Graded Pulmonary Vascular Changes and Hemodynamic Findings in Cases of Atrial and Ventricular Septal Defect and Patent Ductus Arteriosus

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With use of a previously described system of grading, a study was made of the relation between each of the grades of hypertensive pulmonary vascular disease and the hemodynamic findings in the lesser circulation in 15 cases of atrial septal defect, 19 cases of ventricular septal defect, and 6 cases of patent ductus arteriosus.

In a previous paper, histologic grades of hypertensive pulmonary vascular disease were defined on the basis of study of 67 cases of congenital septal defect of the heart and 2 cases of idiopathic pulmonary hypertension. In 40 of these 67 cases of atrial or ventricular septal defect or patent ductus arteriosus, detailed physiologic studies had been carried out. These data are now employed to demonstrate the relation of each grade of the suggested pathologic classification to the level of pulmonary arterial blood pressure and flow and to age. In many instances the physiologic data were obtained while the patient was breathing air and 100 per cent oxygen respectively. Similar data from 3 cases of idiopathic pulmonary hypertension, 2 of which were included in the previous paper, are included for purposes of comparison.

Methods and Material

Forty cases were studied and these were subdivided into 2 groups according to the type of septal defect present.

The first group consisted of 15 patients with interatrial communication (cases 1 to 15). Their ages ranged from 10 to 55 years. Patients 1 to 8 had an atrial septal defect of the foramen ovale type as the sole congenital defect. Patients 9 to 12 had a partial anomalous pulmonary venous connection in association with an atrial septal defect, usually located in the upper part of the atrial septum, as described by Swan and associates. Patients 13 and 14 each had a partial common atrioventricular canal (that is, with no interventricular communication). Patient 15 had an unusual form of atrial septal defect in which the evidence indicated that the pulmonary hypertension had been present from birth. The age, sex, diagnosis, and grade of hypertensive pulmonary vascular diseases of each of these patients are shown in table 1.

The second group consisted of 25 patients with congenital heart disease characterized by a large interventricular communication (cases 16 to 20 and 22 to 35) or a wide patent ductus arteriosus (cases 36 to 41). The ages of the patients in this group ranged from 10 months to 46 years. The age, sex, additional malformations, and grade of hypertensive pulmonary vascular disease of each of these patients are shown in table 2. In only 1 patient (case 17) was pulmonary stenosis present, and it was of mild degree.

No patients with congenital or acquired mitral stenosis were studied, but 3 additional patients with idiopathic pulmonary hypertension (cases 42 to 44) were included for purposes of comparison.

The physiologic data were obtained by catheterization of the right chambers of the heart and the pulmonary arteries, and by puncture of systemic arteries. The blood pressures and the data on oxygen saturation in the pulmonary and radial arteries, together with the oxygen consumption in cubic centimeters per minute, were measured while
the patient was at rest and while breathing air and, in most instances, 100 per cent oxygen. In some instances only air or oxygen inhalation was employed (for example, cases 17 to 20). These data were used to calculate the pulmonary blood flow, the total pulmonary resistance, and the percentage intracardiac shunts in both directions.

Blood Pressure in Pulmonary Artery. The mean and systolic blood pressures in the pulmonary and radial arteries for each of the cases included in groups 1 and 2 are shown in tables 1 and 2 respectively. Normal values for pulmonary-artery blood pressure in millimeters of mercury were considered to be systolic 22, and diastolic 12. The mean blood pressure in the pulmonary artery was calculated by adding the diastolic pressure to one third of the pulse pressure, giving a normal value of 15 mm. Hg.

Pulmonary Blood Flow. The total pulmonary and systemic blood flows in liters per minute were calculated from the oxygen consumption and the arteriovenous oxygen difference in each of the 2 circulations, according to the following formula based on the Fick principle:

\[
\frac{O_2 \text{ consumption (ml./min.)}}{O_2 \text{ content in artery} - O_2 \text{ content in vein (vol. %)}} \times 10
\]

To allow for the different sizes of the patients and obtain comparable values for pulmonary blood flow we used the pulmonary index of blood flow:

\[
\text{Total pulmonary blood flow in L./min.} = \frac{\text{Total pulmonary blood flow}}{\text{Surface area in } M^2}\]

We regarded the normal pulmonary index of flow as being in the range of 2.5 to 4.4 L./min./M.². (See reference 3.)
Pulmonary Resistance. Total resistances in the pulmonary and systemic circulations were calculated in dynes/sec./cm.\(^{-5}\) according to the formula:

\[
\text{Mean arterial pressure (mm. Hg)} \times \left( \frac{1,332 \times 60}{1,000} \right)
\]

Arteriolar resistance was not calculated.

