The Experimental Production of Intercorony Arterial Anastomoses and their Functional Significance

By Herrman L. Blumgart, M.D., Paul M. Zoll, M.D., A. Stone Freedberg, M.D., and D. Rourke Gilligan, A.M.

Animal experiments were done to learn the degree of coronary narrowing required to produce the larger intercorony collateral channels, their speed of development, and the degree of protection afforded the myocardium. Twelve or more days of 75 per cent narrowing were required to produce sufficiently rich anastomotic communications to protect the myocardium from damage, and to permit survival after superimposed acute complete occlusion. The physiologic and pathologic significance of the intercorony collateral communications and the clinical implications in coronary artery disease are discussed.

The clinical manifestations of acute myocardial infarction are no longer regarded to be solely the result of an acute occlusion of a coronary artery. In some instances, acute myocardial infarction occurs in the absence of fresh narrowing or occlusion, while in others the effects of acute occlusion may be partly neutralized by the presence of collateral circulation consequent to previous narrowing. Thus, acute myocardial infarction is to be regarded rather the resultant of two opposing processes; namely, the obstruction to blood flow by occlusive processes, and the compensatory development of collateral circulation which serves to offset the dire effects of coronary narrowing and occlusion.

Despite excellent studies of the collateral coronary circulation, the speed with which interarterial connections develop and the degree to which they protect the myocardium are imperfectly understood. Clinical and pathologic data on hearts with old coronary occlusion and with collateral circulation do not yield decisive answers. On examining such a human heart post mortem, only the net end result of the obstructive process and the compensatory bypasses is witnessed; one cannot determine accurately, even by microscopic study, how long previously the narrowing or complete occlusion occurred or when the collateral circulation developed.

To elucidate these problems, which are so important in the clinical management of coronary disease, recourse to animal experimentation was necessary. The experimental investigation reported below was designed to discover (1) whether acute narrowing of a coronary artery in an otherwise normal heart leads to the development of a collateral circulation; (2) the length of time necessary to establish such a collateral circulation; (3) whether the coronary collateral circulation developed after such a sudden narrowing is functionally effective in protecting the myocardium from the effects of a superimposed acute occlusion.

Methods and Technic

Choice of Animal: A word of caution should be expressed regarding studies on the hearts of dogs. To be certain that any collateral circulation observed post mortem is due to the experimental procedure, one must be confident that such collateral pathways are not present normally in the heart of the experimental animal. In our original experiments undertaken on the dog with the Schlesinger technic of injection plus dissection of the coronary arteries, the hearts of dogs often showed relatively large interarterial connections normally. In many experiments we could not conclude that the collateral vessels observed post mortem had been produced by us. Similar connections between the right, anterior descending, and left circumflex coronary arteries in the unoperated heart of the dog have been observed by Pianetto, using the same technic of injection with colored lead-agar mass.

Some preliminary injections of normal pig hearts showed no interarterial coronary communications. In subsequent injections of 44 normal pig hearts (table 1, A), only one showed interarterial coronary
communications. They consisted of very fine, faintly visible twigs connecting the left anterior descending and right coronary arteries on the surface near the apex and were not large enough for transfer of color of the injection mass from one arterial territory to another. It should be noted that the communications established following narrowing of the coronary arteries are profuse, different in location, and of an entirely different magnitude, permitting a definite mixing of colored mass among the arteries over many parts of the heart.

Experimental Technic: Young pigs weighing from 4.6 to 20.0 kilograms received 0.5 mg. atropine sulfate preoperatively. Intratracheal ether anesthesia was employed.

The heart was exposed through an intercostal incision. The pericardium was opened; one of the major coronary arteries, the left anterior descending, left circumflex, or right, was carefully dissected from its bed and a ligature passed around it. A wire of known diameter was placed alongside the vessel and the ligature was tied snugly around both the wire probe and the artery. The probe then was withdrawn quickly; the duration of complete occlusion in this procedure was fifteen to forty seconds. Many control experiments showed that the temporary complete occlusion of the artery was not a factor in the production of collateral circulation. Prior studies have shown that brief complete occlusion does not cause cardiac lesions.

The lumen of the artery within the tie was narrowed thereby approximately to the size of the wire probe. The wires utilized were 0.4 mm. to 1.2 mm. in diameter. The degree of narrowing produced by a wire of given size shows some variations. If the ligature is tied too tightly, the intima of the opposing sides of the vessel may become adherent or damaged and the vessel may remain occluded even after withdrawal of the wire. It is important to assure the re-establishment of patency of the lumen by gently prodding the artery with the finger and observing the flow of blood through it. In some animals, the failure of the artery to open after withdrawing the wire is probably due to the spasm of the artery induced by mechanical stimulation. Undue traction on the ligature, however, as it is tied around the wire and the artery may injure the intima and lead to progressive narrowing and final occlusion (Animals 41 and 42, table 3, C). In Animal 42, a thrombus had formed. If the ligature is drawn too loosely, the resulting lumen of the artery will be unduly large. This variation, however, has been reduced by experience. In any event, the degree of narrowing that has been produced can be measured with considerable accuracy post mortem. Subsequently the same artery was narrowed even more, occluded completely, or the animal was sacrificed without reoperation.

