The Effect of Nitroglycerin on the Systemic and Coronary Circulation in Man and Dogs

Myocardial Blood Flow Measured with Xenon\textsuperscript{133}

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Although nitrates have been used for the treatment of angina pectoris for almost a century,\textsuperscript{1,2} the mechanism of the action of glyceryl trinitrate U.S.P. (nitroglycerin) (TNG) remains in doubt. Coronary vasodilatation has been demonstrated arteriographically in patients following sublingual TNG,\textsuperscript{3,4} but no studies to date have shown an increase in myocardial blood flow (MBF) in patients with diseased coronary arteries.\textsuperscript{5,6}

The development of the radioisotope method that uses direct coronary artery injection of xenon\textsuperscript{133} permits rapid repeated determinations of MBF in intact dogs and man.\textsuperscript{7} This method has been used to study the pharmacodynamics of TNG administered sublingually and also by direct injection into the coronary arteries by means of an arteriographic catheter.\textsuperscript{8} The intracoronary route of administration was selected to study the effects of the drug on the coronary circulation uncomplicated by the effects of the systemic circulation. An increase in myocardial blood flow has been demonstrated to occur after the intracoronary administration of TNG in patients with arteriographically proven coronary artery disease.

Methods

Dogs

Eighteen closed-chest mongrel dogs weighing 15 to 25 Kg. were anesthetized with intravenous pentobarbital sodium (30 mg./Kg.) and ventilated with room air by a respiratory pump. Arterial pressure was recorded continuously from the descending aorta with a PE 240 catheter and a pressure transducer. Cardiac output was determined by dye dilution with indocyanine green injected into the right atrium through a PE 60 catheter inserted via the femoral vein and sampled from the femoral artery with a PE 240 catheter. With image amplifier fluoroscopy, the left coronary artery was catheterized via the left carotid artery and the coronary sinus via the right jugular vein with Sones catheters. MBF was measured by the selective injection of xenon\textsuperscript{133} in saline into the left coronary artery and calculated in ml./min./100 Gm. from the precordial disappearance of radioactivity.

The oxygen content of blood samples drawn from the aorta and coronary sinus was measured by the Van Slyke technic and myocardial oxygen consumption calculated in ml./min./100 Gm. Left ventricular work (Kg.M/min.) and mechanical efficiency were also calculated.\textsuperscript{9} Systemic vascular resistance was determined in dynes sec. cm.\textsuperscript{-5} and coronary vascular resistance in mm. Hg per ml./min./100 Gm.

Eighteen dogs were studied. Following control measurements in 13 dogs (group 1), observations were repeated 3 minutes after each of four intravenous injections of TNG at doses of 0.075, 0.15, 0.3, and 0.6 mg., respectively. Duplicate control measurements were made in 12 animals to assess variability of measurements. In five dogs (group 2), 44 observations were made 1/2 and 2 1/2 minutes after injection of 0.1 mg. of TNG in 1 ml. of 5 per cent glucose directly into the
left coronary artery via the Sones catheter. In all dogs, control measurements were made following intracoronary artery injection of 1 ml. of 5 per cent glucose.

**Man**

Thirty patients undergoing selective coronary arteriography for the evaluation of chest pain were studied. The patients were fasting and premedicated with morphine (8 to 10 mg.), atropine (0.6 mg.), pentobarbital (100 mg.) and diphenhydramine (50 mg.). Coronary artery catheterization was carried out via a right brachial arteriotomy with Sones catheters and MBF measured as in the animal experiments except that the coronary arteries were selectively engaged for each injection and then the catheter was immediately removed. The coronary sinus was catheterized in eight patients through a right antecubital vein.

Cardiac output was measured with indocyanine green, and the oxygen content of blood samples drawn simultaneously from the aorta and coronary sinus determined by Van Slyke analysis. Left ventricular work, myocardial oxygen consumption, mechanical efficiency, and systemic and coronary vascular resistance were calculated as previously described.

The 30 patients were divided into two groups. Group 1 consisted of 18 patients in whom measurements were made at approximately 3 minutes and at 6 to 8 minutes after the sublingual administration of 0.4 mg. of TNG. Group 2 included 12 patients in whom measurements were made 1/2 and 4 to 6 minutes after the intracoronary injection of 0.1 to 0.2 mg. of TNG dissolved in 1 ml. of 5 per cent glucose. Control measurements were made in all studies following the intracoronary injection of 1 ml. of 5 per cent glucose. A typical example is illustrated in figure 1.

