equal to 0.9 ml./100 cm²/min., and their largest flow (16 ml./100 ml./min.) would be equal to 29 ml./100 cm²/min.

The observation that during body cooling to approximately 1.2 per cent of the cardiac output (taken as 3.0 L/min./M²). Since, however, the torso and more proximal portions maintain temperatures much above 21°C, the actual circulation at maximal vasoconstriction in the distal parts of the extremities probably drops considerably below this figure. In view of the uncertainties involved, it is not possible to attempt any further approximation to the actual blood flow without direct measurement. Hoobler and associates⁵ reported average maximum flows of 10.0 and minimum flows of 2.04 the temperatures in the fingers and toes were lower than those in the more proximal portions of the extremities is similar to those reported elsewhere in the literature. However, it is of considerable interest that all of the vasodilator procedures which produced maximal vasodilation, resulted in higher cutaneous temperatures (and thermal indices) in the fingers and toes, than in the more proximal portions. Evidently the maximal flow possible in the fingers and toes is greater than in the more proximal portions of the extremities and the torso. This
would fit with the presence of arteriovenous channels in these regions.

Burton\(^4\) found the maximum range for the thermal index in the toe to be 0.16 to 1.9, a 12-fold change and concluded that vasomotor reactions probably do not contribute much to the regulation of body temperature. Our findings, however, of changes of thermal circulation indices of the order of 0.06 to 4.7 (a 78-fold change) in response to body warming and cooling demonstrates to the contrary, that such vasomotor reactions must play a very prominent part in regulation of body temperature.

The magnitude of the change in heat loss per unit area of the skin is much less than the magnitude of the change in flow due to the fact that at low rates of flow much more heat is removed from each ml. of blood flowing through the skin, than is the case with higher rates of flow. The magnitude of the change of heat loss can be roughly computed by multiplying the thermal circulation index by the difference between body temperature (arterial blood temperature) and that of the skin (venous blood temperature). For an index of 0.06 (cutaneous temperature of 21 C.) the heat loss would be proportional to 0.96 (= 0.06 \times 16), while for an index of 4.7 (cutaneous temperature of 34 C.) the heat loss would be proportional to 14.1 (4.7 \times 3), or a 15-fold change in heat loss as compared with 78-fold change in cutaneous blood flow.

Some investigators, in discussing the use of vasodilator procedures, emphasize the change in temperature\(^5\) or the change in blood flow.\(^5\) However, the change that could possibly occur would be dependent on the state of initial vasoconstriction. This was frequently much less intense in previous studies than in our series. Of more importance is the maximum temperature (or thermal circulation index), i.e., the maximum blood flow reached, since this indicates the maximum flow capacity, and any reduction of this value is a measure of the degree of organic occlusion. For this reason we have omitted from our tables any reference to the change of temperature.

Our procedure of allowing one hour for cooling the body was used primarily to produce a state of strong vasoconstriction in order to see if our vasodilating procedures could overcome this degree of vasoconstriction. The results demonstrate that TEAC alone in doses approximating 20 mg./Kg. readily accomplishes this in the feet (but not the hand). Previous investigations, including our own, have been limited to 500 mg. total, and this dose has frequently failed to give maximal vasodilatation. In the hand, body warming was required with TEAC, and for both hand and foot, Priscoline required the application of body warming to produce maximal vasodilation. When so used in doses of approximately 20 mg./Kg. or 2 mg./Kg., respectively, both were satisfactory. This synergistic effect of body warming is in accord with our previous findings, and indicates the importance of keeping the patient warm and even of applying heat to the body when using these agents for their maximum therapeutic or diagnostic vasodilator effects.

The similarity of the responses to spinal anesthesia, TEAC, and Priscoline plus body warming is excellent evidence of the value of these three procedures. In addition the similarity of the results in patients with occlusive disease, we believe, demonstrates the ability of all three to prognosticate the severity of the occlusive disease and the probability of satisfactory therapy with the drugs or with surgical sympathectomy.

Our subjects expressed no preference for either TEAC or Priscoline. The degree of discomfort produced by either drug was about the same, although the symptoms were different. All subjects who took a spinal anesthesia also took either TEAC or Priscoline or both, and all preferred the drugs.

