Interarterial Coronary Anastomoses in the Human Heart, with Particular Reference to Anemia and Relative Cardiac Anoxia

By Paul M. Zoll, M.D., Stanford Wessler, M.D., and Monroe J. Schlesinger, M.D.

In an unselected series of 1050 human hearts the coronary arteries were uniformly injected at necropsy with a standardized radiopaque mass. Interarterial coronary anastomoses were clearly demonstrated by this method and were studied with respect to their incidence and pathogenesis. Anastomoses were significantly increased in hearts with coronary artery occlusion or marked narrowing in cor pulmonale, in cardiac hypertrophy and valvular lesions, and also in normal hearts from patients with anemia. Relative cardiac anoxia is present in all these conditions; it appears to be a common underlying stimulus for the development of interarterial coronary anastomoses.

The clinical effects of coronary arteriosclerosis, in the form of angina pectoris, myocardial infarction and congestive failure, constitute a large portion of the serious cardiac disabilities that the physician constantly faces. Studies of atherosclerosis may, at some future date, lead to the prevention of these lesions. In the meantime, it has become clear that narrowing or even occlusion of the coronary arteries, under certain circumstances, does not always produce clinical symptoms or myocardial damage. This apparent inconsistency between the presence of long-standing obstructive lesions and the absence of pathologic or clinical evidence of myocardial damage has been dispelled by the demonstration in man of larger than normal interarterial coronary anastomoses. These anastomoses serve as bypasses or detours whereby blood reaches vessels distal to occlusions. These observations have been confirmed in the experimental animal. Other collateral channels, such as extracardiac anastomoses and communications of the thebesian types and communications of the arteries and veins, have not appeared to be significant in the maintenance of adequate coronary blood flow.

Any regimen that would produce interarterial anastomoses so that the coronary arteries were no longer functionally end-arteries would mitigate the clinical manifestations of coronary artery disease. Knowledge of the factors influencing the development of interarterial coronary anastomoses, therefore, would be of great practical value.

This paper presents the results of a study of coronary interarterial anastomoses in a series of 1271 human hearts examined by a uniform technic of injection and dissection. This unique body of data has provided a better understanding of the role of interarterial coronary anastomoses in normal and diseased states: insight into the basic mechanism of their production.
has been gained and several factors affecting their development have been identified.

The subject of coronary interarterial anastomoses has been investigated in many different ways since 1669 when Lower stated, "The vessels which carry blood to the heart come together again, and here and there communicate by anastomoses." Simple dissections of coronary vessels in both human and animal hearts have been supplemented by injections with various materials. Water, air, suet, wax, oils, turpentine, dyes, inks, starch, bacteria, Wood’s metal, mercury, iron, bismuth and lead compounds, microscopic glass spheres, radioactive erythrocytes, celloidin, gelatin, latex and liquid nylon have been used. For the most part, these studies have confirmed and led to the general acceptance of the idea that interarterial coronary anastomoses exist. Occasional disagreements have resulted largely from differences in materials or technics of injection, from anatomic variations among species, from varying pathologic conditions in the same species or, most frequently, from differences in interpretation of results.

All investigators agree that, when watery solutions or suspensions of very fine particles like India ink are injected into one coronary artery, they appear promptly in the other coronary arteries and their branches. Such materials, however, traverse the capillary bed and reach the coronary venous system. They cannot, therefore, be used to determine at which level (artery, arteriole or capillary) intercoronary arterial communications occur.

To circumvent this difficulty it is necessary to use injection masses which do not traverse the capillary bed. The lead-agar mass employed in this investigation was regularly found in vessels as small as 40 microns in internal diameter, irregularly penetrated as far as vessels from 40 to 10 microns in diameter but was not found in vessels under 10 microns in diameter. These measurements of vessel size were made on stained microscopic sections prepared from tissue fixed in formalin and embedded in paraffin; they are therefore subject to a correction of about 50 to 100 per cent for shrinkage from the fresh unfixed state. The actual diameter of injected vessels is less important than their nature (i.e., arteriole, capillary or venule): with this method the lead-agar mass did not enter the capillary bed and did not appear in the venous system.

The level of penetration of injected material probably depends on many other physical properties in addition to the size of the particles. Although most of the individual particles of lead phosphate in the lead phosphate-agar mass measured about one micron in size and exhibited brownian movement in aqueous suspension, a suspension of them did not penetrate vessels many times larger. Differences in extent of penetration of the mass in different hearts, from “stumpy” injection of only the larger arterioles to very “fine” injections with filling of smallest arterioles could be produced by purposeful variations in technic.

Our earlier studies on smaller numbers of hearts injected by this technic revealed interarterial coronary anastomoses in 10 to 22 per cent of human hearts that were otherwise normal at autopsy. The occurrence of anastomoses was found to be unrelated to age and sex, but it was definitely increased in the presence of valvular disease and coronary artery narrowing. Anastomoses were always found in hearts with old complete coronary artery occlusions. These observations have been confirmed by other workers.

**Method and Material**

An autopsy series of 1271 unselected human hearts has been studied at the Beth Israel Hospital, Boston, by a uniform injection plus dissection technic. Briefly this method consisted of the following steps:

1. Injecting radiopaque lead-agar mass of different colors into the main coronary arteries at a pressure of 150 to 200 mm. Hg.
2. Unrolling the heart so that the coronary arterial tree lay in one plane.
3. Taking a roentgenogram of the unrolled heart.
4. Carefully dissecting and opening the coronary arteries, using the roentgenogram as a guide.

With this method the demonstration of narrowings, occlusions and anastomoses in the coronary arteries was greatly facilitated. The technic of unrolling the heart reduced the difficulty in following the three-dimensional course of the vessels on a two-dimensional film.