The coronary arteries were examined post mortem according to the injection plus dissection technic. In addition to cannulation of the left descending and the right main coronary arteries, the left circumflex artery was cannulated by transecting the artery just distal to its origin from the main left coronary artery. The usual lead-agar mass was used—colored blue for the left descending, red for the right coronary, and yellow for the left circumflex coronary arteries. In order to fill more completely any interarterial communications the technic of injection was slightly modified by application of

| TABLE 1.—Interarterial Anastomoses by Injection Method in Control Pig Hearts |
|--------------------------|-----------------|-----------------|-----------------|
|                         | Anastomoses      | Remarks        |
|                         | Total Number     | Anatomoses      |                  |
|                         | Number           | Degrees*        |                  |
| A. Normal pig hearts    | 44               | 1               | +               |
| B. Operative controls without coronary narrowing or occlusion | 11               | 1               | +               |
|                         |                  | Collagen values for left ventricle range from 0.38 to 0.57 grams% (average 0.49) |

* Graded on scale of + to +++.

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Experiments in which no Inter coronary Anasto motic Connections Were Produced

Control Experiments of the Surgical Procedure: As in all experimental work, the possibility arose of having produced collateral circulation by adventitious factors in the operative procedure itself. In eleven experiments (table 1, B) exactly the same operative technic was practiced. These animals were killed after various stages of the operative procedure were performed; included in this group are animals killed during the operation and up to seven days thereafter. In 10 hearts no intercoronary anastomoses were visible. In one animal fine intercommunicating twigs were seen among the branches of the left anterior descending coronary artery. No communications with the right or left circumflex arteries were observed. In 4 instances the collagen content of the left ventricle was determined; the values were 0.38 to 0.57 grams per cent of the net weight of tissue.

Control Experiments with Slight Narrowing: In three experiments, only very slight narrowing was produced intentionally to learn whether such relatively slight reduction in the lumen was sufficient to produce visible intercoronary connections (table 2, A). No anastomotic vessels were discernible on injection and dissection. The collagen values were in the normal range.

Experiments in which Coronary Narrowing or Occlusion Caused Cardiac Death: In 18 animals, cardiac death occurred within the first day after marked narrowing or complete occlusion of one of the major coronary arteries (table 2, B). In all instances, evidence of disturbed cardiac function was immediately obvious in the form of arrhythmias or cardiac dilatation. Ventricular fibrillation or cardiac standstill was observed within three to twenty minutes in 14 of the 18. In the other four experiments, the chest was closed and the heart was not visible but, post mortem, the territory of the occluded artery exhibited the discoloration indicative of early infarction and edema or necrosis of the muscle. In 17 hearts no intercoronary anastomotic connections were visible (fig. 1, B). In Animal 5, fine intercommunicating twigs among the branches of the anterior descending artery were visible over the apex of the heart. In this experiment, the onset of ventricular fibrillation within three minutes after marked narrowing testifies to the functional inadequacy of these communications which are rarely seen in the normal pig heart. In all but 2 (Animals 24 and 29) of these 18 animals the coronary artery had been suddenly narrowed to less than 13 per cent of its original cross-sectional area. It may be concluded, therefore, that sudden narrowing to less than 13 per cent of the original area of the left anterior descending or right coronary arteries is generally incompatible with survival. The collagen values were normal in 5 or 6 instances, and on microscopic examination there was no myocardial fibrosis.

Experiments with Narrowing in which Animals Died of Noncardiac Causes: In 8 animals which died of noncardiac causes the interarterial coronary communications were absent (table 2, C). In the 2 animals (Animals 12 and 40), which had survived seven to fourteen days with a reduction to 8 to 21 per cent of the original cross-sectional area, intercoronary communications which one might have anticipated

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**Fig. 1, A**.—(Pig No. 4.) Normal pig heart. Blue mass injected into left anterior descending, yellow mass injected into left circumflex, and red mass injected into right coronary artery. Each injection mass is confined to a single arterial tree. There is no intermixing of color.

**Fig. 1, B**.—(Pig No. 35.) Acute occlusion of mid-zone of right coronary artery was followed by death in three hours. Peripheral portion of right coronary artery was uninjected; no interarterial anastomoses. Early infarction of right ventricular myocardium.

**Fig. 1, C**.—(Pig No. 32.) Mid-zone of right coronary artery was narrowed twenty-five days before sacrifice; superimposed complete occlusion one day before sacrifice without subsequent infarction. Peripheral portion of right coronary filled with injection mass from left descending and left circumflex arteries by extensive anastomoses.
### Table 2.—Experiments in Which No Intercorony Anastomotic Connections Were Produced

