The Syndrome of Patent Ductus Arteriosus with Pulmonary Hypertension

By Herbert Hultgren, M.D., Arthur Selzer, M.D., Ann Purdy, M.D., Emile Holman, M.D., and Frank Gerbode, M.D.

Eight cases of patent ductus arteriosus associated with marked pulmonary hypertension are presented with complete cardiac catheterization studies in six patients and autopsy studies in three cases. Four patients had clear evidence of a "reversed" shunt through the ductus, three presenting the clinical picture of cyanotic congenital heart disease. The authors discuss the nature of the increased resistance of the pulmonary vascular bed which is the basis of the circulatory changes in these cases.

The usual uncomplicated patent ductus arteriosus presents a fairly constant clinical picture with the following diagnostic features usually present: (1) a continuous murmur in the pulmonic area; (2) an increased pulse pressure; (3) an electrocardiogram without evidence of right ventricular hypertrophy; (4) absence of cyanosis; (5) x-ray evidence of left ventricular dilatation with dilatation and active pulsation of the pulmonary arteries.

In most instances an accurate diagnosis can be made by ordinary clinical methods of study and only rarely is cardiac catheterization or angiocardiography necessary. Occasionally, however, these characteristic features may be absent and accurate diagnosis may then be more difficult. This may occur in infancy and more rarely in older children and adults. The absence of a continuous murmur in infancy may be physiologic and related to the decrease in the pressure gradient between the pulmonary artery and the aorta that is present at that time. As the child becomes older the continuous character of the murmur usually appears and the correct diagnosis can then be made. Ziegler has recently emphasized the diagnostic features of such cases.

In older children and adults an increasing number of instances of patent ductus arteriosus with an atypical clinical picture are being encountered. Most of these cases have been instances of isolated patency of the ductus arteriosus in which some or even all of the usual diagnostic features have been missing, the most common feature usually being the absence of a continuous murmur. Studies made in some of these cases have demonstrated either marked elevation of pulmonary artery pressure or postmortem evidence of its presence in the form of marked right ventricular hypertrophy.

The correct clinical recognition of this syndrome is important, for it is possible that it may be more common than the few reported cases suggest. It is important also to study these patients carefully in order to investigate the nature of the increased pulmonary vascular resistance, for this may have broad implications regarding vascular diseases of the pulmonary circulation in other conditions.

For these reasons this report of eight cases of patent ductus arteriosus with pulmonary hypertension and atypical clinical manifestations has been prepared.

Methods of Study

All cases were studied either on the wards of the Stanford Hospital (seven cases) or at the San Francisco Hospital (one case).

Cardiac catheterization studies were performed as described by Courand. Oxygen analyses were performed in a Van Slyke apparatus and single samples analyzed in different machines agreed within 0.2 volume per cent. Pressures were recorded by

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means of a Hamilton manometer with a deflection of the light beam of approximately 3 cm. for every 50 mm. Hg. Mean pressures were determined by planimetric integration of the area under the pressure curve. All intracardiac pressures were measured, using the midpoint of the chest as the reference zero. In those cases in which oxygen consumption was not determined, a normal oxygen consumption was assumed, using corrections for the patient’s age and body surface area. Cardiac outputs, pulmonary blood flow and the flow through the ductus were calculated, using the Fick principle. In patients with a reversed shunt the approximate volume of the right to left shunt through the ductus was approximated in the following manner: It was assumed that 60 per cent of the peripheral blood flow goes to the lower portion of the body. That this is approximately correct is suggested by these facts: (1) The cross section area of the descending portion of the thoracic aorta immediately below the left subclavian artery is 55 per cent of the cross section area of the aorta just above the aortic valves, using 2.0 cm. as the diameter of the descending aorta and 2.7 as the diameter of the aorta above the valves. (2) Blalock’s study of blood flow in the superior and inferior venae cavae gave a ratio of 60 per cent of the venous return flowing through the inferior cava and 40 per cent flowing through the superior vena cava, which is roughly comparable to these figures. (3) Studies of inferior vena cava and superior vena cava flows done in this laboratory, using the Fick principle, gave similar ratios. The left ventricular output was assumed to be equal to the total pulmonary blood flow. If 60 per cent of the left ventricular output enters the descending aorta and mixes with blood of a lower oxygen saturation coming through the ductus, the volume of this shunt through the ductus can be crudely calculated by the following general mixing formula:

\[ O_2 \text{ content}_{DA} = \frac{\text{Flow}_{DA} \times (O_2 \text{ content}_{PA}) + \text{Flow}_{PD} \times (O_2 \text{ content}_{P})}{\text{Flow}_{DA} + \text{Flow}_{PD}} \]