We regarded the normal total pulmonary resistance in older children and adults as being in the range of 90 to 300 dynes/sec./cm.\(^{-5}\), with a mean value of 200 dynes/sec./cm.\(^{-5}\), and the normal systemic resistance as being in the range of 750 to 1,600 dynes/sec./cm.\(^{-5}\), with a mean value of 1,200 dynes/sec./cm.\(^{-5}\). These mean values give a normal ratio of pulmonary to systemic resistance of 0.16.

Shunts Through the Congenital Defect. Percentage left-to-right and right-to-left shunts were calculated from the oxygen saturations\(^4\) in the pulmonary artery (Spa), pulmonary vein (Spv), radial artery (Sa), and systemic veins (Sv) according to formulas:

\[
\begin{align*}
\text{Percentage left-to-right shunt} &= \frac{\text{Spa} - \text{Sv}}{\text{Spv} - \text{Sv}} \times 100 \\
\text{Percentage right-to-left shunt} &= \frac{\text{Spv} - \text{Sa}}{\text{Spv} - \text{Sv}} \times 100
\end{align*}
\]

Results

Results in Group 1 Cases (Interatrial Communication). Figure 1 shows the relation between grade of hypertensive pulmonary vascular disease and age. In the cases of interatrial communication, grade 1 lesions were found alike in children (case 9) and adults more than 40 years of age (cases 1 to 4). No patient, however, with vascular changes included in the range of grades 2 to 6 was less than 25 years of age (cases 6 to 8, 10 to 13, 5 and 15). In those patients, usually more than 25 years of age, in whom pulmonary hypertension was found, structural changes were present in the pulmonary arteries. The lack of an obvious relation between age and grade of hypertensive pulmonary vascular disease in this group may well indicate that the duration of the elevated blood pressure in the pulmonary artery is not determined by the patient's age alone in interatrial communication.

Figures 2 and 3 show the relation between grade of hypertensive pulmonary vascular disease and pulmonary resistance. In the patients with interatrial communication there was a relation between the level of total pulmonary vascular resistance and the grade of structural changes in the pulmonary arteries. In 5 of the 6 patients with grade 1 lesions (cases 1 to 4, and 9) the resistance was normal at 200 dynes/sec./cm.\(^{-5}\) or less, and in the sixth (case 14) it was 400 dynes/sec./cm.\(^{-5}\). In patients with grade 3 lesions (cases 6 and 7) the resistance was 700 dynes/sec./
TABLE 2.—Group 2 Cases. Grade of Hypertensive Pulmonary Vascular Disease and Blood Pressures in 19 Cases of Large Interventricular Communication and 6 Cases of Widely Patent Ductus Arteriosus