Patient groups 1 and 2 were further subdivided according to the coronary arteriographic findings. Patients with minimal or no abnormality were classified as groups 1A and 2A; patients with major obstructive lesions of the coronary arteries were classified as groups 1B and 2B.

**Results**

**Dogs**

**Variability of Measurements**

In 12 dogs, duplicate control measurements were made 3 minutes apart. The determinations of MBF are illustrated in figure 2; the mean difference between the first \( C_1 \) and the second \( C_2 \) measurement was 16.8 ml./min./100 Gm., i.e., 17.3 per cent of the average control value for MBF. There was no systematic change observed between paired observations.

*Figure 1*

*Original recording (above) of precordial disappearance of radioactivity replotted (below) on a semilogarithmic scale following the injection of xenon\(^{133} \) (Xe) into the right coronary artery (RCA). Patient J.W. with severe atherosclerosis of right and left coronary arteries. Left, control \( T_{1/2} = 57 \text{ sec.} \); middle, ½ min. following 0.1 mg. of intracoronary nitroglycerin (TNG) into RCA \( T_{1/2} = 35.5 \text{ sec.} \); right, 4 min. later \( T_{1/2} = 43 \text{ sec.} \).*
NITROGLYCERIN AND CORONARY CIRCULATION

change in MBF was +59.1 per cent (p < 0.001) and coronary vascular resistance −34.1 per cent (p < 0.001). Two and one-half minutes after TNG, the average change from the control in mean aortic pressure was −18.4 per cent (p < 0.05), MBF −6.3 per cent (p < 0.4), and coronary vascular resistance −15.2 per cent (p < 0.3).

Man

Variability of Measurement

Two control measurements were made in 22 patients 5 minutes apart. The first and second determinations of MBF are illustrated in figure 2; the mean difference between first and second measurements was 7.53 ml./min./100 Gm., i.e., 14.5 per cent of the average control measurement. No systematic change was observed between paired observations.

Systemic and Coronary Hemodynamic Changes with Intravenous TNG

The changes observed in 13 dogs (group 1) 3 minutes after the intravenous injection of TNG (doses of 0.075, 0.15, 0.3, and 0.6 mg.) are shown in table 1. Myocardial oxygen consumption and efficiency were measured in five of the 13 dogs. With 0.6 mg. of TNG, the mean changes from the control measurements were aortic pressure −25.5 per cent (p < 0.005), cardiac output −29.1 per cent (p < 0.2), left ventricular work −48.7 per cent (p < 0.001), systemic vascular resistance +15.3 per cent (p < 0.3), MBF −25.7 per cent (p < 0.1), coronary vascular resistance +1.7 per cent (p < 0.95), myocardial oxygen consumption −28.0 per cent (p < 0.2), and mechanical efficiency −30.2 per cent (p < 0.02). The average change in mean aortic pressure, cardiac output, and left ventricular work was directly related to dose.

Coronary Hemodynamic Changes with Intracoronary TNG

The effect of 0.1 mg. of TNG ½ to 2½ minutes after its intracoronary injection in five dogs (group 2) is shown in table 3 and figure 4. At ½ minute, mean aortic pressure was not significantly changed, while the average

Figure 2

Left. Relationship between first measurement (C1) and second (C2) of MBF (ml./min./100 Gm.) in dogs. (Average difference between paired controls 16.83 ± 14.24 ml./min./100 Gm., 17.3 per cent of mean control.) Right. Similar observations in man. (Average difference between paired controls 7.53 ± 8.34 ml./min./100 Gm., 14.5 per cent of mean control.)