The following abbreviations are used: AA equals abdominal aorta or that portion of the aorta distal to the orifice of the ductus. DA equals descending aorta or that portion of the thoracic aorta proximal to the orifice of the ductus but distal to the origin of the left subclavian artery. PD equals patent ductus. The vascular resistance of the pulmonary circulation was calculated according to the formula:

\[ R = \frac{P_A \times 1332 \times 60}{PF} \]

R equals vascular resistance in dynes per centimeter\(^4\) per second; \(P_A\) equals mean pressure in the pulmonary artery in mm. Hg; \(PF\) equals pulmonary blood flow in liters per minute. Predicted resistances were obtained using normal mean pressures and blood flows and corrected for body surface area.

Kerosene perfusion of the lungs obtained at autopsy was performed in one case. The technic is similar to that used in previous studies of the coronary and renal vascular bed. After rigor has disappeared the lungs are inflated in an air-tight chamber by a negative chamber pressure of 7 mm. Hg and repeated perfusions are performed at various pressures until duplicate measurements agree to within 5 per cent. After perfusion a lead carbonate and gelatin injection mass is forced into the pulmonary artery and roentgenograms are made.

**CASE REPORTS**

Four cases exhibited varying degrees of cyanosis and polycythemia with evidence of a reversal of flow through the ductus.

**Case 1, J. J.** This 16 year old schoolgirl entered the Stanford Hospital on June 19, 1948. At the age of 9 months, a heart murmur was noted. Easy fatigue and exertional dyspnea had been noted since childhood. Five months prior to entry dyspnea had become more severe, and one month prior to entry the patient developed intractable vomiting which subsided only after being placed in an oxygen tent. During the preceding 10 years she had experienced frequent attacks of "pneumonia" with cough, increased dyspnea and fever.

Physical examination revealed a moderately dyspneic young girl with distinct cyanosis of the lips and nail beds. The blood pressure was 110/96. At the third intercostal space along the left sternal border a loud diastolic murmur and a diastolic thrill were noted. The second pulmonic sound was loud and a presystolic gallop was heard at the apex. A tender liver edge was felt 2 cm. below the costal margin. There was distinct clubbing of the fingers.

The erythrocytes were 6.1 million with 18.7 Gm. of hemoglobin and the packed cell volume was 65 per cent. The blood area was 80 mg. per 100 ml. and the arm-to-tongue circulation time (Decholin) was 34 seconds. The venous pressure was 18 cm. of saline above the midchest. The electrocardiogram (fig. 1) revealed a right axis deviation, tall P waves in leads II and III and a deep S wave in lead CR. A phonocardiogram (fig. 2) revealed a split first sound, a presystolic gallop and a prominent diastolic murmur along the left sternal border. X-ray films of the heart and lungs (fig. 3) revealed enlargement of the right ventricle and a marked prominence of the pulmonary artery and its branches. Digitalis was given without producing improvement and the patient became more dyspneic, finally comatose and died on the thirteenth hospital day.

The pertinent autopsy findings were confined to the heart and lungs. The heart was grossly enlarged and weighed 400 Gm. The right ventricle was
hypertrophied and dilated and its myocardium measured 5 mm. in thickness compared with that of the left ventricle which measured 9 mm. in thickness. When both ventricles were dissected away from the septum the right ventricle weighed 167 Gm. and the left 78 Gm. The pulmonary artery was dilated and its wall was as thick as the wall of the aorta. A patent ductus arteriosus measuring 8

**FIG. 1.** Electrocardiograms from all patients. The upper four tracings from patients demonstrating right to left shunts show pattern of right ventricular hypertrophy.
mm. in diameter and 4 mm. in length connected the aorta and pulmonary artery (fig. 4). The foramen ovale was closed and the interventricular septum was intact. The smaller branches of the pulmonary artery were thickened and stood out prominently from the cut surface of the lung. The lungs weighed 450 Gm. together and they appeared normal.