Criteria were established for the determination of anastomotic communications. It was found that the roentgenograms alone could not be relied upon
to prove the existence of such communications. Overlapping vessels, like the bare branches of adjacent trees,\textsuperscript{4} often deceptively gave the appearance of intercommunications. Conversely, anastomoses could be clearly demonstrated on careful dissection which were not visible on the roentgenogram. On the basis of careful dissection three types of proof of anastomoses were accepted: (1) demonstration of a continuous, stained, endothelial-lined connecting channel filled with mass between two coronary arteries; (2) presence of injection mass of any color distal to a complete occlusion and (3) visualization of a mixture of color in the injection mass.

(1) \textit{Demonstration of a Continuous, Endothelial-Lined, Connecting Channel Filled with Mass between}

was important in supporting the validity of the other two methods of demonstrating interarterial anastomoses.

(2) \textit{Presence of Injection Mass of Any Color Distal to a Complete Occlusion.} Since a complete coronary artery occlusion prevented direct filling of the peripheral vascular tree, mass of any color found beyond an occlusion must have gotten there by collateral pathways. Interarterial anastomoses could be demonstrated by finding mass of the same color both proximal and distal to an occlusion.

(3) \textit{Visualization of a Mixture of Colors in the Injection Mass.} Since the color of the injected mass identified its source, mixture of colors necessarily indicated a connecting pathway between two coro-

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig1.png}
\caption{Colored roentgenogram of injected heart (A 43-128) with multiple coronary artery occlusions and extensive interarterial coronary anastomoses. Anastomoses are demonstrated by (a) grossly dissectible channel between two coronary arteries; (b) injection mass of any color distal to complete occlusion; (c) mixture of colors of injection mass. (The use of color in this illustration was made possible by a grant from Wyeth, Incorporated, to the publication fund of the American Heart Association.)}
\end{figure}

\textbf{Two Coronary Arteries.} Communications were proved to be unquestionable interarterial anastomoses only when a continuous, intact, vascular pathway could be demonstrated connecting two coronary arteries. Grossly dissectible anastomoses were demonstrable when the vessel was about 0.2 mm. in diameter or larger, but vessels, less than 0.5 mm. in diameter were not readily opened. Smaller anastomoses 60 to 70 microns in diameter could be traced along their entire course by laborious study under the dissecting microscope in tissue cleared by the Spalteholz technique\textsuperscript{100} or by reconstruction of a complete series of microscopic sections. Vessels of this caliber were not visible on the roentgenogram. Indisputable demonstration of grossly dissectible pathways in this way was possible in only about one-fifth of the hearts in which anastomoses were accepted as present. Although somewhat infrequent, this method

nary arteries. This was the most common method by which interarterial communications were demonstrated. The validity of accepting mixture of colors as evidence of an interarterial anastomosis rather than of an artificial extravascular connecting channel or of a common capillary bed between two arteries depended upon three lines of supporting evidence: (a) the absence of gross or microscopic evidence of extravasations of mass; (b) the absence of mass in capillaries or veins and (c) the frequent gross or microscopic demonstration of a continuous, indisputable endothelial-lined vessel connecting two coronary arteries in hearts in which mixture of colors was found. Figure 1 shows the colored roentgenogram of an injected heart in which intercoronary arterial anastomoses were demonstrated by all three methods.

Although areas of even slight narrowing stood
out on the film as irregularities in the shadow of the injected mass, the presence and extent of suspected coronary artery narrowings or occlusions were determined primarily in the dissection, when the arteries were commonly opened down to small branches. The solidified mass found in them as a cast of the lumen facilitated determination of the degree of narrowing or the presence of complete occlusions. The staining of the intima by dye diffused from the mass also aided dissection of small or permitted classification according to the presence or absence of anastomoses, cardiac hypertrophy, valvular and congenital heart disease, coronary artery narrowings and occlusions and cor pulmonale. Tabulation was also made of clinical data of possibly related significance such as age, sex, arterial hypertension, pulmonary, renal and metabolic diseases, chronic wasting disease, prolonged cardiovascular collapse, surgical operations, duration of terminal illness and anemia.

![Fig. 2. The incidence of intercoronary arterial anastomoses in relation to anemia, cardiac hypertrophy, valvular and coronary artery disease.](image)

<table>
<thead>
<tr>
<th>WITHOUT CARDIAC HYPERTROPHY</th>
<th>WITH CARDIAC HYPERTROPHY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NO CORONARY ARTERY DISEASE</strong></td>
<td><strong>WITH CORONARY ARTERY DISEASE</strong></td>
</tr>
<tr>
<td>GROSSLY NORMAL</td>
<td>VALVULAR DISEASE</td>
</tr>
<tr>
<td>101 91</td>
<td><strong>5 5</strong></td>
</tr>
<tr>
<td>No. = total number in group</td>
<td>70 50</td>
</tr>
</tbody>
</table>

* * too few for separate analysis
* all cases grouped together without reference to anemia or hypertrophy
* with anemia
* without anemia

For purposes of simplicity, 92 of the cases with adequate data in all the above categories were omitted from the present series because they exhibited combinations of valvular heart disease and coronary artery pathology.

**Results**

Table 1 presents the complete data on these 1050 hearts in all their subdivisions; some of the groups are presented individually in tables 2 to 5. Of this selected group, 480 (46 per cent) showed interarterial coronary anastomoses. Figure 2 presents an analysis of all hearts with anastomoses with respect to the relative frequency of the groups into which these 480 cases fall.

**The Normal Heart and Coronary Artery Anastomoses**

**Criterion of the Normal Heart.** Of the 1050 hearts in the series, only 244 (23 per cent) were considered as a normal, control group (table 1). All these hearts weighed less than 350 Gm. and did not show any valvular or congenital lesions, right ventricular hypertrophy or coronary artery narrowing or occlusion. Heart
weights under 350 Gm. were considered normal for reasons which will be discussed in the section on cardiac hypertrophy. Hearts with very little or questionable coronary artery narrowing were rejected from this normal, control group. This was done in order to preserve the integrity of the normal, control group which was to serve as a standard of comparison for the entire series. It was deemed preferable thus to include some almost normal hearts in the group with slight coronary artery narrowing rather than to include them in the normal, control group.