<table>
<thead>
<tr>
<th>Animal Number</th>
<th>Artery Constricted</th>
<th>Size Lumen after Ligation (% Original Area)</th>
<th>Time before Death</th>
<th>Collagen (Grams %)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Experiments in which Slight Narrowing Was Induced</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>RC</td>
<td>77</td>
<td>21 d</td>
<td>0.45</td>
<td>Sacrificed</td>
</tr>
<tr>
<td>49</td>
<td>RC</td>
<td>72</td>
<td>21 d</td>
<td>0.51</td>
<td>Sacrificed</td>
</tr>
<tr>
<td>51</td>
<td>RC</td>
<td>56</td>
<td>21 d</td>
<td>0.49</td>
<td>Sacrificed</td>
</tr>
<tr>
<td><strong>B. Experiments in which Narrowing or Occlusion Caused Cardiac Death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>LAD</td>
<td>—</td>
<td>5 h</td>
<td>—</td>
<td>Second marked narrowing was followed immediately by ventricular fibrillation and death. Fine surface anastomotic twigs between branches of LAD (graded +)</td>
</tr>
<tr>
<td>9</td>
<td>LAD</td>
<td>16</td>
<td>22½ h</td>
<td>—</td>
<td>Death from ventricular fibrillation</td>
</tr>
<tr>
<td>11</td>
<td>LAD</td>
<td>3</td>
<td>6 m</td>
<td>0.55</td>
<td>Death from cardiac standstill</td>
</tr>
<tr>
<td>14</td>
<td>LAD</td>
<td>5</td>
<td>20 m</td>
<td>0.58</td>
<td>Ventricular fibrillation. Discolored myocardium suggesting early infarction; no necrosis microscopically</td>
</tr>
<tr>
<td>16</td>
<td>LAD</td>
<td>12</td>
<td>17 d</td>
<td>0.88</td>
<td>Ventricular fibrillation immediately after complete occlusion at second operation. No myocardial fibrosis or necrosis</td>
</tr>
<tr>
<td>19</td>
<td>LAD</td>
<td>9</td>
<td>12 m</td>
<td>0.39</td>
<td>Ventricular fibrillation</td>
</tr>
<tr>
<td>20</td>
<td>LAD</td>
<td>9</td>
<td>15 m</td>
<td>0.48</td>
<td>Ventricular fibrillation</td>
</tr>
<tr>
<td>24</td>
<td>LAD</td>
<td>27</td>
<td>20 m</td>
<td>—</td>
<td>Ventricular fibrillation. Discolored myocardium suggesting early infarction. Edema of myocardium microscopically</td>
</tr>
<tr>
<td>25</td>
<td>LAD</td>
<td>0</td>
<td>6 m</td>
<td>—</td>
<td>Ventricular fibrillation</td>
</tr>
<tr>
<td>29</td>
<td>RC</td>
<td>22</td>
<td>6 h</td>
<td>0.64</td>
<td>Early infarction; acute necrosis microscopically</td>
</tr>
<tr>
<td>31</td>
<td>RC</td>
<td>17</td>
<td>21 d</td>
<td>—</td>
<td>Cardiac standstill immediately after complete occlusion at reoperation</td>
</tr>
<tr>
<td>33</td>
<td>RC</td>
<td>13</td>
<td>18 m</td>
<td>—</td>
<td>Ventricular fibrillation. Discolored myocardium suggesting early infarction; no necrosis microscopically</td>
</tr>
<tr>
<td>35</td>
<td>RC</td>
<td>0</td>
<td>3 h</td>
<td>—</td>
<td>Discolored myocardium suggesting early infarction; edema of septum, no necrosis microscopically</td>
</tr>
<tr>
<td>37</td>
<td>RC</td>
<td>13</td>
<td>14-21 h</td>
<td>—</td>
<td>Discolored myocardium suggesting early infarction; edema of myocardium microscopically</td>
</tr>
<tr>
<td>38</td>
<td>RC</td>
<td>0</td>
<td>13 m</td>
<td>—</td>
<td>Ventricular fibrillation</td>
</tr>
<tr>
<td>44</td>
<td>RC</td>
<td>0</td>
<td>45 m</td>
<td>—</td>
<td>Complete occlusion from intimal tear; edema of septum microscopically</td>
</tr>
<tr>
<td>53</td>
<td>RC</td>
<td>100</td>
<td>7 d</td>
<td>—</td>
<td>Loose nonconstricting tie at original operation; subsequent complete occlusion at same point followed by cardiac standstill and death</td>
</tr>
<tr>
<td>55</td>
<td>RC</td>
<td>0</td>
<td>5 m</td>
<td>—</td>
<td>Ventricular fibrillation</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>8</td>
<td>LAD</td>
<td>32</td>
<td>48 h</td>
<td>—</td>
<td>Respiratory death</td>
</tr>
<tr>
<td>12</td>
<td>LAD</td>
<td>21</td>
<td>7 d</td>
<td>—</td>
<td>Hemorrhage at reoperation</td>
</tr>
<tr>
<td>13</td>
<td>LC</td>
<td>7</td>
<td>5-10 h</td>
<td>—</td>
<td>Animal found dead</td>
</tr>
<tr>
<td>17</td>
<td>LAD</td>
<td>15</td>
<td>35 m</td>
<td>0.68</td>
<td>Coincidental infectious disease</td>
</tr>
<tr>
<td>22</td>
<td>LC</td>
<td>25</td>
<td>35 m</td>
<td>0.46</td>
<td>Respiratory death; no myocardial necrosis microscopically</td>
</tr>
<tr>
<td>23</td>
<td>LAD</td>
<td>22</td>
<td>3 h</td>
<td>—</td>
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</tr>
<tr>
<td>27</td>
<td>RC</td>
<td>40</td>
<td>3 d</td>
<td>0.39</td>
<td>Animal decerebrate following operation</td>
</tr>
<tr>
<td>40</td>
<td>RC</td>
<td>8</td>
<td>14 d</td>
<td>0.48</td>
<td>Sacrificed. Myocardium normal microscopically</td>
</tr>
</tbody>
</table>

**KEY:**
- LAD—Left anterior descending coronary artery.
- LC—Left circumflex coronary artery.
- RC—Right coronary artery.
- d—Days.
- h—Hours.
- m—Minutes.
on the basis of our other results were not visualized.