Figure 3

The effect of 0.4 mg. of TNG administered sublingually to 18 patients. Aortic pressure, myocardial blood flow, and coronary vascular resistance are expressed as a per cent of control values. Each point represents an observation in a single patient. Solid symbols indicate patients with abnormal arteriograms and open symbols those with normal arteriograms.
Table 1

Effect of Intravenous Nitroglycerin on Systemic and Coronary Hemodynamics in Dogs (Group 1)

<table>
<thead>
<tr>
<th></th>
<th>MAP, mm. Hg</th>
<th>CO₉, L. min.</th>
<th>LVW, Kg. M. min.</th>
<th>SVR, dynes sec. cm⁻¹</th>
<th>MBF, ml./min./100 Gm.</th>
<th>CVR, mm. Hg per ml./min./100 Gm.</th>
<th>MQ₀₂, ml./min./100 Gm.</th>
<th>ME, %</th>
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<tbody>
<tr>
<td>Control</td>
<td>120</td>
<td>2.57</td>
<td>4.40</td>
<td>4144</td>
<td>97.4</td>
<td>1.34</td>
<td>11.7</td>
<td>19.4</td>
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<tr>
<td>TNG (0.075 mg.)</td>
<td>108</td>
<td>2.01</td>
<td>3.15</td>
<td>4656</td>
<td>85.2</td>
<td>1.45</td>
<td>10.0</td>
<td>16.4</td>
</tr>
<tr>
<td>% Δ</td>
<td>-13.3</td>
<td>-18.7</td>
<td>-28.4</td>
<td>+8.6</td>
<td>-16.0</td>
<td>+6.5</td>
<td>-16.4</td>
<td>-14.4</td>
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<tr>
<td>p &lt;</td>
<td>0.2</td>
<td>0.5</td>
<td>1.4</td>
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<td>0.5</td>
<td>0.9</td>
<td>0.6</td>
<td>0.4</td>
</tr>
<tr>
<td>TNG (0.15 mg.)</td>
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<td>2.90</td>
<td>4768</td>
<td>81.3</td>
<td>1.35</td>
<td>10.3</td>
<td>14.9</td>
</tr>
<tr>
<td>% Δ</td>
<td>-17.9</td>
<td>-20.9</td>
<td>-33.0</td>
<td>+10.3</td>
<td>-15.9</td>
<td>-0.9</td>
<td>-9.2</td>
<td>-25.3</td>
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<td>p &lt;</td>
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<td>0.4</td>
<td>0.05</td>
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<td>0.3</td>
<td>0.975</td>
<td>0.6</td>
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<td>TNG (0.3 mg.)</td>
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<td>3.27</td>
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<td>80.4</td>
<td>1.34</td>
<td>8.6</td>
<td>16.4</td>
</tr>
<tr>
<td>% Δ</td>
<td>-19.0</td>
<td>-14.3</td>
<td>-30.6</td>
<td>+4.7</td>
<td>-18.6</td>
<td>0.0</td>
<td>-25.2</td>
<td>-17.9</td>
</tr>
<tr>
<td>p &lt;</td>
<td>0.4</td>
<td>0.8</td>
<td>0.2</td>
<td>0.7</td>
<td>0.2</td>
<td>-</td>
<td>0.3</td>
<td>0.5</td>
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<tr>
<td>TNG (0.6 mg.)</td>
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<td>1.65</td>
<td>2.06</td>
<td>4761</td>
<td>71.4</td>
<td>1.32</td>
<td>7.6</td>
<td>12.2</td>
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<tr>
<td>% Δ</td>
<td>-25.5</td>
<td>-29.1</td>
<td>-48.7</td>
<td>+15.3</td>
<td>-25.7</td>
<td>+1.7</td>
<td>-28.0</td>
<td>-30.2</td>
</tr>
<tr>
<td>p &lt;</td>
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<td>0.2</td>
<td>0.001</td>
<td>0.3</td>
<td>0.1</td>
<td>0.95</td>
<td>0.2</td>
<td>0.02</td>
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</table>

MAP, mean aortic pressure; CO, cardiac output; LVW, left ventricular work; SVR, systemic vascular resistance; MBF, myocardial blood flow; CVR, coronary vascular resistance; MQ₀₂, myocardial oxygen consumption; ME, mechanical efficiency.