Of the 244 normal hearts rigidly selected in this way, 55 (23 per cent) showed interarterial coronary anastomoses (table 1). This figure is similar to that reported in an earlier study.\textsuperscript{123} No correlation was found between the incidence of coronary artery anastomoses and anatomic variants such as the relative length of right and left circumflex coronary arteries\textsuperscript{124} or the presence of a conus artery.\textsuperscript{123}

**Anemia and Coronary Artery Anastomoses**

In an effort to disclose some clinical feature that might be related to coronary artery anastomoses, the clinical records of the entire group of patients with normal hearts were reviewed. The following factors were evaluated: (1) age, (2) sex, (3) arterial hypertension, (4) severe pulmonary disease, (5) renal disorders, (6) thyroid or other metabolic diseases, (7) chronic or debilitating disease, (8) prolonged cardiovascular collapse, (9) surgical procedures, (10) duration of terminal illness and (11) anemia. Of all these factors a definite correlation was found only between coronary artery anastomoses and anemia.

**Criterion of Anemia.** Determination of anemia was based on hematocrit or hemoglobin levels. Hemoglobin determinations were made by the Sahli colorimetric or Evelyn photoelectric technics; 15.5 Gm. hemoglobin per cent was considered 100 per cent hemoglobin. Hematocrit determinations were made by adequate centrifugation of blood in Wintrobe tubes. When necessary, hematocrit levels were equated with hemoglobin percentages by considering a hematocrit of 45 per cent equivalent to 100 per cent hemoglobin.

All patients in the series were classified with respect to anemia as follows: (1) patients with hemoglobin levels of 75 per cent or more were placed in a nonanemic group; (2) those with hemoglobin levels of 70 per cent or less were placed in an anemic group; (3) the remainder with intermediate or indeterminate levels were discarded from the analysis of anemia. This last group consisted of patients with hemoglobin levels between 70 and 75 per cent and those with marked hemoglobin fluctuations. A few cases were also discarded in which hematologic data were not available or were unreliable. Finally all patients in whom anemia had been present for five days or less before death were also discarded. Experimental studies on the production of intercoronary arterial anastomoses in the dog\textsuperscript{125} and the pig\textsuperscript{1} offer some support to this choice of a five day limit.

The correlation demonstrated between anemia and anastomoses was not altered significantly by moving the criterion for anemia to 75 or 80 per cent hemoglobin, or by enlarging the intermediate, discarded group to include levels of 70 to 80 per cent hemoglobin. Such changes, however, reduced the number of cases available for analysis of other factors and thereby lowered the statistical validity of the data.

**Effect of Anemia.** Of the 244 patients with normal hearts, 101 were in the nonanemic category; 91 showed anemia as defined above. These 192 cases were used in a correlation of anemia and anastomoses (table 2 and fig. 2). Coronary artery anastomoses were present in only nine (9 per cent) of the nonanemic control group and in 35 (39 per cent) of the anemic group. This difference is highly significant statistically as measured by the chi square test or standard error of difference.\textsuperscript{*26} Further analysis of the group of 91 cases with anemia was carried out to determine the relative effect of varying degrees of anemia upon anastomosis. No significant difference was found in the incidence of anastomoses in groups with differing degrees of anemia. For example, of 52 cases with hemoglobin levels consistently below 60 per cent, 16 (31 per cent) showed anastomoses; of 31 cases with anemia between 60 and 70 per cent.

\* Differences were considered to be statistically significant if they were 2.5 times the standard error of the difference.
### Table 1.—Incidence of Interarterial Coronary Anastomoses in All Groups of Total Series

<table>
<thead>
<tr>
<th>Anemia</th>
<th>Total Number Hearts</th>
<th>Normal Weight</th>
<th>Cardiac Hypertrophy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Hearts with Anastomoses</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Number</td>
<td>Per Cent</td>
<td>Dissectible</td>
</tr>
<tr>
<td>A. No Coronary or Valvular Disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonanemic</td>
<td>101</td>
<td>9</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Anemic</td>
<td>91</td>
<td>35</td>
<td>39</td>
<td>4</td>
</tr>
<tr>
<td>Total*</td>
<td>244</td>
<td>55</td>
<td>23</td>
<td>4</td>
</tr>
<tr>
<td>B. Valvular Disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonanemic</td>
<td>5</td>
<td>1</td>
<td>†</td>
<td>0</td>
</tr>
<tr>
<td>Anemic</td>
<td>5</td>
<td>3</td>
<td>†</td>
<td>0</td>
</tr>
<tr>
<td>Total*</td>
<td>13</td>
<td>4</td>
<td>31</td>
<td>0</td>
</tr>
<tr>
<td>C. Slight Coronary Artery Narrowing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonanemic</td>
<td>28</td>
<td>5</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td>Anemic</td>
<td>19</td>
<td>2</td>
<td>33</td>
<td>0</td>
</tr>
<tr>
<td>Total*</td>
<td>45</td>
<td>11</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>D. Moderate Coronary Artery Narrowing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonanemic</td>
<td>19</td>
<td>3</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>Anemic</td>
<td>15</td>
<td>5</td>
<td>33</td>
<td>1</td>
</tr>
<tr>
<td>Total*</td>
<td>34</td>
<td>11</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>E. Marked Coronary Artery Narrowing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonanemic</td>
<td>8</td>
<td>5</td>
<td>63</td>
<td>0</td>
</tr>
<tr>
<td>Anemic</td>
<td>3</td>
<td>2</td>
<td>†</td>
<td>0</td>
</tr>
<tr>
<td>Total*</td>
<td>11</td>
<td>12</td>
<td>63</td>
<td>1</td>
</tr>
<tr>
<td>F. Coronary Artery Occlusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total†</td>
<td>275</td>
<td>262</td>
<td>95</td>
<td>72</td>
</tr>
<tr>
<td>G. Cor Pulmonale</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total†</td>
<td>15</td>
<td>11</td>
<td>73</td>
<td>3</td>
</tr>
<tr>
<td>Grand Total of Entire Series</td>
<td>1050</td>
<td>480</td>
<td>46</td>
<td>94</td>
</tr>
</tbody>
</table>