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Sex, age (years)</th>
<th>HPVD (grade)</th>
<th>Associated anomaly*</th>
<th>Arterial blood pressure in mm. Hg</th>
<th>Pulmonary</th>
<th>Systolic</th>
<th>Radial</th>
<th>Systolic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean</td>
<td>Air</td>
<td>100% O₂</td>
<td>Mean</td>
<td>Air</td>
</tr>
</tbody>
</table>
| Large interventricular communication
| 16 M2    | 2 O             | 34 — 82      | 66 — 89             |       |       |        |       |       |        |       |       |        |       |
| 17 F22   | 1 PS            | 44 — 63      | 89 — 116            |       |       |        |       |       |        |       |       |        |       |
| 18 M1½   | 1 O             | 45 — 69      | 57 — 88             |       |       |        |       |       |        |       |       |        |       |
| 19 M10/12| 1 ASD           | 48 — 85      | 60 — 91             |       |       |        |       |       |        |       |       |        |       |
| 20 F1    | 1 ASD           | 48 — 78      | — 55 — 76           |       |       |        |       |       |        |       |       |        |       |
| 22 F5    | 3 MI            | 53 — 73      | 48 — 72             | 74 — 100 | 97    |        |       |       |        |       |       |        |       |
| 23 M15/12| 3 O             | 54 — 76      | — —                 |       |       |        |       |       |        |       |       |        |       |
| 24 F15   | 1 MI            | 56 — 85      | 75 — 97             | 74 — 100 | 96    |        |       |       |        |       |       |        |       |
| 25 F10   | 1 O             | 64 — 89      | 74 — 96             | 74 — 100 | 96    |        |       |       |        |       |       |        |       |
| 26 M2    | 2 PDA           | 66 — 91      | 63 — 89             | 67 — 105 | 78    |        |       |       |        |       |       |        |       |
| 27 M3½   | 3 AVC           | 66 — 87      | 67 — 78             | 67 — 105 | 78    |        |       |       |        |       |       |        |       |
| 28 M1½   | 2 AVC           | 66 — 89      | 68 — 122            | 68 — 105 | 90    |        |       |       |        |       |       |        |       |
| 29 F11   | 1 O             | 69 — 98      | 77 — 101            | 77 — 105 | 94    |        |       |       |        |       |       |        |       |
| 30 F21   | 3 O             | 70 — 115     | 79 — 115            | 79 — 105 | 90    |        |       |       |        |       |       |        |       |
| 31 M13   | 1 T             | 70 — 100     | 77 — 114            | 77 — 105 | 109   |        |       |       |        |       |       |        |       |
| 32 F23   | 3 O             | 73 — 120     | 79 — 110            | 79 — 110 | 110   |        |       |       |        |       |       |        |       |
| 33 M24   | 3 O             | 73 — 108     | 81 — 117            | 81 — 117 | 119   |        |       |       |        |       |       |        |       |
| 34 F37   | 2 ASD           | 75 — 140     | 75 — 118            | 75 — 118 | 135   |        |       |       |        |       |       |        |       |
| 35 F17   | 5 O             | 87 — 127     | 100 — 159           | 100 — 159 | 158   |        |       |       |        |       |       |        |       |
| Widely patent ductus arteriosus
| 36 M21   | 5 O             | 48† — 129$    | 92 — 117            |       |       |        |       |       |        |       |       |        |       |
| 37 M5    | 2 C             | — 70         | — 58 — 67           |       |       |        |       |       |        |       |       |        |       |
| 38 F10   | 3 O             | 76 — 101     | 77 — 105            | 77 — 105 | 67    |        |       |       |        |       |       |        |       |
| 39 F20   | 5 O             | 81 — 106     | 73 — 99             | 73 — 99 | 100   |        |       |       |        |       |       |        |       |
| 40 F34   | 5 O             | 84 — 109     | 88 — 115            | 88 — 115 | 118   |        |       |       |        |       |       |        |       |
| 41 F46   | 5 C (mild)      | 102 — 145    | 91 — 145            | 91 — 145 | 151   |        |       |       |        |       |       |        |       |

*O, none; ASD, atrial septal defect; PS, mild pulmonary stenosis; PDA, patent ductus arteriosus; C, coarctation of aorta; T, corrected transposition of great vessels; AVC, common atrioventricular canal; MI, mitral incompetence.
†Aortic blood pressure.
‡Right ventricular blood pressure.

There was no obvious relation between the grade of hypertensive pulmonary vascular disease and the degree of fall in total pulmonary resistance on breathing of 100 per cent oxygen. Patient 7 with grade 3 lesions showed a substantial fall in total pulmonary resistance on inhalation of 100 per cent oxygen, whereas patients 10 and 12 with grade 4 lesions showed no fall. However, patients 5, 11, and 15, with the severest grades of structural change (grades 5 and 6), showed falls in total pul-

1 cm.², and in patient 15 with grade 6 lesions it was 2,900 dynes/sec./cm.², all the figures quoted so far being obtained while the patients were breathing air. While, for the group as a whole, the total pulmonary resistance tended to rise with progressive vascular changes, there was variation in any one group of similar grade of structural change. Thus, 2 patients with grade 4 lesions had a resistance of 300 dynes/sec./cm.² (case 10) and 800 dynes/sec./cm.² (case 12) respectively.
monary resistance on inhalation of oxygen. In patients 7, 10, and 11, with grade 3, 4, and 5 lesions respectively, the residual resistance after inhalation of oxygen was 400 dynes/sec./cm.\(^{-5}\) or less. In patients 5 and 12, with grade 5 and 4 lesions respectively, the total pulmonary resistance was 750 dynes/sec./cm.\(^{-5}\) or more on inhalation of 100 per cent oxygen. In patient 15, with grade 6 lesions, the residual total pulmonary resistance was 2,300 dynes/sec./cm.\(^{-5}\) after inhalation of oxygen.