Microscopically many of the smaller branches of the pulmonary artery were occluded by thrombi, some of which were recent and showed beginning organization as manifested by invasion of fibroblasts. Other thrombi were recanalized so that two or more distinct endothelial lined lumina were present, some of which contained red cells (fig. 5). Many small arteries and arterioles had a conspicuous thickening of the media and the elastica interna. There was no evidence of arteritis and the lung tissue appeared normal. The aorta adjacent to the ductus was normal. The intima of the ductus was thickened and a definite elastica interna was present. The media was composed largely of collagenous tissue. The other organs were not remarkable.

Both lungs perfused with kerosene. A marked decrease in perfusibility was observed, amounting to less than one tenth that of the perfusibility of normal lungs. During perfusion of the pulmonary artery backflow of kerosene through the bronchial arteries was noted. These arteries were 1 to 2 mm. in outside diameter at their origins. After perfusion the pulmonary arterial tree of one lung was injected, roentgenograms were made and compared with a normal lung similarly treated (fig. 4). In contrast to the fine, branching vascular pattern of the normal lung the patient's lung revealed an obliteration of the finer terminal branches, the injection mass ending abruptly in vessels approximately 1 mm. in diameter. A few fine long vessels were seen which paralleled the main branches and which may have been bronchial collateral vessels filled by retrograde injection.
Case 2, G. F. This 34 year old white American housewife entered Stanford Hospital on May 15, 1950. Cyanosis had been noted by the parents at the age of two. Her activity had been moderately restricted in school because of exertional dyspnea and weakness. Fluoroscopic examination at 24 because of a cough revealed cardiac enlargement. Her exercise tolerance had been good and she had been able to do all her own housework and outdoor work on a ranch as well.

Physical examination revealed a well developed woman with a diffuse dusky cyanosis of the mucous membranes. The blood pressure in the right arm was 100/70. A slight bulge of the rib cage was present over the precordium to the left of the sternum. The second pulmonic sound was moderately loud and split. No murmurs were heard. The femoral pulses were easily felt. There was no clubbing of the fingers but distinct clubbing of the toes was present.

The erythrocytes were 8.0 million with 24 Gm. of hemoglobin and the packed cell volume was 65 per cent. The vital capacity was 3.7 liters and the venous pressure was 8.5 cm. of saline above the midpoint of the chest. The arm-to-lung circulation time (ether) was 11.5 seconds and the arm-to-tongue circulation time (Decholin) was 21 seconds. The electrocardiogram (fig. 1) revealed changes compatible with right ventricular hypertrophy. X-ray films of the chest (fig. 3) revealed enlargement of the right ventricle with prominence of the pulmonary conus. The lung fields were clear. An angiocardiogram using 30 cc. of 75 per cent Neoipax

![Fig. 3. Anteroposterior roentgenograms of chests showing enlargement of pulmonary arteries. Left anterior oblique view of patient E. B. indicates moderate degree of left ventricular enlargement.](http://circ.ahajournals.org/)

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Fig. 4.  
A. Patient J. J. Artist's drawing of gross specimen.
B. X-ray photograph of portion of normal lung above and a similar portion of lung from patient J. J. below. The pulmonary artery has been injected with a radio-opaque medium.
C. Patient V. M. Autopsy specimen of heart showing location of ductus. Note marked hypertrophy of right ventricle.
D. Patient D. P. Looking down at the cut ends of the pulmonary artery (below) and the aorta (above) showing probe in the ductus. Note dilatation and atherosclerosis of pulmonary artery.
revealed prompt opacification of the right ventricle, pulmonary artery and descending aorta. Some of the contrast media was also seen in the arch of the aorta as well. The results of the cardiac catheterization studies are indicated in table 1A.

In May 1951, the patient re-entered the hospital for additional studies. There had been no change in symptoms, physical examination or x-ray examination. The erythrocytes were 7.2 million, the hemoglobin 22.3 Gm. and the packed cell volume was 65 per cent. Under local anesthesia Cournand needles were inserted into the left femoral and left brachial arteries and blood samples were withdrawn at rest and immediately after exercise with the results indicated in table 1B.

Comment. The evidence of arterial unsaturation in the lower extremities, clubbing of the toes but not of the fingers and marked polycythemia clearly establishes the diagnosis of a patent ductus arteriosus with pulmonary hypertension and a right to left shunt. The striking clinical feature was the absence of any detectable heart murmur although the pulmonary second sound was clearly accentuated.