* Totals include additional cases with intermediate or indeterminate hemoglobin levels.
† Too few in number.
‡ All hemoglobin levels and weight groups combined in single tabulation.

Hemoglobin, 15 (48 per cent) showed anastomoses.

The small group of nine patients without anemia in whom the hearts were normal but nevertheless showed coronary artery anastomoses was reinvestigated in detail. Severe pul-
monary disease was found in six of them. The possible relation of pulmonary disease to coronary artery anastomoses is discussed below.

Cardiac Hypertrophy and Coronary Artery Anastomoses

Criterion of Hypertrophy. A review of the literature on cardiac hypertrophy did not disclose any simple, generally accepted criterion for this factor. The 103 hearts in the entire group which weighed 300 Gm. or more but were otherwise normal and which came from nonanemic patients were subdivided according to weight into four comparable groups of (1) 450 Gm. or more, (2) 449 to 400 Gm., (3) 399 to 350 Gm. and (4) 349 to 300 Gm.

TABLE 2.—The Incidence of Interarterial Coronary Anastomoses in Relation to Anemia in Cases without Cardiac Hypertrophy, Valvular or Coronary Disease

<table>
<thead>
<tr>
<th>Hemoglobin Levels</th>
<th>Anastomoses</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Nonanemic</td>
<td>92</td>
<td>9 (9%)</td>
</tr>
<tr>
<td>Anemic</td>
<td>56</td>
<td>35 (39%)</td>
</tr>
</tbody>
</table>

Total 148 44 192

The frequency of anastomoses was high and constant in each of these small groups above 350 Gm. and dropped sharply in the group below 350 Gm. The entire group of 70 hearts above 350 Gm. may therefore be considered homogeneous. In this way the selection of a heart weight of 350 Gm. or more was supported as the criterion for cardiac hypertrophy throughout this study.

Effect of Hypertrophy. Among the 1050 hearts in the series were 153 which were normal in all pathologic respects except for hypertrophy as above defined. In the 70 hearts from this group that came from patients without anemia, the incidence of interarterial coronary anastomoses was 26 per cent (fig. 2). This incidence is significantly higher (2.9 times the standard error of the difference) than the 9 per cent in the normal, control group without hypertrophy.

Effect of Anemia Plus Hypertrophy. Coronary artery anastomoses were found in 14 (28 per cent) of the 50 hypertrophied hearts from anemic patients (fig. 2). This incidence does not differ significantly from the 26 per cent in the group of cardiac hypertrophy without anemia or from the 39 per cent in the normal hearts with anemia. Anemia and cardiac hypertrophy individually were associated with an increased incidence of anastomoses in the human coronary artery system, but combination of the two did not show an additive effect with a still higher incidence.

Valvular Heart Disease and Coronary Artery Anastomoses

Criterion of Valvular Disease. Valvular heart disease without coronary artery disease was

TABLE 3.—The Incidence of Interarterial Coronary Anastomoses in Relation to Cardiac Hypertrophy in Cases without Anemia, Valvular or Coronary Disease

<table>
<thead>
<tr>
<th>Heart Weight</th>
<th>Total Number of Hearts</th>
<th>Hearts with Anastomoses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Number</td>
</tr>
<tr>
<td>450 Gm. or more</td>
<td>25</td>
<td>6</td>
</tr>
<tr>
<td>419 to 400 Gm.</td>
<td>21</td>
<td>6</td>
</tr>
<tr>
<td>399 to 350 Gm.</td>
<td>24</td>
<td>6</td>
</tr>
<tr>
<td>349 to 300 Gm.</td>
<td>33</td>
<td>2</td>
</tr>
</tbody>
</table>

found in 75 hearts. The valves presented definite organic stenosis, insufficiency or a combination of defects. Only hearts with valvular disease thus established at autopsy were included in this category.

Effect of Valvular Disease. Coronary artery anastomoses were present in 27 (36 per cent) of all 75 hearts with valvular disease (table 1). This group is heterogeneous in that hypertrophy or anemia or both were present together with the valvular disease in all but five cases. The largest homogeneous subgroup of 32 hearts with valvular disease plus hypertrophy from nonanemic patients (table 1 and fig. 2) showed an incidence of anastomoses of 28 per cent, which is essentially the same as the 26 per cent in hearts with hypertrophy alone. Furthermore, upon addition of anemia to valvular disease and hypertrophy, a similar incidence of anastomoses of 32 per cent in 19 cases was found (table 1 and fig. 2). The three factors of anemia, hypertrophy and valvular disease,
whether taken singly or in any combination, showed similar frequencies of anastomoses, from 26 to 39 per cent, without additive effect (fig. 2).