Hearts in which Intercorony Anatomoses Were Produced Experimentally

Hearts with Intercorony Anatomoses: Functional Adequacy Not Tested: In 4 animals (table 3, A) with survival times of sixteen to twenty-five days after narrowing of the right coronary artery, anatomic evidences of abundant collateral circulation were observed. The lumens had been reduced to 10 to 21 per cent of the original cross-sectional area. In Animal 30, a branch of the right coronary artery proximal to and distant from the point of previous narrowing was completely occluded two days before sacrifice. The anastomotic connections visualized were distal to the original narrowing. No such connections were present in relation to the recently occluded branch. It is of interest that although the collateral channels in this animal were widespread, they were nevertheless tailored specifically to the narrowing which had evoked them. They did not develop indiscriminately or generally in the coronary tree and were not available as preformed anastomoses to obviate the effects of the new occlusion in the distant branch of the right coronary artery. Time is required for the development of such communications in the area immediately about an occlusion.

Hearts with Intercorony Anatomoses which Were Functionally Inadequate: In the second group of experiments (table 3, B) definite intercorony anastomoses were visualized, but death occurred at the second or third operation, when the previously narrowed artery was suddenly and completely occluded. In the animal surviving three hours after the initial narrowing (Animal 7) there was the faintest trace of injection mass derived from collateral pathways in the occluded artery. Somewhat more filling with mass from collateral vessels was present in the animal surviving fifty-two hours (Animal 10). In the animal (Animal 15) surviving seven days, abundant collateral circulation was demonstrated in the complete filling of the territory of the occluded vessel by mass from the other coronary arteries.

It may be stated, therefore, that collateral vessels of the size disclosed by the Schlesinger technic may rarely begin to appear within hours, and occasionally after days, but that these collateral vessels in their early development are inadequate to sustain the heart after a superimposed sudden complete occlusion.

Hearts with Intercorony Anatomoses and Survival after Complete Occlusion: In our experience (table 2, B), no pig had survived sudden complete occlusion of the left anterior descending or right coronary artery. In 3 animals (Animals 32, 36, and 43, table 3, C) in which a major coronary artery had been narrowed and the animals permitted to survive thirteen to twenty-five days, the previously narrowed artery was suddenly and completely occluded one to two days prior to sacrifice. Abundant intercorony communications were displayed post mortem in each heart (fig. 1, C). The fact that, in contrast to the experiments of tables 2, B and 3, B, these animals endured acute coronary occlusion, permits one to conclude that the collateral circulation demonstrated anatomically was functionally serviceable in protecting the heart and thereby enabled the animals to survive. In 2 additional instances (Animals 41 and 42) in which complete occlusion occurred gradually over a period of twelve to thirteen days, similar abundant intercorony anastomoses were demonstrated.

In none of the hearts of table 3, C were gross evidences of acute myocardial infarction discernible. This was particularly significant in Animals 32, 36, and 43 in which complete occlusion was imposed one to two days before sacrifice. Moderate amounts of microscopic necrosis were present in two of these hearts; in the heart of Animal 32, there was no microscopic necrosis at all. Estimation of the amount of fibrosis by microscopic examination and by determination of the collagen content of the left ventricular muscle showed a slight increase or no change (table 3, C). These observations are further evidences of the functional serviceability of the collateral circulation produced experimentally in these animals.