Control, average control; TNG, average of observations 3 minutes following 0.075, 0.15, 0.3, and 0.6 mg. of intravenous nitroglycerin; % Δ, average per cent change.
### Table 2

**Effect of 0.4 Mg. of Sublingual Nitroglycerin on Systemic and Coronary Hemodynamics in Man**

<table>
<thead>
<tr>
<th></th>
<th>MAP, mm. Hg</th>
<th>CO₂, L./min.</th>
<th>LVW, Kg.M/min.</th>
<th>SVR, dynes sec. cm⁻¹</th>
<th>MBF, ml/min./100 Gm.</th>
<th>CVR, mm. Hg per ml/min./100 Gm.</th>
<th>MQ̄, ml/min./100 Gm.</th>
<th>ME, %</th>
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<td><strong>Group 1A (10 patients)</strong></td>
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<td></td>
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<tr>
<td><strong>Normal arteriography</strong></td>
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<td></td>
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<tr>
<td>Control</td>
<td>101</td>
<td>5.67</td>
<td>7.85</td>
<td>1446</td>
<td>54.2</td>
<td>1.99</td>
<td>6.4</td>
<td>29.8</td>
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<td>TNG (3 min.)</td>
<td>89</td>
<td>5.37</td>
<td>6.78</td>
<td>1401</td>
<td>51.3</td>
<td>1.88</td>
<td>5.9</td>
<td>28.7</td>
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<tr>
<td>% Δ</td>
<td>-11.9</td>
<td>-5.3</td>
<td>-13.6</td>
<td>-3.1</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-7.8</td>
<td>-3.7</td>
</tr>
<tr>
<td>p &lt;</td>
<td>0.05</td>
<td>0.7</td>
<td>0.4</td>
<td>0.8</td>
<td>0.7</td>
<td>0.8</td>
<td>0.6</td>
<td>0.8</td>
</tr>
<tr>
<td>TNG (6-8 min.)</td>
<td>80</td>
<td>4.46</td>
<td>4.95</td>
<td>1405</td>
<td>41.8</td>
<td>1.87</td>
<td>4.0</td>
<td>29.3</td>
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<tr>
<td>% Δ</td>
<td>-20.8</td>
<td>-21.3</td>
<td>-36.9</td>
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<td>-22.9</td>
<td>-6.0</td>
<td>-37.5</td>
<td>-1.7</td>
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<tr>
<td>p &lt;</td>
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<td>0.05</td>
<td>0.02</td>
<td>0.8</td>
<td>0.05</td>
<td>0.6</td>
<td>0.05</td>
<td>0.9</td>
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<tr>
<td><strong>Group 1B (8 patients)</strong></td>
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<td></td>
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<td><strong>Abnormal arteriography</strong></td>
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<tr>
<td>Control</td>
<td>113</td>
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<td>8.32</td>
<td>1620</td>
<td>58.72</td>
<td>1.96</td>
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<td>4.71</td>
<td>5.63</td>
<td>1532</td>
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<td>1.85</td>
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<td>% Δ</td>
<td>-21.2</td>
<td>-16.9</td>
<td>-32.3</td>
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<td>-17.0</td>
<td>-5.6</td>
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<td>p &lt;</td>
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<td>0.6</td>
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<tr>
<td>TNG (6-8 min.)</td>
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<td>4.60</td>
<td>6.12</td>
<td>1827</td>
<td>48.59</td>
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<td>5.3</td>
<td>34.9</td>
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<tr>
<td>% Δ</td>
<td>-15.0</td>
<td>-18.9</td>
<td>-26.4</td>
<td>+12.8</td>
<td>-17.3</td>
<td>+4.6</td>
<td>-17.2</td>
<td>-22.6</td>
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<td>p &lt;</td>
<td>0.2</td>
<td>0.05</td>
<td>0.1</td>
<td>0.6</td>
<td>0.1</td>
<td>0.7</td>
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*See legend table 1.
Systemic and Coronary Hemodynamic Changes with Sublingual TNG

The results in 18 patients studied 3 and 6 to 8 minutes after 0.4 mg. of sublingual TNG are shown in table 2 and figure 3. Ten patients (group 1A) had minimal or no abnormality detected by coronary arteriography, and eight (group 1B) had 50 per cent narrowing or complete occlusion of at least one major coronary artery branch. In eight of the 18 patients, myocardial oxygen consumption and mechanical efficiency were measured. In group 1A, at 3 minutes, the average changes from control values were mean aortic pressure -11.9 per cent (p<0.05), cardiac output -5.3 per cent (p<0.7), left ventricular work -13.6 per cent (p<0.4), systemic vascular resistance -3.1 per cent (p<0.8), MBF -5.3 per cent (p<0.7), coronary vascular resistance -5.3 per cent (p<0.8), myocardial oxygen consumption -7.8 per cent (p<0.6), and mechanical efficiency -3.7 per cent (p<0.8). Observations at 6 to 8 minutes revealed similar changes with significant decreases in mean aortic pressure, cardiac output, left ventricular work, and MBF. The changes seen in group 1B were similar to group 1A.