Coronary Heart Disease and Coronary Artery Anastomoses

Criterion of Coronary Artery Narrowing and Occlusion. All the hearts in the series were classified in five categories according to the condition of the coronary arteries: (1) 472 hearts without any coronary artery narrowing, already discussed under the various headings of the normal heart, anemia, hypertrophy and valvular disease; (2) 122 hearts with slight coronary artery narrowing; (3) 100 hearts with moderate coronary artery narrowing; (4) 60 hearts with marked coronary artery narrowing, but without complete occlusions; (5) 275 hearts with complete coronary artery occlusions, old or recent. In 15 additional hearts cor pulmonale was the primary pathologic condition; in them the degree of coronary artery narrowing ranged from none to moderate and was disregarded.*

This classification of the degree of coronary artery disease was based on judgments by different observers at the time of dissection and subsequently on re-examination of the roentgenogram of the injected heart. Multiple, independent observations were made frequently on individual hearts by several observers with close agreement. In some of the hearts the internal diameters of the major vessels were measured by a series of graduated probes, so that the degree of reduction in diameter at sites of narrowing was quantitatively determined by comparison with adjacent zones. It was found that estimates of slight narrowing corresponded to a reduction in diameter approximately 25 per cent or less; marked narrowing was equivalent to reductions of 75 per cent or more. The term "occlusion" always denoted complete occlusion of a coronary artery; a complete break in the continuity of the lumen was demonstrated in the dissection by the absence of mass or colored intima in such areas. Occlusions were further classified as recent or old largely on the basis of their gross appearance. Microscopic estimation of the duration of the occlusive process was made only in relatively few, selected instances.

Effect of Coronary Artery Narrowing. All 288 cases with coronary artery narrowing were classified according to the degree of narrowing, the presence of hypertrophy and anemia (fig. 2). The incidence of anastomoses in the groups with slight and moderate narrowing did not differ significantly from their appropriate comparison groups without narrowing. Every subdivision with marked narrowing, however, showed a significantly high incidence of coronary artery anastomoses: anastomoses were found in 58 per cent of all hearts with marked coronary artery narrowing. Anastomoses were found in only 26 to 39 per cent, however, of hearts without coronary narrowing to which were added the factors of anemia, hypertrophy and valvular disease, singly or in combination. Again, anemia and hypertrophy were not effective in increasing coronary artery anastomoses in the presence of marked coronary artery narrowing, just as combinations of them were not additive in the absence of marked coronary narrowing.

Effect of Recent Coronary Artery Occlusions. Among the 275 hearts with complete occlusions of the coronary arteries were 121 with one or more points of recent occlusion (table 4 and fig. 2). Interalteral coronary artery anastomoses were demonstrated in 108 (89 per cent) of these 121 hearts. Anemia and cardiac hypertrophy were not important in the development of anastomoses in this group.

More than one recent occlusion was present in 27 of these 121 hearts, so that the total number of recent occlusions was 163 (table 4). Analysis of the local anatomic relation of the anastomoses to each of these 163 individual recent occlusions throws light on the mechanism of development of interarterial anastomoses. Anastomotic filling of those branches of the coronary arteries directly peripheral to recent occlusions was demonstrated only in 110 of the 163 instances (68 per cent). Many of the recent coronary artery occlusions were clearly superimposed on the site of previous marked coronary artery narrowing. Marked narrowing

* It will be noted that there are no hearts with combinations of coronary and valvular disease; all such hearts were discarded from the series to simplify the analysis.
alone without occlusion has already been shown to be associated with an incidence of 58 per cent of anastomoses. Hence it appears likely that the localized anastomoses found distal to recent occlusions were induced in most instances by previous coronary artery narrowing.

Effect of Old Coronary Artery Occlusions. The group of 154 hearts with at least one old occlusion and no recent occlusions in the coronary artery tree comprised 15 per cent of the total series of 1050 hearts. Intercoronary anastomoses were present in every one of these 154 hearts. In the larger group of 236 hearts with old coronary artery occlusions (including 82 with recent occlusions as well), all but three hearts. Anastomoses were demonstrated in the coronary arteries directly distal to all but 13 of these 349 sites of old occlusion (96 per cent). Even when the instances of old occlusions found in hearts with both recent and old occlusions were added, the incidence of anastomoses directly distal to old occlusions remained high at 91 per cent (table 4).

The special means of demonstrating anastomoses in hearts with coronary artery occlusions by finding injection mass of the same color on both sides of an occlusion was the sole evidence of anastomoses in only 12 (8 per cent) of these 154 hearts. It was, therefore, not a significant factor in the high incidence of anastomoses in hearts with old occlusions. Similarly, anemia was infrequent (13 per cent) in the 154 patients with old coronary artery occlusions and, therefore, not significant in producing all the anastomoses.

Cor Pulmonale and Coronary Artery Anastomoses

Criterion of Cor Pulmonale. Uncomplicated cor pulmonale was present in 15 of the 1050 hearts studied. In these 15 instances additional factors that might produce anastomoses, such as anemia, valvular disease, marked coronary artery narrowing or occlusion, were absent. Relative right ventricular hypertrophy, usually secondary to pulmonary fibrosis, was taken as the distinctive criterion of cor pulmonale.

<table>
<thead>
<tr>
<th>Table 4.—The Incidence of Intercellular Coronary Anastomoses in Hearts with Coronary Artery Occlusions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group</strong></td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Hearts with Recent Occlusions Only</td>
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<td>Hearts with Recent Plus Old Occlusions</td>
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<tr>
<td>Hearts with Old Occlusions Only</td>
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<tr>
<td>Total of Hearts with Occlusions</td>
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</table>

(99 per cent) showed intercellular coronary anastomoses (table 4). In these three exceptional instances existing anastomotic pathways may have been blocked by the terminal acute occlusion. This almost invariable occurrence of anastomoses in hearts with old coronary artery occlusions is striking, whether it be compared with the incidence of anastomoses in normal hearts (9 per cent), in hypertrophied hearts (26 per cent), in hearts from patients with anemia (39 per cent), in hearts with marked coronary artery narrowing (55 per cent), or in hearts with recent coronary artery occlusions (74 per cent).