These data suggest that the total pulmonary resistance in these cases was compounded of 2 elements, one with a functional, and the other an organic basis. The functional element, defined here as being that part of the total pulmonary resistance removed completely or partially on the inhalation of 100 per cent oxygen, was of major importance in grade 3 lesions and was still present in some patients with grade 4 and 5 lesions. However, in the severest grades, even after administration of 100 per cent oxygen there was still a residual resistance which wholly or in part probably had its basis in organic changes in the pulmonary arteries. By expressing the total pulmonary resistance as a ratio of the systemic vascular resistance and plotting the ratio obtained against the grade of hypertensive pulmonary vascular disease (fig. 3) it is shown that, while breathing air, patients with grade 1 or grade 2 lesions had a ratio of 0.3 or less, whereas those with severest structural changes had a ratio of 0.4 or more in most instances. This ratio is of questionable functional significance, however, in patients with interatrial communication, since the lesser and systemic circulations are not directly connected to a common pumping chamber, as in large ventricular septal defect.

Figure 4 shows the relation between grade of hypertensive pulmonary vascular disease and pulmonary blood flow. In patients with grade 1 lesions the lowest pulmonary flow found was 6.0 L./min./M.\(^2\); this is an abnormally high figure, for the highest value in the range of normal is 4.4 L./min./M.\(^2\). (See reference 3.) In patients with grade 2, 3 and 4 structural changes, the pulmonary flow was still higher than normal or at the upper limit of normal. In the 3 patients with grade 5 lesions, patient 11 had a pulmonary flow at the upper range of normal, patient 5 had a flow in the normal range, and patient 13 had an abnormally low flow. The patient with grade 6 lesions (case 15) had an abnormally low flow. Figure 4 demonstrates the inverse relationship between pulmonary blood flow and rising grades of vascular change.
When the patients inhaled 100 per cent oxygen, there was frequently a rise in the pulmonary blood flow in patients with vascular lesions in the range of grades 1 to 3 (cases 3, 14, 8, and 7). This occurred only exceptionally in patients with a more severe degree of vascular change (case 11), for in grades 4 to 6 there was little or no change in the level of pulmonary flow after inhalation of oxygen (cases 10, 12, 5, and 15).

Figure 5 shows the relation between grade of hypertensive pulmonary vascular disease and percentage of blood shunted in each direction through atrial septal defect. These data show a close relation between the direction and magnitude of shunts through the interatrial communication and the severity of structural changes in the pulmonary arteries in any one case of atrial septal defect.

The patients who had interatrial communication with grade 1 and 2 lesions had large left-to-right shunts and little or no shunting of blood from right to left through the interatrial communication. Of the 2 patients with grade 4 lesions, one (case 10) had a large left-to-right shunt and no reversed shunt, but the other had bidirectional shunts. In the 3 patients with grade 5 lesions (cases 5, 11, and 13) and the patient with grade 6 lesions (case 15), the right-to-left shunt was appreciable. While 2 of these patients (cases 5 and 11) also had demonstrable left-to-right shunts, the others (cases 13 and 15) did not. Patient 7 with grade 3 lesions behaved in an exceptional manner in having not only a left-to-right shunt but also a large right-to-left shunt more commensurate with severer grades of hypertensive pulmonary vascular disease.

On the inhalation of 100 per cent oxygen there was in general a slight increase in the magnitude of the left-to-right shunt and, in the patients with the higher grades of vascular change, a considerable decrease in the magnitude of the reversed shunt (cases 7, 5, 11, and 13). Case 12 was an exception in this respect.