Evidence of Extracardiac Collateral Circulation: Although not a primary objective of these experiments, it was of interest to observe whether extracardiac collateral vessels devel-
<table>
<thead>
<tr>
<th>Animal Number</th>
<th>Artery Constricted</th>
<th>Size Lumen after Ligation % Original Area</th>
<th>Time before Death</th>
<th>Anastomoses Location</th>
<th>Degree</th>
<th>Collagen (Grams %)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Experiments in which Functional Adequacy of Anastomoses Was not Tested</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>RC</td>
<td>15</td>
<td>21 d</td>
<td>LC-RC</td>
<td>+++</td>
<td>0.89</td>
<td>Complete occlusion for 8 minutes without arrhythmia or other cardiac effect before sacrifice. No myocardial fibrosis or necrosis microscopically</td>
</tr>
<tr>
<td>30</td>
<td>RC</td>
<td>21</td>
<td>25 d</td>
<td>LAD-RC</td>
<td>++++</td>
<td>0.73</td>
<td>Ocluded branch of RC not injected. Moderate amount of fibrosis and necrosis microscopically</td>
</tr>
<tr>
<td>34</td>
<td>RC</td>
<td>11</td>
<td>24 d</td>
<td>LAD-RC</td>
<td>++++</td>
<td>0.72</td>
<td>No myocardial fibrosis or necrosis</td>
</tr>
<tr>
<td>39</td>
<td>RC</td>
<td>10</td>
<td>16 d</td>
<td>LAD-RC</td>
<td>++</td>
<td>0.74</td>
<td>Complete occlusion for 2½ minutes without arrhythmia or other cardiac effect before sacrifice</td>
</tr>
<tr>
<td>B. Experiments in which Anastomoses Were Functionally Inadequate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>LAD</td>
<td>19</td>
<td>3 h</td>
<td>RC-LAD</td>
<td>+</td>
<td>—</td>
<td>Ventricular fibrillation immediately after complete occlusion with death in 16 minutes</td>
</tr>
<tr>
<td>10</td>
<td>LAD</td>
<td>53</td>
<td>52 h</td>
<td>RC-LAD</td>
<td>++</td>
<td>0.65</td>
<td>Acute myocardial infarction.</td>
</tr>
<tr>
<td>15</td>
<td>LAD</td>
<td>15</td>
<td>7 d</td>
<td>RC-LAD</td>
<td>+++</td>
<td>0.69</td>
<td>Ventricular fibrillation immediately after complete occlusion. Single area of necrosis measuring 75 micra in diameter</td>
</tr>
<tr>
<td>C. Experiments with Interarterial Anastomoses and Survival after Complete Occlusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>RC</td>
<td>27</td>
<td>25 d</td>
<td>LAD-RC</td>
<td>++++</td>
<td>0.66</td>
<td>No myocardial fibrosis or necrosis</td>
</tr>
<tr>
<td>36</td>
<td>RC</td>
<td>10</td>
<td>22 d</td>
<td>LAD-RC</td>
<td>++++</td>
<td>0.59</td>
<td>Slight fibrosis and moderate amount of necrosis microscopically</td>
</tr>
<tr>
<td>41</td>
<td>RC</td>
<td>13</td>
<td>13 d</td>
<td>LAD-RC</td>
<td>++++</td>
<td>0.74</td>
<td>Artery narrowed at operation was found completely occluded 13 days later by fibrosis about ligature, indicating long-standing occlusion. Slight amount of fibrosis and necrosis microscopically</td>
</tr>
<tr>
<td>42</td>
<td>RC</td>
<td>0</td>
<td>12 d</td>
<td>LC-RC</td>
<td>++++</td>
<td>0.78</td>
<td>See remarks #41. Moderate amount of necrosis microscopically</td>
</tr>
<tr>
<td>43</td>
<td>RC</td>
<td>—</td>
<td>13 d</td>
<td>LAD-RC</td>
<td>++++</td>
<td>0.75</td>
<td>Slight fibrosis and moderate amount of necrosis microscopically</td>
</tr>
</tbody>
</table>

* Graded on scale of + to +++

**KEY:**

LAD—Left anterior descending coronary artery.
LC—Left circumflex coronary artery.
RC—Right coronary artery.
Br—Branch of main coronary artery.

Adhesions were present near or over a portion of the myocardium in the territory of the narrowed or occluded coronary artery. Despite...
collateral vessels in the vicinity, in no instance did the injection mass traverse the pericardial adhesions.

**Discussion**

The question whether intercoronary anastomoses exist has been the subject of vigorous discussion for many decades. Intense interest in this problem has been provoked not only because of its scientific importance but also because of the direct clinical implications for our understanding of angina pectoris and acute myocardial infarction. The impossibility of measurements of the coronary flow in man during life and the manifold variations in techniques of post mortem studies in man and in experimental conditions in animals have led to conflicting and even contradictory opinions.

Failure to appreciate the differences in the architecture of the coronary tree in man, in dog, and other experimental animals; the variations in the observations resulting from diverse experimental conditions and techniques; lack of agreement regarding the terminology employed; the paucity of evidence regarding the functional significance of the anastomoses observed, and, at times, neglect in discriminating between the normal and the changes induced by disease—all these have from time to time served to confuse the issue. To interpret the relation of our results to the work of others, some of these questions require brief discussion.

The Types of Coronary Arterial Anastomoses: Extracardiac anastomoses of the coronary arteries repeatedly have been observed with the vessels leading to adjacent structures, i.e., the venae cavae, the aorta, the pulmonary vessels, the reflections of the parietal pericardium, and across the adhesions in the presence of pericarditis. The functional significance of these communications under normal circumstances and their usefulness in providing accessory channels of blood flow in the presence of coronary arterial occlusion have been studied by many investigators. No anastomotic communications across pericardial adhesions of the size disclosed by lead-agar injection mass were observed in our experimental studies, despite the favorable fact that adhesions developed immediately after coronary narrowing or occlusion directly over the infarcted or ischemic myocardium. Our previous studies with the Schlesinger injection mass in man have likewise failed to disclose collateral channels across pericardial adhesions formed after acute myocardial infarction and pericarditis.

Coronary-luminal communications have been considered as a source of nourishment for the myocardium by many observers since their demonstration by Vieuxsens and Thebesius. These vessels presumably are connections in the intramural coronary circulation between the chambers of the heart and the various subdivisions of the coronary arterial tree (arterioles, capillaries, venules, and sinusoids). They have not been demonstrated by the lead-agar mass employed by Schlesinger in the normal or abnormal hearts of man, dog, or pig. Nor have other communications such as coronary arteriovenous shunts been seen by us.

Intercoronary arterial anastomoses have engaged the main interest of investigators because of their serviceability after occlusion of a coronary artery in supplying blood from a neighboring unaffected artery to the capillaries and tissue of the potentially infarcted area.