In the 154 hearts with old coronary artery occlusions there were 349 separate points of old occlusion, or over two old occlusions per
even with a normal total heart weight. All these patients had suffered from severe, chronic pulmonary disease. In these 15 hearts the right ventricle measured 5 mm. or more in thickness or was greatly enlarged and dilated. The roentgenogram of the unrolled heart showed clearly the relative size and density of the soft tissue shadows of the right and left ventricles. In this way it provided valuable confirmatory data to the observations made at the autopsy table concerning right ventricular hypertrophy.

Effect of Cor Pulmonale. Anastomoses were present in 11 (73 per cent) of these 15 hearts

<table>
<thead>
<tr>
<th>Table 5.—Incidence of Etiologic Factors in 480 Hearts with Interarterial Coronary Anastomoses</th>
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<tbody>
<tr>
<td>Factor</td>
</tr>
<tr>
<td>Marked Coronary Artery Disease (complete occlusion or marked narrowing)</td>
</tr>
<tr>
<td>Slight to Moderate Coronary Artery Narrowing</td>
</tr>
<tr>
<td>Cardiac Hypertrophy</td>
</tr>
<tr>
<td>Antemortem Anemia</td>
</tr>
<tr>
<td>Valvular Heart Disease</td>
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<tr>
<td>Cor Pulmonale</td>
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<tr>
<td>Grossly Normal Hearts</td>
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(1) their total incidence, whether they occurred alone or in combination, and (2) their individual incidence in hearts with a single, uncomplicated factor. Marked coronary artery disease, cardiac hypertrophy and anemia were the most frequent etiologic factors.

The relative frequency of these factors in hearts with anastomoses reflects not only their etiologic effect in inducing anastomoses, but also their frequency in this particular series of 1050 hearts. The individual efficacy of these factors in inducing anastomoses has already been considered in the presentation of the percentage of hearts with anastomoses in the various groups. Both tabulations indicate the preponderant role of marked coronary artery disease in inducing interarterial coronary anastomoses and the less marked effects of cardiac hypertrophy and anemia.

Grossly Dissectible Anastomoses

Grossly dissectible communicating pathways were found in 94 hearts (20 per cent) of the 480 hearts with anastomoses (table 1); 72 of them occurred in the 275 hearts with coronary artery occlusions. More particularly, they were found in 70 (30 per cent) of the 236 hearts with old coronary artery occlusions and in only two (5 per cent) of the 39 hearts with recent occlusions alone. This latter incidence is lower than the 9 per cent found in the 66 hearts with marked coronary artery narrowing and the 20 per cent found in the 15 hearts with cor pulmonale. Grossly dissectible anastomoses were of a similar low frequency in the remainder of the series, occurring in four (4 per cent) of the 100 hearts with moderate coronary artery narrowing, in two (2 per cent) of the 122 hearts with slight coronary artery narrowing, in three (4 per cent) of the 75 hearts with valvular disease and in four (1 per cent) of the 307 remaining hearts in the series without coronary or valvular disease (table 1).

Myocardial Histopathology

Multiple, individually labeled microscopic sections from precisely localized areas of the myocardium were studied in 509 of the 1050 hearts in this series. These 509 hearts are not consecutive and do not form a representative
sample of the entire group of injected hearts. Nevertheless, certain broad relations between anastomoses and histopathologic changes in the myocardium could be determined. Microscopic abnormalities noted included myocardial degeneration, necrosis, inflammation and fibrosis. Although these lesions varied considerably, qualitatively and quantitatively, in different hearts, they were grouped together and are presented in summary form here insofar as they are pertinent to the problem of coronary artery anastomoses.

As might be expected, few of the grossly normal hearts without hypertrophy, valvular or coronary disease showed histopathologic abnormalities. Nevertheless, like anastomosis, histopathology was significantly more frequent in the anemic hearts than in the nonanemic hearts of this group. In general, a parallel increasing association was found between hypertrophy, valvular and coronary lesions and the presence of histopathology and anastomosis.

Of 319 hearts with histopathology, however, interarterial anastomoses were absent in 98. Conversely, it was of particular interest to find seven hearts without any microscopic myocardial pathology among the 114 with one or more complete old occlusions in which multiple microscopic sections were studied. In each of these instances there were found well-developed, extensive interarterial coronary anastomoses which may have protected the myocardium from the effects of arterial occlusion.

Time Necessary for Development of Anastomoses following Sudden Occlusion of a Coronary Artery

The relatively low incidence (58 per cent) of coronary artery anastomoses directly distal to recent coronary artery occlusions in comparison with the 96 per cent incidence of anastomoses directly distal to old occlusions suggests that the time interval between the occurrence of the recent vascular occlusion and death was insufficient in some instances for the development of compensatory anastomoses. Valuable information concerning the time necessary for the development of collateral circulation might be obtained by relating the age of a recent complete occlusion to the presence or absence of an anastomosis associated with it.

In such a study it would be necessary to know the age and rate of development of the recent occlusion and how much narrowing was present in the vessel before the recent occlusion occurred. Gross observations are too crude to establish these facts. Numerous microscopic sections, preferably serial sections, through each zone of recent occlusion would provide such reliable information, but they were not available in the present series of hearts.

An attempt was made to fix the time of the terminal fresh coronary artery occlusion from the clinical record. As might be expected, however, it was unsuccessful because correlations between major episodes of cardiac pain and coronary artery occlusion are unreliable. Such episodes of pain, even associated with myocardial infarction, may occur without concomitant fresh occlusion in the coronary artery tree and fresh coronary artery occlusions, furthermore, may occur without clinical manifestations.

In this series clearly defined, well-timed clinical episodes appeared in only 73 of the 121 patients dying with recent coronary artery occlusions. Furthermore, most of the 73 also had multiple, prolonged attacks of cardiac pain. Consequently, we were not able in this study to determine the rate of development of coronary interarterial anastomoses in man.