Case 3, J. W. This 31 year old white Canadian bus driver entered the Stanford Hospital on April 23, 1951. During childhood his parents had noted that he became dyspneic easily. A faint heart murmur was first noted at 20 years in a routine examination. His exercise capacity had been only slightly impaired and he had worked as a laborer for many years. During the past six months he had noted more dyspnea, occasional attacks of precordial pain and cyanosis of the lips occurring on exertion.

Physical examination revealed a muscular man with moderate erythema of the lips. The blood pressure in the right arm was 120/80. A diffuse precordial heave was palpable and the second pulmonic sound was loud and split. At the fourth intercostal space along the left sternal border there was a grade II, well localized systolic murmur. A nondenter liver edge was felt at the costal margin. There was slight but distinct clubbing and erythema of the tips of fingers and toes.

The hemoglobin was 21 Gm. and the packed cell volume 64 per cent. The electrocardiogram (fig. 1) revealed changes compatible with right ventricular hypertrophy. X-ray films (fig. 3) revealed right ventricular enlargement with prominence of the pulmonary artery. There was no evidence of left ventricular enlargement. A phonocardiogram (fig. 2) revealed a split first sound (1), an auricular sound (a) and a grade II systolic murmur (SM). On April 23, 1951, cardiac catheterization studies were performed and the results are summarized in table 2. Four hours after the procedure a sample of femoral artery blood was removed for oxygen analyses.

Comment. It is of interest that distinct clubbing of both fingers and toes was present despite the distinct difference in oxygen saturations between brachial and femoral arteries. The very low oxygen content of femoral artery blood suggests a very large right to left shunt.

Case 4, C. P. This 21 year old white American student entered the hospital on Feb. 19, 1952. At the age of 5 years a heart murmur was detected during a routine examination. Since that time cyanosis of the lips and extremities had been noted during exertion and in cold weather. Exercise capacity had always been moderately limited and severe exertion produced weakness of the legs and dyspnea. There was no history of hemoptyses, squatting or symptoms of heart failure.

Physical examination revealed a thin boy with distinct erythema of the cheeks, lips and tips of fingers and toes. The neck veins were not distended. The blood pressure in the right arm was 110/80 mm. Hg. There was a slight bulge of the precordium along the left sternal border. The second pulmonic sound was loud and accompanied by a faintly palpable shock. In the fifth intercostal space along the left sternal border a grade III blowing murmur filled systole. At the pulmonic area a somewhat fainter systolic murmur was present which became loudest just before the second sound. The femoral and pedal pulses were easily felt. There was no clubbing of the digits.

The hemoglobin was 22.7 Gm. and the packed cell volume varied from 67 to 69 per cent. The electrocardiogram (fig. 1) revealed changes compatible with right ventricular hypertrophy. X-ray films (fig. 3) revealed right ventricular enlargement and moderate prominence of the pulmonary arteries which did not show diminished pulsations. A phonocardiogram (fig. 2) confirmed the presence of the murmurs noted clinically. On March 14, 1952, cardiac catheterization studies were performed with the results indicated in table 3. Angiocardiography was performed, using 35 cc. of Neopaque. Slow filling of the right ventricle and pulmonary artery vessels occurred and the aorta and ductus arteriosus were not visualized.

Comment. The difference in oxygen content between the brachial and femoral arteries clearly indicates the presence of a reversed shunt through the ductus.

Four cases exhibited no evidence of a right to left shunt through the ductus but had an atypical clinical picture with marked pulmonary hypertension.

Case 5, V. M. This 7 year old white American child from the San Joaquin Valley entered the hospital on Jan. 9, 1950. At the age of 2 months a persistent cough appeared and a heart murmur was heard. X-ray films revealed cardiac enlargement. Since infancy the child became tired easily and
Fig. 5 A. Patient V. M. Small pulmonary artery at upper left with marked luminal narrowing due to intimal proliferation and medial hypertrophy. Tubercle of coccidioidomycosis below with adjacent lymphocytic infiltration. Hematoxylin and eosin X 112.


D. Patient V. M. Occlusion of small pulmonary artery by fibrous tissue with recanalization by small endothelial lined lumina containing erythrocytes. H. and E. X 48.