For reporting the results of our studies to the referring physician we have constructed a composite graph from the results obtained from the 20 normal subjects when body heat plus TEAC or Priscoline were used to abolish vasomotor tone in the toes (see figure 7). These curves represent the maximum and the minimum temperatures and the average temperatures reached by either the large or small toe in the 20 subjects tested. We consider that any response which produces a curve that lies outside the lower curve to have a probability of only 0.05 of being normal. Arbitrarily we have considered that: if the upper limit reached is 28-31 C., minimal occlusive disease is present;
The skin temperature method of evaluating peripheral vascular diseases has several inherent disadvantages and limitations: (1) Organic occlusive disease would have to be fairly extensive to be detectable by these methods since as indicated in the section on methods a considerable decline in thermal circulation index is present before cutaneous temperature declines extensively. Thus a limited reduction in blood flow may be attended by little drop in skin temperature responses. (2) A marked drop in diastolic blood pressure (30 mm. or more) could reduce blood flow sufficiently to influence skin temperatures. (3) The procedure becomes somewhat boring and tiresome to some people because of the length of time required (about three hours).

The advantages of this method are: (1) The procedure is extremely simple to perform. (2) The results are significant in that if organic disease causes a sufficient impairment in blood flow to produce symptoms or to be functionally important, it will be revealed. (3) When severe occlusive disease is present, even small increments in blood flow in response to vasodilator procedures are readily detected. (4) The probable therapeutic effectiveness of TEAC or Priscoline is revealed. (5) The dosages of the drugs used are usually well tolerated. (6) We can readily determine whether an individual's peripheral vascular disease is primarily organic or vasospastic. (7) The results are consistent, and readily reproducible.

SUMMARY

1. In order to determine the degree of organic occlusive disease that may be present, it is necessary to determine the maximum blood flow that can exist after all neurogenic or humoral vasoconstriction is abolished. This paper is a study of methods for abolishing such vasoconstriction.

2. Blood flow was estimated from continuous records of cutaneous temperature obtained with iron-constantin thermocouples, while the subjects were kept in a room maintained at a temperature of approximately 20 C.

3. The relative blood flow was computed from the thermal circulation index (r) therapeutic purposes because of the possibility of respiratory embarrassment due to chronic accumulative toxic effects.12
where \( T_a \) = cutaneous temperature; \( T_a \) = air temperature; \( T_{ab} \) = arterial blood temperature; \( K \) = a constant dependent upon various factors, but principally the rate of air circulation in the room; and \( F_b \) = the rate of blood flow in the skin. Under the conditions of our experiments, the average minimal indices of 0.05 to 0.1 and average maximum indices of 4.8 were obtained for the large toe.

4. All subjects were initially exposed, lightly clad, to a room temperature of approximately 20 C. to cause maximal vasoconstriction and the skin temperature changes caused by various vasodilating procedures were recorded while the subject remained in this environment.

5. Ten normal subjects received approximately 20 mg./Kg. of body weight of TEAC alone and again with body heat. Ten normal subjects received approximately 2 mg./Kg. of body weight of Priscoline alone and again with body heat. Three of the above normal subjects also received a spinal anesthesia.

6. The results obtained with the use of TEAC plus body heat and with Priscoline plus body heat and with TEAC alone were closely comparable with those obtained by spinal anesthesia in the feet. All toe temperatures approximated the forehead temperatures. It is thus believed that the use of body heat plus TEAC or Priscoline or TEAC alone will produce practically complete inhibition of vasomotor tone in the feet. In addition, body heat plus TEAC or Priscoline caused all finger temperatures to approximate forehead temperature and it is believed that these procedures also produced practically complete inhibition of vasomotor tone here also. The use of Priscoline alone was found unreliable.

7. The average thermal circulation index in the fingers and toes obtained during the period of maximal vasoconstriction in response to body cooling was 0.06, and that during maximal vasodilation in response to the above procedures was 4.7. It is estimated that these may be approximately equivalent to flows of the order of 0.36 and of 8.7 ml./100 cm.\(^2\)/min., respectively.

8. The diagnostic and prognostic uses of the above procedures are discussed.

9. Certain advantages and disadvantages of these procedures are listed.

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