Discussion

A definite, statistically significant relationship has been found between a number of factors and the development of human intercoronary arterial anastomoses. In the absence of these stimulating factors less than 10 per cent of human hearts presented anastomoses. It is also suggested that the incidence of anastomoses in the normal human heart would be still lower if all etiologic factors were known. Thus it is becoming more firmly established that, functionally at least, the coronary arteries in the human heart are end-arteries. It is also clear that, under a variety of stimuli the flexible coronary arterial system readily develops a functioning internal anastomotic collateral circulation to compensate for a
relative insufficiency of blood. Relative insufficiency may originate in the blood itself (anemia), in the aeration of the blood (pulmonary disease), in the myocardium (hypertrophy), in the endocardium (valvular disease) or in the coronary arteries themselves (coronary atherosclerosis).

The previous observation that marked narrowing and complete occlusion of the coronary arteries are most important factors in the production of interarterial coronary anastomoses has been firmly established. Their effectiveness is seen in the high incidence of anastomoses and in the frequency of large, grossly dissectible interarterial pathways under these conditions, as well as the great frequency of marked coronary artery disease in hearts with anastomoses. Slight or moderate coronary artery narrowing is much less effective. The experimental production of intercoronary anastomoses following narrowing and occlusion of the coronary arteries by surgical ligation in pigs and dogs led to similar conclusions concerning these factors. Furthermore, the functional significance of such intercoronary anastomoses was demonstrated experimentally in the prevention of death and the reduction of myocardial damage following complete coronary occlusion.

The detailed histopathologic studies of human hearts with marked narrowing and complete occlusion of the coronary arteries indicate the similar functional importance of such anastomoses in the human heart. The increasing frequency of hearts with myocardial damage with increasing degrees of coronary artery obstruction was anticipated. The few hearts, however, with complete old coronary artery occlusions but without any histopathology in the multiple microscopic sections illustrate pointedly the protective effect of the anastomoses. In these hearts, the development of interarterial coronary anastomoses during gradual coronary artery narrowing must have been so adequate as to prevent organic muscle damage even with final complete occlusion of an artery. These observations find their occasional clinical corollary in the absence of cardiac pain or other symptoms after a proved acute coronary artery occlusion. In these instances, at least, the stimulus for interarterial coronary anastomoses did not lead also to irreversible myocardial damage.

Besides marked coronary artery disease, the factors of hypertrophy and of anemia have each been demonstrated to be associated individually with an increased incidence of intercoronary anastomoses. The addition of cardiac hypertrophy or anemia to other factors did not materially affect the incidence of anastomoses. The absence of a summative effect of several factors was unexpected. It is possible that the underlying fundamental mechanism such as cardiac anoxia is common to all the factors concerned. This mechanism may be activated by any single factor, but is not activated to a greater degree or does not produce a greater effect when stimulated by several factors in combination. Because of the small numbers of hearts available in the various subgroups, a small additive effect might not have been statistically apparent in the present analysis. Furthermore, in any statistical analysis based on the “null hypothesis,” failure to demonstrate “significant” differences does not prove their absence.

The data are inadequate to establish an association of valvular disease per se with increased intercoronary anastomoses, since most of the hearts with valvular disease also showed cardiac hypertrophy. Valvular disease plus cardiac hypertrophy showed the same incidence of anastomoses as hypertrophy alone. Nevertheless, valvular disease alone may be a factor inducing interarterial coronary anastomoses; like anemia and coronary artery disease, an additive effect upon anastomoses may not be demonstrable when it is combined with cardiac hypertrophy.

In half of the 27 hearts with chronic valvular disease in which coronary artery anastomoses were present, there was also marked right ventricular hypertrophy, indistinguishable from that resulting from primary pulmonary disease. In these hearts the mitral valve was usually involved. The development of anastomoses in this group may result from: (1) valvular disease itself, if it is indeed a factor capable of stimulating anastomoses; (2) cardiac anoxia on the basis of diminished oxygenation of the blood from pulmonary insufficiency; or (3) cardiac
hypertrophy with increased need for blood by the enlarged myocardium.

In like manner, the increased intercoronary arterial anastomoses found in cor pulmonale due to pulmonary disease may result from right ventricular hypertrophy or cardiac anoxia secondary to pulmonary insufficiency. These two mechanisms may also be involved in the six “normal” hearts with coronary artery anastomoses but without cardiac hypertrophy which came from patients with marked pulmonary disease, but without anemia. If the mechanisms were more clearly established by which primary pulmonary disease stimulated the development of coronary artery anastomoses, the number of “normal” hearts with unaccountable anastomoses could be reduced to three instead of nine in the series of 1050 hearts. Furthermore, the finding of unexplained myocardial histopathology in a few grossly normal hearts from patients without anemia suggests that the etiologic factors herein considered for the development of coronary artery anastomoses are not complete or definitive.

That anemia might stimulate the development of interarterial coronary anastomoses in otherwise normal hearts might have been anticipated. In 1944, Amadeo38 suggested that the infrequency of clinical coronary disease among the poor rural population of Puerto Rico resulted from the effect of chronic anemia upon the development of collateral anastomotic vessels of the coronary arterial system. In four hearts from patients with anemia, Scott39 found a marked increase in interarterial coronary anastomoses, as demonstrated by injection of the coronary arteries with a barium sulfate suspension in liquid latex.40 In a study of the coronary arteries by Dock’s41 method of perfusion with kerosene, we also found that the rates of flow were greatly increased in four hearts from patients with anemia.40

In the present series the incidence of interarterial coronary anastomoses in “normal human hearts” was reduced from 22 per cent to 9 per cent when the patients with anemia were eliminated from the group of grossly normal hearts. In comparison with this low figure, the incidence of anastomoses in other groups of hearts assumed statistical significance.