E. Patient V. M. Recanalization of fibrous occlusion of small pulmonary artery. Van Gieson X 112.
dyspnea was evident on mild exertion. Bilateral congenital cataracts were repaired surgically at 2 years. Seven months before entry a fever of 104 F. developed and lasted for 12 days. X-ray films revealed a small area of density in the posterior portion of the left upper lobe.

Table 1.—Findings on Catheterization in Case 2

<table>
<thead>
<tr>
<th>Location</th>
<th>O₂ Content cc./100 cc. and % Saturation</th>
<th>Pressure mm. Hg s/d/mean</th>
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<td>A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inf. v.c.</td>
<td>17.0</td>
<td></td>
</tr>
<tr>
<td>Sup. v.c.</td>
<td>20.1</td>
<td></td>
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<tr>
<td>Av. both v.c.</td>
<td>18.6</td>
<td></td>
</tr>
<tr>
<td>Upper rt.</td>
<td>19.3</td>
<td></td>
</tr>
<tr>
<td>Mid. rt.</td>
<td>18.8</td>
<td></td>
</tr>
<tr>
<td>Low rt.</td>
<td>19.2</td>
<td></td>
</tr>
<tr>
<td>Low rt. vent.</td>
<td>19.4</td>
<td></td>
</tr>
<tr>
<td>Lat. rt.</td>
<td>19.2</td>
<td></td>
</tr>
<tr>
<td>High rt. vent.</td>
<td>19.3</td>
<td></td>
</tr>
<tr>
<td>P.A.</td>
<td>20.1</td>
<td></td>
</tr>
<tr>
<td>P.A.</td>
<td>20.5</td>
<td></td>
</tr>
<tr>
<td>Rt. br. art.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>26.3 (93)</td>
<td>88/56/74</td>
</tr>
<tr>
<td>Exercise</td>
<td>25.7 (91)</td>
<td></td>
</tr>
<tr>
<td>O₂ cap.</td>
<td>28.3</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lt. br. art.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>26.8 (91)</td>
<td></td>
</tr>
<tr>
<td>Exercise</td>
<td>25.7 (87)</td>
<td></td>
</tr>
<tr>
<td>Left fem. art.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>24.7 (84)</td>
<td></td>
</tr>
<tr>
<td>Exercise</td>
<td>20.9 (71)</td>
<td></td>
</tr>
<tr>
<td>O₂ cap.</td>
<td>29.6</td>
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Physical examination revealed a thin, pale, stoop-shouldered little girl with bilateral, repaired cataracts. There was moderate kyphosis of the dorsal spine and a prominent bulge of the rib cage over the left precordium. The blood pressure in the right arm was 100/60. There was a prominent precordial heave. The second pulmonic sound was very loud and it was followed by a harsh diastolic murmur heard along the left sternal border. A loud systolic murmur was present over the pulmonic area. There was a moderate systolic pulsation of the neck vessels but no venous distention. There was no clubbing of the digits.

Table 2.—Findings on Catheterization in Case 3

<table>
<thead>
<tr>
<th>Location</th>
<th>O₂ Content cc./100 cc. and % Saturation</th>
<th>Pressure mm. Hg s/d/mean</th>
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<td>Inf. v.c.</td>
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<td>Sup. v.c.</td>
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<tr>
<td>Av. both v.c.</td>
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<td>Rt. at. (rest)</td>
<td>18.4</td>
<td>8/0</td>
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<td>Low rt. vent.</td>
<td>18.0</td>
<td></td>
</tr>
<tr>
<td>High rt. vent.</td>
<td>17.8</td>
<td>134/12</td>
</tr>
<tr>
<td>P.A.</td>
<td></td>
<td></td>
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<tr>
<td>Rest</td>
<td>19.1</td>
<td>130/82/106</td>
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<tr>
<td>Exercise</td>
<td>11.5</td>
<td>168/106/137</td>
</tr>
<tr>
<td>Rt. br. art.</td>
<td>24.2 (86)</td>
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<tr>
<td>Left br. art.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>25.5 (91)</td>
<td>128/76/9</td>
</tr>
<tr>
<td>Exercise</td>
<td>24.9 (89)</td>
<td>171/96</td>
</tr>
<tr>
<td>Fem. art. *(rest)</td>
<td>17.2 (61)</td>
<td></td>
</tr>
<tr>
<td>O₂ cap.</td>
<td>28.1</td>
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</table>

* Sample obtained four hours after cardiac catheterization.