Normal Intercoronary Anastomoses as Demonstrated Anatomically: Species Differences: In 1669, Richard Lower stated that "...the vessels which carry blood to the heart ... come together again, and here and there communicate by anastomoses." Anatomic investigations in men and animals with injection materials such as water, air, suet, wax, dyes, inks, mercury, bismuth, lead, and radioactive phosphorus to supplement dissections of the heart confirmed Lower's finding of intercoronary arterial anastomoses and led to their general acceptance. Occasional assertions to the contrary were expressed, largely because variations consequent to species differences, differences in health and disease, as well as differences in technic were not appreciated.

Our own observations clearly indicate that in the normal heart of the dog, pig, and man, fine interarterial coronary communications exist. Colored watery solutions injected...
into one coronary artery promptly appear in the other coronary arteries and their branches. Similarly, Prinzmetal and co-workers\textsuperscript{106} have noted that watery solutions of fluorescein appear in different arteries after injection into one of the coronary vessels.

Injection materials may be used which do not regularly fill the capillary bed. The lead-agar mixture utilized in the Schlesinger technic regularly fills vessels down to 40 microns and irregularly penetrates to vessels from 40 to 10 microns in diameter. The above diameters of the arterial system apply to the vessels as seen in fixed tissues in stained microscopic preparations; to apply to vessels in the fresh or natural state, the measurement would be approximately double.\textsuperscript{116} The mass does not fill the capillary bed or appear in the venous system. These findings have been confirmed, in general, by others.\textsuperscript{107, 117, 118} In approximately 15 per cent of normal human hearts, the interarterial communications are of sufficient size to be demonstrated by the lead-agar mass, that is, a continuous injected pathway was visible grossly between arterial branches, or the colored injection mass passed from one arterial tree to another by way of invisible connections.\textsuperscript{118}

In contrast to our findings in man, interarterial coronary anastomoses were seen in almost all dog hearts. In many dog hearts, the interarterial communications are visible to the naked eye, i.e., larger than 60 to 80 microns in diameter, and correspond to vessels arteriolar or arterial in nature. It was this finding that led us to abandon the dog as the subject for the experimental induction of such anastomoses.

The increased incidence and caliber of the interarterial anastomoses in the normal dog heart\textsuperscript{7, 31, 32, 89, 94, 98, 102, 107} as compared to the human must be borne in mind in the critical evaluation of the large volume of experimental work on dogs. The inconstancy of experimental infarction in occurrence and size, noted in the work of others, is explicable on those grounds.\textsuperscript{98, 119–122} In the dog, additional factors in the variable effect of occlusion of the left anterior descending coronary artery are variations in the gross architecture of the coronary tree. The septum is supplied anteriorly in the dog by a single large vessel\textsuperscript{7, 94, 102, 110, 123} arising at a variable location from the left anterior descending coronary artery; in man the septum is supplied by a brushwork of small vessels from the left anterior descending artery. Ligation of the left anterior descending coronary artery in the dog would have a greatly different effect upon the heart muscle depending upon whether or not this septal branch was occluded. Furthermore, in the dog, the left circumflex coronary artery is always relatively long in comparison to the right coronary artery and gives rise to the posterior descending branch. This pattern corresponds to the most infrequent type seen in man.\textsuperscript{97, 98, 112, 124, 126}

The pig was chosen as the subject of this investigation because interarterial communications were witnessed in only 2 animals of 55 with the Schlesinger technic (table 1). In these two hearts they were superficial, few in number, and could be distinguished readily from those produced experimentally. The uniform production of acute infarction or, more frequently, sudden death from cardiac standstill or ventricular fibrillation following coronary occlusion is in accordance with these anatomic observations. Furthermore, the right coronary artery is relatively long in the pig and the posterior descending branch arises from it rather than from the left circumflex coronary artery. In this way, the pig heart corresponds to the most common type "right coronary preponderant pattern" found in man. Because of its relative predominance, ligation of the right coronary artery also resulted uniformly in extensive infarction or death in the pig.

Functional Significance of the Normal Inter coronary Anastomoses: The physiologic significance of the normal interarterial connections and the circumstances which may lead to their magnification have been the subject of intensive study.\textsuperscript{4, 5, 19, 27, 31, 32, 46, 50, 59, 91, 94, 107, 110, 111, 113, 114, 119, 126–146} To the anatomist, an end artery is an artery which does not communicate with other arteries through any anastomotic connection, so that its capillary bed receives blood from no other artery. To the physiologist, an end artery is an artery which alone supplies sufficient blood to an area to maintain its function and integrity; when this vessel is occluded the dependent area undergoes loss of function.
or necrosis because other arteries do not supply the given area sufficiently. These two definitions differ widely from each other; anatomic studies in other parts of the body have repeatedly demonstrated interarterial communications among vessels which are clearly end arteries physiologically. Wiggers has cogently remarked that "...it has long been accepted that the coronaries are terminal arteries, for when plugged by emboli or thrombi in man or when artificially occluded in animals an infarct results. The rapid necrosis of cardiac tissue could scarcely occur, were adequate anastomoses present." The failure of the supplied area to contract within one or two minutes following sudden occlusion and the electrocardiographic evidence of immediate injury are further manifestations of functional inadequacy, as is indeed the common catastrophic clinical experience with patients suffering from acute coronary occlusion. Experimentally in the dog, the area peripheral to the coronary ligature becomes swollen, cyanotic, and engorged, and the veins appear full. Prinzmetal and associates have recently reported that the amount of blood in such stagnant areas may be equal to two-thirds or more of the normal.