Hemodynamic Change with Intracoronary TNG

The results ½ and 4 to 6 minutes after the intracoronary injection of 0.1 to 0.2 mg. of TNG in 12 patients are shown in table 3 and figure 4. Minimal or no coronary artery disease was detected arteriographically in seven patients (group 2A) and severe disease in five (group 2B). No significant change in aortic pressure was seen following intracoronary injection of TNG in groups 2A and 2B.

Table 3

Effect of Intracoronary Artery Nitroglycerin on Coronary Hemodynamics in Dogs and Man

<table>
<thead>
<tr>
<th>Dogs (0.1 mg. TNG)</th>
<th>Group 2 (5 dogs)</th>
<th>44 Injections</th>
<th>MAP, mm Hg</th>
<th>MBF, ml/min/100 Gm</th>
<th>CVR, mm Hg/ml/min/100 Gm</th>
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<td></td>
<td></td>
<td></td>
<td>Control</td>
<td>124.2</td>
<td>94.2</td>
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<td></td>
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<td>TNG % min.</td>
<td>121.3</td>
<td>149.8</td>
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<td></td>
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<td>% Δ</td>
<td>-2.3</td>
<td>+59.1</td>
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<td></td>
<td></td>
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<td>p &lt;</td>
<td>0.9</td>
<td>0.001</td>
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<td>TNG 2% min.</td>
<td>101.3</td>
<td>88.2</td>
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<td></td>
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<td>% Δ</td>
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<td>-6.3</td>
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<td>p &lt;</td>
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<td>95.1</td>
<td>48.4</td>
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<td>TNG % min.</td>
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<td>% Δ</td>
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<td>TNG 4-6 min.</td>
<td>90.5</td>
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<td></td>
<td></td>
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<td>Control</td>
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Circulation. Volume XXXIII, January 1966
NITROGLYCERIN AND CORONARY CIRCULATION

Left. The effect of 0.1 mg. of intracoronary artery TNG expressed as a per cent change from the control on mean aortic pressure (upper), MBF (middle) and coronary vascular resistance (lower) in dogs. Right. Similar measurements in man following the intracoronary injection of 0.1 to 0.2 mg. of TNG.

The lack of adequate methods for the measurement of MBF has limited the study of the mechanism of action of TNG on the coronary circulation in the intact animal and man. While studies in dogs with use of flowmeters to measure MBF indicated that TNG causes a rapid increase in MBF within 30 seconds of administration,11-15 studies in patients with coronary artery disease or increased left ventricular work revealed no significant changes in MBF or coronary vascular resistance.5, 6, 16 The failure to demonstrate an increase in MBF coupled with the consistent finding of a decrease in cardiac work lead to the conclusion that the mechanism of action of TNG in the relief of angina pectoris was dependent upon a decrease in cardiac work and changes in myocardial metabolism.5, 6, 17

The methods previously used for the study of the pharmacodynamics of TNG in man were unsuitable for the evaluation of rapid changes in MBF, and, furthermore, the measurements were not commenced until 4 minutes after the sublingual administration of the drug.5, 6 The radioisotope technic used in this study permitted a measurement of MBF to be completed within 1 minute, and this made the evaluation of the early effects of TNG possible. This method has been shown in correlative studies with independently monitored coronary flow in dogs to measure accurately MBF per unit mass of myocardium.7 The studies in dogs with intracoronary TNG revealed that the method was clearly able to demonstrate the early increase in MBF previously reported by others employing continuous measurement of coronary flow,11-15 and similarly demonstrated that the increase in MBF did not persist after the arterial blood pressure decreased.

Following the sublingual administration of TNG, cardiac output and aortic pressure decreased as previously described,5, 18-21 but there was no statistically significant change in MBF. It seemed possible that the systemic effects of the drug were masking its direct effects on the coronary circulation. The intracoronary injection experiments were designed to permit observations of the effect of TNG on the coronary circulation uncomplicated by the effects on the systemic circulation. An increase in coronary flow similar to that observed in dogs was recorded in patients both with and without arteriographic evidence.