Insight into the basic mechanism stimulating intercoronary anastomoses is afforded by the demonstration of the roles of anemia and of cor pulmonale. Relative reduction in oxygen supply to the heart (anoxia) is obviously common to these two conditions. Anoxia is associated also with all the other factors related to increased anastomoses. Accumulation of metabolites, lack of substances other than oxygen or mechanical factors such as differential pressure gradients in different parts of the coronary system consequent to anoxia, may be other mechanisms that are effective in stimulating anastomoses.

The precise site at which the anoxia is the critical stimulus for the development of anastomoses is also a matter of speculation. It may be in the coronary vessels themselves. The relative insufficiency of oxygen results either from reduced blood flow in the presence of coronary artery narrowing and occlusion or from increased demand for blood by the myocardium in cardiac hypertrophy and valvular disease. In anemia and cor pulmonale there may be no reduction in the relative volume of blood flow through the coronary arteries, but there is a reduction in the oxygen content of the blood, resulting from diminished hemoglobin and oxygen capacity in anemia and from diminished oxygen saturation in cor pulmonale.

Intercoronary arterial anastomoses have been found in some instances without myocardial histopathologic changes. Cardiac anoxia of various origins may thus stimulate interarterial coronary anastomoses without necessarily progressing to the stage of irreversible tissue damage. The reverse observations of hearts with myocardial damage but without anastomoses were also made in all categories. Many conditions may thus damage heart muscle irreversibly without necessarily stimulating the development of anastomoses. Nevertheless, in the control group of hearts with no intrinsic gross pathology, myocardial damage was infrequent in comparison with the histopathology found in hearts with hypertrophy, valvular disease and coronary artery disease. These normal microscopic findings add validity to the criteria that were used for the selection of the “normal, control group.”
In this control group there were positive correlations between myocardial damage, anemia and anastomosis. Deleterious effects of anemia on heart muscle have been reported by others. Our observations indicate that anemia per se may or may not produce some myocardial damage and that this potentiality is intimately related to its capacity to stimulate anastomoses.

Anemia differs from most of the other conditions associated with the development of intercoronary anastomoses in that it may be transient and can be voluntarily produced and controlled in man and in laboratory animals. Any desired level of anemia may be reached and maintained by repeated venesections at appropriate intervals. Furthermore, a critical degree of anemia may be found which will stimulate the development of anastomoses and yet will not result in significant myocardial lesions. Anemia might therefore be used as a readily controllable investigative tool in studies pertaining to intercoronary arterial anastomoses.

The data available in the present study do not indicate clearly the duration and severity of the anemia that is necessary to stimulate anastomoses. Anemia of less than six days' duration appears to be without such effect and marked degrees of anemia seem no more effective than moderate anemia. The question also remains unanswered whether the newly developed interarterial coronary anastomoses are permanent or whether they disappear if the stimulus provoking them is withdrawn. Amadeo came to similar conclusions about the degree of anemia. He also assumed that intercoronary anastomoses produced during the period of neonatal anemia persist throughout life.

Anemia may conceivably have some therapeutic application in the treatment of coronary artery disease. The presence of anemia for six months before death in five of the seven patients whose heart muscle was entirely normal histologically despite old complete coronary artery occlusions suggests that pre-existing anastomoses produced by the anemia may have helped protect the muscle completely against the effects of the severe coronary artery disease. The old occlusions in these patients did not produce clinical manifestations, however, so that their temporal relation with the anemia could not be determined. It would theoretically be desirable to produce intercoronary anastomoses before the onset of coronary artery narrowing or occlusion; coronary atherosclerosis would be much less disastrous if the coronary arteries were not originally functional end arteries. The possibly favorable effects of anemia on the coronary circulation in experimental animals are now under investigation in this laboratory.

It is a plausible assumption that the condition (anoxia) which stimulates the formation of coronary artery anastomoses also produces the microscopic myocardial abnormalities that are frequently found in the same hearts. On this basis, interarterial coronary anastomosis may also be regarded as an organic abnormality, especially since it is so infrequent in normal hearts. The functional and organic abnormalities of anemia, chronic pulmonary disease, cardiac hypertrophy, valvular heart disease and coronary artery disease then may be regarded as etiologic factors in the genesis of physiologic states of relative myocardial anoxia, and thereby, of the two anatomic abnormalities of anastomoses and myocardial histopathology. The latter two abnormalities tend to appear together in the same heart but are not necessarily directly interrelated. The development of the organic abnormality of coronary artery anastomosis is a compensatory response to these etiologic conditions. In some instances it is sufficiently protective to forestall or diminish the development of the less desirable organic abnormality of myocardial damage. These assumptions are supported by our data not only in the large group with coronary artery disease where they might be considered axiomatic, but in every category discussed above.

Conclusions

In a series of 1050 human hearts studied by a method of injection plus dissection of the coronary arteries, increased interarterial coronary anastomoses were found in coronary heart disease, cor pulmonale, antemortem anemia, cardiac hypertrophy and valvular heart disease. In 101 grossly normal hearts from nonanemic
patients the incidence of interarterial coronary anastomoses was 9 per cent.

In 89 grossly normal hearts from anemic patients the incidence of anastomoses was 39 per cent.

In the remaining abnormal hearts the incidence of interarterial coronary anastomoses was 89 to 100 per cent with coronary artery occlusion, 11 to 63 per cent with coronary artery narrowing, 73 per cent with cor pulmonale, 26 per cent with cardiac hypertrophy and 28 per cent with valvular disease.

The factor of relative cardiac anoxia that is present in all these conditions appears to be a common underlying stimulus for the development of interarterial coronary anastomoses.

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Interarterial Coronary Anastomoses in the Human Heart, with Particular Reference to Anemia and Relative Cardiac Anoxia

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