Although the intercoronary anastomotic channels in the normal heart do not prevent infarction after sudden occlusion, they do have some functional significance. It has been observed that following experimental or clinical acute occlusion of a coronary artery, the area of infarction is smaller than the entire territory of the distribution of this artery and its branches. Indeed, in some dogs, gross infarction does not appear at all because of the richer intercoronary connections. Furthermore, following the acute occlusion of a coronary artery in the normal dog heart, cannulation of the cut artery peripheral to the tie reveals retrograde flow amounting to as much as 7.2 cc. per minute. By gasometric analysis, this blood was found to be arterial in nature and, therefore, must have been derived from precapillary interarterial connections.

Prinzmetal and his associates injected radioactive erythrocytes, tagged with P32 (Na2HPO4), at various times in relation to ligation of the left anterior descending artery of the dog. Several moribund patients were also studied. Surface measurements of the beta radiation were converted by calculation into amounts of blood per gram of tissue. The calculation that the subepicardial ischemic myocardium contains as much blood as neighboring uninfarcted portions makes one hesitant to interpret the measurements into terms of blood flow. Furthermore, their ingenious technic is complex and contains some variables, such as, the amount of radiation contributed by the blood in the surface veins, possible capillary extravasations incurred by infarction and rapid freezing, and the diffusibility of P32 from the red cells into the plasma during even short periods of time, particularly if hemolysis has occurred. As pointed out by these investigators, the usual presence of cyanosis despite blood circulating through the ischemic area, indicates that the normal interarterial communications permit less blood flow in such areas than in other portions of the myocardium. They further observed by means of watery solutions of fluorescein that, as in the normal heart, the fine communications permit entrance of the dye to all parts of the heart including the infarcted region beyond the tie. The subendocardial portions of the heart contained less blood than normal in the ischemic region. When applying such experimental results to man, the relative abundance and magnitude of the collateral vessels observed in the normal dog must be borne in mind.

Interarterial Anastomoses in Relation to Coronary Narrowing and Occlusion in Man: Only approximately 15 per cent of normal human hearts reveal interarterial communications large enough to be disclosed by the Schlesinger lead-agar mass; when found, they are few in number. In contrast, 98 per cent of hearts with occluded arteries reveal collateral channels which are more numerous, occasionally visible to the naked eye, and of great functional significance. This has been demonstrated in hearts in which, despite complete occlusions, the potentially infarcted myocardium has been free of fibrosis or other structural abnormality.

When narrowing progresses gradually, complete occlusion in one or even in all three main
coronary arteries may be compatible with continued life, 4, 5, 29, 37, 59, 66, 71, 91, 101, 117, 118, 127, 134, 136, 146, 149, 165, 171, 172 Most patients with such hearts experience angina pectoris or congestive failure. Injection of these hearts demonstrates an extraordinarily rich network of anastomoses. All semblance of end arteries is lost.

Experimental Augmentation and Functional Significance of Anastomoses Following Coronary Narrowing or Occlusion: Bed rest after acute myocardial infarction serves a twofold purpose: (1) it reduces the work of the heart, favors healing of the infarct, and lessens liability to cardiac rupture, (2) an opportunity is provided for development of a more adequate intercoronary collateral circulation. It is consequently of practical as well as of theoretical importance to know the length of time required to establish such communications after sudden acute narrowing of the coronary artery and to learn whether the communications developed after a given interval of time are functionally adequate to protect the myocardium from the dire effects of the acute occlusion. As already stated, studies of human hearts cannot yield clear answers to these questions.

Experimental studies by others have disclosed interesting and significant data. Acute or gradual occlusion of the coronary artery in the dog is associated with enlargement of collateral vessels and does not necessarily result in infarction of the myocardium. 31, 32, 120, 121, 163-165 Following acute coronary occlusion in the dog, retrograde flow, derived mainly from other arteries, increases within a few hours and progresses steadily for some hours thereafter. 170 In animals surviving acute or gradual coronary occlusions for long periods (thirty-six to three hundred and sixty-five days), the peripheral coronary pressure is greatly increased, at times approaching the prevailing aortic pressures, and the retrograde flow coming from the peripheral end of the occluded artery may amount to 105 cc. per minute (values immediately after occlusion up to 1.5 cc. per minute). 165 Furthermore, after a minimum of seven weeks, the ischemic areas are able to contract. As the authors point out, it is highly improbable that retrograde flows of such magnitude, as were obtained experimentally against atmospheric pressure, exist in the intact heart when the occluded artery is not permitted to bleed. Likewise, the animals studied represent a select group of those which were able to survive acute complete occlusion. They may well be those which possessed natural interarterial connections larger than most. The more abundant collateral circulation in the dog heart compared to man renders application of these results to human experience somewhat uncertain.

These experimental studies have concerned themselves mainly with the effects of sudden complete occlusion or have simply demonstrated the development of collaterals after gradual narrowing. The degree of narrowing and the time interval necessary for the development of collaterals and the functional significance of such collaterals at various stages of their development were not determined.