Abbreviations as in table 1.

Table 3.—Findings on Catheterization in Case 4

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<tr>
<th>Location</th>
<th>O₂ Content cc./100 cc. and % Saturation</th>
<th>Pressure mm. Hg s/d/mean</th>
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<td>Inf. v.c.</td>
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</tr>
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<td>Sup. v.c.</td>
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</tr>
<tr>
<td>Av. both v.c.</td>
<td>19.5</td>
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</tr>
<tr>
<td>Rt. at.</td>
<td>19.5</td>
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<tr>
<td>Low rt. vent.</td>
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<tr>
<td>High rt. vent.</td>
<td>20.2</td>
<td>134/10</td>
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<tr>
<td>Main P.A.</td>
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<td>127/64/100</td>
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<td>Main P.A.</td>
<td>21.1</td>
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<td>Rt. P.A.</td>
<td>20.3</td>
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<tr>
<td>Br. art. (rest)</td>
<td>27.8 (95)</td>
<td>110/80</td>
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<tr>
<td>Fem. art. (rest)</td>
<td>24.0 (82)</td>
<td>110/66/84</td>
</tr>
<tr>
<td>O₂ cap.</td>
<td>29.2</td>
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</table>

The hemoglobin was 14.0 Gm. and the packed cell volume was 40 per cent. The electrocardiogram (fig. 1) revealed changes which were compatible

F. Patient J. J. Small pulmonary arteries containing recanalized organized thrombi.

G. Patient D. P. Small pulmonary artery showing fibrous intimal thickening with moderate luminal narrowing. The surrounding lung tissue shows dense erythrocytic infiltration of the alveoli. H. and E. X 112.

H. Patient D. P. Section through wall of main pulmonary artery. Note marked thickening of intima (top) with typical atheroma formation. A tiny fibrous scar is present in the outer portion of the media. The adventitia (bottom) is normal. Van Gieson X 48.

I. Patient E. B. Pulmonary arteriole showing obliteration of lumen by cellular fibrous tissue and recanalization by prominent endothelial lined spaces containing erythrocytes.
PATENT DUCTUS ARTERIOSUS WITH PULMONARY HYPERTENSION

with right ventricular hypertrophy. X-ray films (fig. 3) revealed cardiac enlargement involving largely the right ventricle and prominence of the pulmonary arteries with moderate pulmonary congestion. Exaggerated pulsations of the pulmonary arteries were noted during fluoroscopy. A 3 cm. irregular density was present in the second left intercostal space. Phonocardiograms (fig. 2) confirmed the presence of the murmurs noted clinically. An angiocardiogram, using 75 per cent Diodrast, revealed an enlarged right ventricle, dilated pulmonary arteries and possibly late recirculation of the contrast material through the pulmonary vessels. Cardiac catheterization studies were performed on Jan. 11, 1950, using Avertin and local anesthesia. The results are summarized in table 4.

On July 29, 1950, the child was admitted to the Childrens Hospital of San Francisco. Three weeks prior to entry she had developed a nonproductive cough, and fever and edema of the feet had been noted. Physical examination revealed a heart rate of 128 per minute, a blood pressure of 110/80 and a rectal temperature of 37.4. There was distention of the neck veins, moist rales throughout both lung fields, enlargement of the liver and moderate peripheral and sacral edema. Despite the prompt administration of digitoxin and oxygen, the child died 12 hours after entry.

The principal findings of the autopsy examination were related to the heart and lungs. The heart was greatly enlarged due to dilatation and hypertrophy of both ventricles (fig. 4). The right ventricular myocardium measured 7 mm. in thickness and the left ventricular myocardium 12 mm. The pulmonary valve leaflets were fused at the commissures and the free edges were smooth but thickened and retracted so as to produce an insufficiency without stenosis. The pulmonary artery was enlarged and its wall was as thick as that of the aorta. The pulmonary artery measured 5.7 cm. in circumference just above the valve and the aorta 4 cm. in circumference at a comparable level. All of the branches of the pulmonary artery were thick walled and dilated and their cut ends protruded rigidly from the cut surface of the lungs. No emboli or thrombi were noted in any of the branches. At a point 1 cm. beyond the bifurcation of the left pulmonary artery the opening of a short but widely patent ductus arteriosus was present; the ductus measured 3 mm. long and 4.5 mm. in diameter after formalin fixation. No vegetations were present in or near either end of the ductus. The foramen ovale was functionally closed but admitted a 1 mm. probe. The ventricular septum was intact. No intracardiac thrombi were noted.