Discussion
The lack of adequate methods for the measurement of MBF has limited the study of the mechanism of action of TNG on the coronary circulation in the intact animal and man. While studies in dogs with use of flowmeters...
of coronary artery disease after direct intracoronary injection of TNG. The degree of change appeared inversely related to the severity of the disease.

We have purposely selected relatively large doses of TNG for intracoronary administration to determine whether MBF can be increased by the action of TNG on a diseased coronary vascular system. These studies clearly indicate that this is so, although it is recognized that the dosage used (0.1 to 0.2 mg.) and the route of administration (intracoronary) probably result in a concentration of the drug in coronary blood which exceeds that achieved following sublingual administration. No attempt was made to determine the minimal concentration of TNG that would be effective by intracoronary injection in man, but it can be stated that the intracoronary injection of 0.05 mg. of TNG resulted in an increase in myocardial blood flow in dogs. The time course of the increase in MBF following intracoronary injection was consistent with the clinical observation that TNG is usually effective in the relief of angina pectoris within seconds of its administration. It seems likely that the efficacy of TNG in the relief of angina pectoris is at least due in part to a direct vasodilatory action on the coronary arteries. The increase in myocardial blood flow is transient, and it may be that it brings about prompt relief of pain by the removal of metabolites that have accumulated in ischemic muscle.

The failure to demonstrate significant decrease in coronary vascular resistance following sublingual administration may have two explanations. First, it is possible that due to the time course of absorption of TNG, measurements may not have been made at the appropriate time to detect the relatively transient change in coronary vascular resistance. Secondly, it is possible that the demonstrated decrease, while not statistically significant, may still be clinically effective.

The results of this study are consistent with the theory that TNG relieves angina pectoris by its action on the coronary as well as the systemic circulations. Therefore, the pharma-
experiments of Fam, Sekelj, and McGregor\textsuperscript{28} tend to support this explanation.

\textbf{Summary}

The pharmacodynamics of nitroglycerin have been studied in dogs and man.

In dogs, intravenous nitroglycerin (TNG) caused a decrease in left ventricular work, myocardial blood flow (MBF), and myocardial oxygen consumption, and no significant change in coronary vascular resistance.

Intracoronary artery TNG in dogs caused an immediate increase in MBF and a decrease in coronary vascular resistance that persisted until arterial pressure fell.

In man, sublingual TNG (0.4 mg.) caused a decrease in left ventricular work, MBF, and myocardial oxygen consumption, and no significant decrease in coronary vascular resistance in patients with and without arteriographically proven coronary artery disease.

The injection of doses of 0.1 to 0.2 mg. of TNG directly into the coronary artery in man caused an immediate increase in MBF and a decrease in coronary vascular resistance in patients with and without arteriographically proven coronary artery disease.

The hypothesis proposed for the mechanism of action of TNG in the relief of angina pectoris is first, a decrease in coronary vascular resistance due to its effect on the coronary circulation, and, secondly, a decrease in cardiac work due to its effect on the systemic circulation.

\textbf{References}

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23. GREGG, D. E., AND SHIPLEY, R. E.: Augmentation of left coronary inflow with elevation of left ventricular pressure and observations on the mechanisms for increased coronary inflow with increased cardiac load. Am. J. Physiol. 142: 44, 1944.

One wonders whether the rare ability to be completely attentive to, and to profit by, nature’s slightest deviation from the conduct expected of her is not the secret of the best research minds and one that explains why some men turn to most remarkably good advantage seemingly trivial accidents. Behind such attention lies an unremitting sensitivity, analagous, I suspect, to that strange experience we all have of encountering a new word two or three times within the first week after we have learned it.—ALAN GREGG: The Furtherance of Medical Research. New Haven, Yale University Press, 1941, p. 98.
The Effect of Nitroglycerin on the Systemic and Coronary Circulation in Man and Dogs: Myocardial Blood Flow Measured with Xenon133
L. BERNSTEIN, G. C. FRIESINGER, P. R. LICHTLEN and R. S. ROSS

Circulation. 1966;33:107-116
doi: 10.1161/01.CIR.33.1.107

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