The relation of angina pectoris, coronary failure, and acute myocardial infarction to coronary arterial narrowing and occlusion and the development of collateral vessels in human hearts have been the subject of previous communications by us. 4 Complete occlusion usually occurs in a previously narrowed artery. Consequently, the present studies of the sequence of events after graded and measured degrees of narrowing afford additional insight into the significance of our data in man. The results of our experiments (tables 1, 2 and 3) clearly demonstrate that narrowing of an artery to 10 to 27 per cent of the original cross-sectional area is commonly followed by the development of the interarterial anastomoses of the size disclosed by the Schlesinger technic (table 3). Acute narrowing to less than 13 per cent of the original lumen area generally leads to death of the animal (table 2, B) whereas only slight narrowing did not stimulate anastomoses during the three weeks of survival prior to sacrifice. Freely communicating anastomoses rarely appeared within hours or days but were abundant after two weeks. The development of such abundant anastomoses was necessary for the protection of the myocardium from sudden, superimposed complete occlusion.

The exact anatomic characteristics of these communications and the mechanism of their development have not been studied. The experi-
mental results clearly demonstrate, however, that anastomoses may develop in the absence of any myocardial necrosis or fibrosis. Factors consequent to the narrowing which may promote the development of anastomoses include the following: the opening of pre-existing or the formation of new collaterals by metabolites, directly or by reflex action, and by differential pressures. It is reasonable that the reduced pressure in a coronary artery distal to the point of narrowing or occlusion results in a pressure gradient between such areas and the neighboring unaffected artery, thereby opening up and dilating the pre-existing small communications. This concept was clearly expressed by Lower:

"... Hence, it sometimes happens that, when the lumen of some artery has been too long obstructed or ligated, the blood busies itself in opening a wider channel for its passage in this vessel, must drive and buffet all the more into the next ones, until it has considerably dilated them to give itself room."

Contrary to the current tendency to advise early ambulation, the slow development of these collateral channels emphasizes the importance of bed rest and reduced activity for many weeks after acute myocardial infarction. Ample evidence exists that reduced cardiac work favors healing of the infarct, reduces the extent of myocardial damage, lessens liability to rupture, and provides time for the development of these anastomotic channels. Similar considerations would seemingly apply to patients in whom angina pectoris suddenly appears or in whom the frequency or intensity of the attacks suddenly increases. If one can exclude temporary factors causing an increased demand for blood (fever, anemia) or physiologic reduction in coronary flow (shock, tachycardia), the sudden inadequacy of blood supply may be ascribed to structural organic narrowing or occlusion. Such sudden imbalance of coronary circulation must always be viewed with gravity, for any new reduction in coronary flow may result seriously in extensive myocardial necrosis if excessive demand is placed upon the heart before equilibrium is re-established by full development of anastomotic pathways. On the other hand, the slow development of a richer anastomotic circulation may be responsible for the occasional clinical improvement of patients with angina pectoris, the collateral channels acting to offset the narrowing or even occlusion which has occurred.

**Summary and Conclusions**

1. The speed with which coronary interarterial anastomoses develop and the degree to which they protect the myocardium from the effects of coronary arterial narrowing and occlusion have been studied.

2. In contrast to human hearts, the hearts of dogs almost always show relatively large interarterial connections normally; the experiments were therefore performed on pigs.

3. In 53 of 55 normal pig hearts, no intercoronary anastomotic connections of the size disclosed by the Schlesinger hearts were visible. In 2 hearts fine superficial intercommunicating twigs, readily distinguishable from those produced experimentally, were seen.

4. Sudden complete occlusion or sudden marked narrowing to less than 13 per cent of the original cross-sectional area of the right coronary artery in its midportion, or of the left anterior descending artery near its origin, was generally incompatible with survival; ventricular fibrillation or cardiac standstill usually occurred within twenty minutes.

5. In three experiments in which moderate narrowing to 15 to 19 per cent of the original lumen was produced, slight evidences of collateral circulation were demonstrated after survival periods of three hours, fifty-two hours, and seven days respectively, but this collateral circulation in its early development was functionally inadequate to protect the heart from the effects of suddenly superimposed complete occlusion of the artery.

6. In nine of the twelve experiments in which the animal survived twelve or more days after moderate narrowing, rich anastomotic communications between the major coronary arteries were demonstrated by the injection technic.

7. Collateral coronary circulation developed in these 9 animals was shown in 5 to be functionally significant, for the heart survived suddenly superimposed, or gradually developing complete obstruction one or more days before the animal was sacrificed.
8. In none of the 5 hearts with functionally adequate collateral vessels were gross evidences of acute myocardial infarction discernible. Estimation of the amount of microscopic fibrosis and necrosis showed none to a moderate increase. The collagen content of the left ventricular muscle showed a slight increase or no change, indicating again the functional serviceability of the collateral circulation produced experimentally in these animals.

9. In seven experiments, definite pericardial adhesions were present near or over a portion of the myocardium in the territory of the narrowed or occluded coronary artery. Despite collateral vessels in the vicinity, in no instance did the injection mass traverse the pericardial adhesions.

10. The physiologic and pathologic significance of the collateral intercoronary communications and the clinical implications in coronary artery disease are discussed.

11. Contrary to the current tendency to advise early ambulation, the slow development of these collateral channels emphasizes the importance of bed rest and reduced activity for many weeks after acute myocardial infarction. Similar considerations would seemingly apply to patients in whom angina pectoris suddenly appears or in whom the frequency or intensity of the attacks suddenly increases.

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The Experimental Production of Intercoronary Arterial Anastomoses and their Functional Significance

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