Figure 6 shows the relation between grade of hypertensive pulmonary vascular disease and mean blood pressure in pulmonary artery. There was a close relation between the grade of structural change and the level of the mean blood pressure in the pulmonary artery. In 5 of the 6 patients with grade 1 lesions (cases 1 to 4, and 9) the mean blood pressure was less than 35 mm. Hg. In the sixth (case 14) it was 48 mm. In all the patients with grade 2 to 6 lesions the mean blood pressure in the pulmonary artery exceeded 45 mm. Hg; these form a group that is distinct from those with grade 1 changes, with the exception of case 14. In this respect, case 14 holds an intermediate position and probably represents a transitional stage.

Some patients with severe vascular change maintained a mean pulmonary-artery blood pressure in the region of 50 mm. Hg (cases 5, 10, and 11). Others showed a higher mean pulmonary-artery blood pressure commensurate with the anatomic changes in the pulmonary arteries (cases 7, 12, 13, and 15). Little change in this mean blood pressure was noted on the inhalation of 100 per cent oxygen.

Results in Group 2 Cases (Interventricular Communication or Widely Patent Ductus Arteriosus). Figure 7 shows the relation between grade of hypertensive pulmonary vascular disease and age. In contrast to the
GRADED PULMONARY VASCULAR CHANGES

Fig. 6 Left. Group 1 cases. Relation between grade of hypertensive pulmonary vascular disease (HPVD) and mean blood pressure in pulmonary artery.

Fig. 7 Right. Group 2 cases. Relation between grade of hypertensive pulmonary vascular disease (HPVD) and age. No patients in group 2 had grade 4 lesions.

observations with respect to atrial septal defect, there was a close relation between age and the severity of the structural changes in pulmonary hypertension in patients with a large ventricular septal defect or patent ductus arteriosus. Eleven of the 13 patients with cardiac septal defects and grade 1 or grade 2 lesions were 15 years of age or less, whereas 8 of the 12 patients with septal defects and grade 3 to 5 lesions were older than this age. The oldest patient who had grade 1 lesions, except patient 17 who had associated pulmonary stenosis, was 15 years of age (case 24). Patients 22, 23, and 27 had grade 3 lesions by the age of 5 years.

In patients with large interventricular communication or widely patent ductus the systemic pulse pressure is freely propagated into the lesser circulation from birth. Hence the age of the patient is synonymous with the duration of the pulmonary hypertension. Exceptions to this general trend in ventricular septal defect occur when the size of the abnormal communication is below a certain critical level or when there is an associated pulmonary stenosis (case 17), as either the small defect or a stenotic pulmonary valve exerts resistance to the propagation of the systemic pulse pressure and flow into the pulmonary arteries. In illustration of this point, patient 27 had a common atrioventricular canal with free subvalvular communication and with a mean pulmonary-artery blood pressure of 66 mm. Hg and grade 3 pulmonary vascular lesions at the age of only 3½ years. In contrast, patient 17 had only grade 1 lesions by the age of 22 years; this is explained by the presence of an associated mild pulmonary stenosis and a mean pulmonary-artery blood pressure of only 44 mm. Hg.

Figure 8 shows the relation between grade of hypertensive pulmonary vascular disease and total pulmonary resistance. In view of their small size, infants have a high total pulmonary resistance no matter what grade of structural change is present in the pulmonary arteries. If we eliminate some of the patients 2 years of age or younger from figure 8 (cases 26, 20, 18, 19), we find that 11 of the remaining 15 patients with vascular changes included in the range of grade 1 to 3 lesions had a total pulmonary resistance of less than 700 dynes/sec./cm.-5. On the other hand, all 4 patients with grade 5 lesions (cases 35, 39, 40, and 41) and 1 patient with grade 3 lesions (case 22) had a total pulmonary resistance exceeding 1,450 dynes/sec./cm.-5. Hence, with infants excluded, the total pulmonary vascular resistance in patients with grade 5 lesions or severe grade 3 lesions was roughly double that found in patients with grade 1 to 3 hypertensive pulmonary vascular disease.

On inhalation of 100 per cent oxygen, in-
fants excluded again, there was a substantial fall in the total pulmonary resistance so that it was at or below 650 dynes/sec./cm.\(^{-5}\) in all patients with grade 1 to 3 lesions except patient 37. In patient 22, for instance, the total resistance fell from 1,750 to 500 dynes/sec./cm.\(^{-5}\). On the other hand, in all 3 patients with grade 5 lesions in whom the total pulmonary resistance had been measured while the patients were breathing air and 100 per cent oxygen respectively, the resistance did not fall below 1,100 dynes/sec./cm.\(^{-5}\).

In infants in our series the total pulmonary resistance was high, exceeding 1,100 dynes/sec./cm.\(^{-5}\). Similar values for resistance were found in older patients with grade 5 hypertensive pulmonary vascular disease during the inhalation of air and 100 per cent oxygen. In patients with grade 1 and 3 lesions the total pulmonary resistance was usually less than 700 dynes/sec./cm.\(^{-5}\).

By expressing total pulmonary resistance as a ratio of total systemic resistance and plotting the ratio obtained in each case against the grade of hypertensive pulmonary vascular disease present in that case (fig. 9), a gradual rise is seen in the ratio commensurate with the progression of anatomic changes in the pulmonary arteries. This rise is more apparent if the patients under the age of 2 years are excluded. For the patients on whom sufficient data were obtained to allow calculation of the ratio it is apparent that, with the exceptions of patients 22 and 38, and infants, during the inhalation of air, the ratio was 0.7 or less in those patients with grade 1 to 3 lesions. In patients with grade 5

**Fig. 8.** Group 2 cases. Relation between grade of hypertensive pulmonary vascular disease (HPVD) and total pulmonary resistance.

**Fig. 9.** Left. Group 2 cases. Relation between grade of hypertensive pulmonary vascular disease (HPVD) and ratio of total pulmonary resistance to total systemic resistance.

**Fig. 10.** Right. Group 2 cases. Relation between grade of hypertensive pulmonary vascular disease (HPVD) and pulmonary blood flow.
lesions the ratio was 0.9 or above; that is, the total pulmonary resistance approached, equalled, or exceeded the total systemic resistance. On the inhalation of 100 per cent oxygen, there was a substantial fall in the ratio of the pulmonary to the systemic resistance, no matter what grade of hypertensive pulmonary vascular disease was present, but it did not fall below 0.5 in the patients with grade 5 lesions.

Figure 10 shows the relation between grade of hypertensive pulmonary vascular disease and pulmonary blood flow. The relation between these 2 factors is the same as that noted in the cases of interatrial communication. All but 3 of the 20 patients with interventricular communication or widely patent ductus arteriosus who had grade 1 to 3 structural changes in their pulmonary arteries had a pulmonary blood flow that exceeded 5 L./min./M.². In other words, all but 3 (cases 22, 23, and 38) had abnormally high pulmonary flows. The 3 exceptions and 2 of the patients with grade 5 lesions (cases 35 and 40) had pulmonary flows within the normal range of 2.5 to 4.4 L./min./M.². (See reference 3.) The other 3 patients with grade 5 lesions (cases 36, 39, and 41) had abnormally low pulmonary flows, that is less than 2.5 L./min./M.². It was in the patients with the more severe forms of grade 3 lesions, where vascular dilatation was associated with vascular obstruction, that the pulmonary flow was at normal and below normal levels.

When the patients breathed 100 per cent oxygen, there was in most instances a rise in the pulmonary blood flow in patients with vascular lesions in the range of grades 1 to 3. In patients with grade 5 hypertensive pulmonary vascular disease there was either little (cases 35, 39, and 40) or no (case 36) increase in pulmonary flow.

Figure 11 shows the relation between grade of hypertensive pulmonary vascular disease and percentage of blood shunted in each direction through ventricular septal defect or patent ductus arteriosus.

Fig. 11 Top. Group 2 cases. Relation between grade of hypertensive pulmonary vascular disease (HPVD) and percentage of blood shunted in each direction through ventricular septal defect or patent ductus arteriosus.

Fig. 12 Bottom. Group 2 cases. Relation between grade of hypertensive pulmonary vascular disease (HPVD) and mean blood pressure in pulmonary artery.

large left-to-right shunts (not so large, however, as in the patients with atrial septal defect) that increased on the inhalation of 100 per cent oxygen. Some had small right-to-left shunts that disappeared on the inhalation of 100 per cent oxygen. In 2 instances (cases 20 and 28) there was right-to-left shunt that exceeded 10 per cent even when oxygen was breathed; in each instance there was a huge left-to-right shunt that equaled or exceeded 75 per cent.

Although patient 35 (with grade 5 vascular changes) had a large left-to-right shunt on breathing 100 per cent oxygen, and patient 40 had a moderate left-to-right shunt while
breathing either air or oxygen, most patients with the severe grades of structural change had predominantly right-to-left shunts. In case 36, for instance, there was a right-to-left shunt of 60 per cent when the patient was breathing either air or 100 per cent oxygen.

Figure 12 shows the relation between grade of hypertensive pulmonary vascular disease and mean pulmonary-artery blood pressure. A range of 44 to 70 mm. Hg in the mean blood pressure in the pulmonary artery was found in association with grade 1 changes. The development of intimal fibrosis (grade 3 changes) was associated with but slight increase in the mean blood pressure in the pulmonary arteries, for the range found was 53 to 76 mm. Hg. However, in patients with generalized and localized "dilatation (grade 5) lesions," the mean blood pressure in the pulmonary artery was increased to the range of 81 to 102 mm. Hg.

These data suggest that the presence of hypertrophied pulmonary arteries and arterioles is associated with a range of mean pulmonary-artery blood pressure that is maintained but not increased much while progression to severe intimal fibrosis occurs. The stage of obstructive lesions that become associated with vascular dilatation is seemingly associated with a further rise in mean blood pressure in the pulmonary artery.

Results in Three Cases of Idiopathic Pulmonary Hypertension (Tables 3 to 5). Three patients with idiopathic pulmonary hypertension (cases 42 to 44) were studied for purposes of comparison. All 3 patients had severe grades of hypertensive pulmonary vascular disease; patient 42 had grade 3 lesions and patients 43 and 44 had grade 5 lesions. All had severe pulmonary hypertension, which showed little or no change on the inhalation of 100 per cent oxygen (table 3). In all, the total pulmonary resistance was high, exceeding 1,300 dynes/sec./cm.², and this resistance either remained unchanged (cases 42 and 43) or rose slightly (case 44) on inhalation of oxygen (table 4). The ratio of the pulmonary to the systemic resistance was 0.6 or more in each instance. The pulmonary blood flow was abnormally low in all cases, and fell when the patients breathed 100 per cent oxygen (table 5).

COMMENT

In general, patients¹ with ventricular septal defect who have structural changes in the pulmonary arteries designated as lying in the range of grades 1 to 3 have a moderately elevated pulmonary resistance, pulmonary hypertension, usually an abnormally high pulmonary blood flow, and a predominantly left-to-right intracardiac shunt. Patients with atrial septal defect and the form of grade 1 changes associated with this disease may have normal pulmonary resistance and normal pulmonary-artery blood pressure. Further studies referred to in the foregoing¹ indicate that these patients have pulmonary hypertension that is largely reversible on closure of the septal defect. Application of some of the present data in a previous study⁶ suggests that pulmonary arteries showing grade 1, grade 2, and early grade 3 lesions might be considered as forming a "high-resistance high-reserve type of vascular bed." In this type of vascular bed with grade 1 to 3 lesions, the reversible component of the pulmonary hypertension is characteristic.

### Table 3.—Grade of Hypertensive Pulmonary Vascular Disease and Blood Pressures in 3 Cases of Idiopathic Pulmonary Hypertension

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Sex, age (years)</th>
<th>HPVD (grade)</th>
<th>Arterial blood pressure in mm. Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pulmonary</td>
</tr>
<tr>
<td></td>
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<td>Mean</td>
</tr>
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<td></td>
<td></td>
<td>Air 100% O₂</td>
</tr>
<tr>
<td>42</td>
<td>M31</td>
<td>3</td>
<td>54</td>
</tr>
<tr>
<td>43</td>
<td>F30</td>
<td>5</td>
<td>66</td>
</tr>
<tr>
<td>44</td>
<td>M23</td>
<td>5</td>
<td>70</td>
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</table>
TABLE 4.—Grade of Hypertensive Pulmonary Vascular Disease and Vascular Resistance in 3 Cases of Idiopathic Pulmonary Hypertension

<table>
<thead>
<tr>
<th>Case no.</th>
<th>HPVD (grade)</th>
<th>Total pulmonary resistance*</th>
<th>Ratio of pulmonary to systemic resistance†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Air 100% O₂</td>
<td>1,350 1,400</td>
</tr>
<tr>
<td>42</td>
<td>3</td>
<td>1,550 1,550</td>
<td>0.7 0.6</td>
</tr>
<tr>
<td>43</td>
<td>5</td>
<td>1,300 1,500</td>
<td>0.9 0.7</td>
</tr>
</tbody>
</table>

*To nearest 50 dynes/sec./cm.²
†To nearest 0.05

The onset of generalized vascular dilatation in the late stage of grade 3 lesions with the subsequent appearance of complex, localized “dilatation lesions” in grade 4, appears to represent an important transitional stage (described previously as the “transitional type of vascular bed”) in the progression of hypertensive pulmonary vascular disease. This stage progresses to that of the grade 5 and 6 lesions, previously termed the high-resistance low-reserve type of vascular bed, in which the pulmonary vasculature appears to become fixed, the pulmonary vascular resistance is grossly elevated, and the pulmonary blood flow is low. This vascular bed is no longer labile, having a predominantly organic basis of structural changes in the pulmonary arteries. The present results show that patients with septal defects of the heart and grade 5 structural changes in the pulmonary arteries have a very high total pulmonary resistance, an abnormally low pulmonary blood flow, and an intracardiac shunt that is predominantly from right to left. Further studies at the time of cardiotomy, which are reported elsewhere, also suggest that patients with grade 5 structural changes in the pulmonary vasculature have irreversible pulmonary hypertension that is on a predominantly organic basis.

Our concept of the progression of vascular occlusion, with associated progressive elevation of pulmonary resistance, diminution of pulmonary blood flow and development of irreversible pulmonary hypertension, depends on the present data, which are derived from isolated cardiac catheterizations in a large number of different patients. It is supported by the finding of a progressive rise in pulmonary vascular resistance in 2 patients with atrial septal defect, each having undergone cardiac catheterization on 3 occasions over a period of 7 years. Furthermore, in regard to ventricular septal defect it is in accord with the description by Dammann and Ferencz of 3 different clinical phases, dependent upon an excessive, a controlled, and a reduced pulmonary blood flow, which together form a characteristic life cycle in patients with malformations of the heart associated with a common ejective force.

Summary

Studies are presented from 15 cases of atrial septal defect, 19 cases of ventricular septal defect, and 6 cases of patent ductus arteriosus, consisting of results of cardiac catheterization correlated with graded changes in the pulmonary arterial system, obtained by histologic study. From the correlations it is concluded that the grading system is valid as an estimate of those factors which determine the type of resistance to flow through the pulmonary vascular bed, if it is realized that in the very young the normal pulmonary bed has a high resistance.

Grades 1 to 3 indicate a vascular bed which, though it may maintain a moderately high resistance, is labile. Grades 5 and 6 indicate a vascular bed that maintains a high resistance and that is no longer labile. Grade 4 seems to represent a transitional stage between these 2 types of vascular beds.

Summario in Interlingua

Es presentate le resultatos de studios in 15 casos de defecto del septo atrial, in 19 casos de
defecto del septo ventricular, en 6 casos de patente ducto arterioso. Datos obtenidos per catheterismo cardiac es correlationate con le grados del alteration in le sistema de arterias pulmonar secondo studio histologic. Le correlation permette le conclusion que le sistema de grados es valide in le estimation del factores que determina le typo de resistentia al fluxo in le vasculatura pulmonar, provide que on prende in consideration que le normal vasculatura pulmonar in subjectos de molto bause etate; es characterisate per un alte resistantia.

Grados 1, 2, e 3 indica un vasculatura que es labile ben que il es possibile que ilo mantene moderatamente alte nivello de resistentia. Grados 5 e 6 indica un vasculatura que mantene un alte nivello de resistantia sed que ha cessate esser labile. Grado 4 pare representar un stadio de transition inter le 2 typos mentionate de vasculatura.

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BEING TRUE TO ONE'S CONVICTIONS

Thomas H. Huxley

English biologist, 1825-1895

Graded Pulmonary Vascular Changes and Hemodynamic Findings in Cases of Atrial and Ventricular Septal Defect and Patent Ductus Arteriosus
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