One hundred and fifty cubic centimeters of clear fluid were present in the right pleural cavity. In the upper lobe of the left lung a pale, firm 4 by 6 cm. area of gray-white tissue was present. It was adherent to the parietal pericardium at one point and in the center of the area was a single, hard, white 15 mm. nodule which contained no calcium. Numerous small 1 to 2 mm. pale nodules were scattered around the periphery of the large mass of tissue. No nodules were present in the left lower lobe or in the right lung. The mediastinal lymph nodes on the left were moderately enlarged but did not appear abnormal externally or after incision. The abdominal organs were moderately congested but otherwise normal.

Sections of the left lung revealed numerous small tubercles, some of which had fused into granulomatous masses in which numerous, multinucleated giant cells of the Langhans variety were present (fig. 5). In occasional giant cells small double contoured spherules characteristic of coccidiomycosis were present. No tubercles were present in the right lung. The smaller branches of the pulmonary artery, throughout both lungs, measuring from 0.1 mm. to 2 mm. in diameter, revealed a diffuse arteritis consisting in occasional areas of an infiltration of all layers of the vessel wall with polymorphonuclear leukocytes, obliteration of the lumen by thrombosis and destruction of the wall. Eosinophils were scarce. Other areas revealed an apparently healed arteritis without evidence of acute inflammation but with fibrous scarring of a disrupted vessel wall and secondary recanalization of a well organized luminal thrombus. The arteritis was not related to the granuloma since it involved the vessels of both lungs and no tubercles or giant cells were present in the arterial lesions. Smaller arterioles revealed concentric intimal thickening with luminal narrowing or obliteration and occasional prominent medial deposits of hyaline material. The pulmonary valve was composed of dense acellular fibrous tissue in which no lymphocytes or blood vessels were seen.

Comment. The very prominent diastolic murmur

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**Table 4.—Findings on Catheterization in Case 5**

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<tr>
<th>Location</th>
<th>$O_2$ Content %</th>
<th>Pressure mm. Hg</th>
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</thead>
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<tr>
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<td>/ /5</td>
</tr>
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was probably related to the deformity of the pulmonary valve as well as to the high pressure in the pulmonary artery. The etiology of the valve deformity is unknown. No other valves were deformed and no scars were found in the heart, hence it was probably not of rheumatic origin. A congenital deformity seems most likely.

Case 6, W. H. This 4 year old white American child entered the hospital on May 25, 1949. Cyanosis was noted during the first weeks of life when oxygen was required frequently and "blue spells" with convulsions occurred during feedings. A heart murmur and thrill were noted at the age of 1 week. Development, however, was subsequently normal. Exercise capacity was moderately limited.

Physical examination revealed a thin boy with a blood pressure of 95/35. There was no venous distention but marked pulsations of the carotid vessels were noted and a distinct thrill was felt during systole in the suprasternal notch. There was a moderate anterior bulge of the chest wall over the left precordium. The heart was enlarged to the right and left. The second pulmonic sound was loud. A rough, grade IV systolic murmur was present over the entire precordium and heard along the carotid and brachial arteries as well. The murmur was accompanied by a prominent thrill. At the apex a short, faint mid-diastolic murmur was present. There was no clubbing of the digits and the femoral arteries were easily felt.

The hemoglobin was 11.7 Gm. and the packed cell volume 34 per cent. The arm-to-tip circulation time (fluorescein) was 10 seconds. The electrocardiogram was thought to be compatible with cardiac hypertrophy, probably involving both ventricles. X-ray films (fig. 3) revealed enlargement of both right and left ventricles with a prominence of the pulmonary arteries and moderate pulmonary congestion. Oblique views revealed moderate enlargement of the left auricle. Phonocardiograms (fig. 2) revealed a loud murmur filling systole and no evidence of a diastolic murmur. Angiocardiograms, using 20 cc. of 75 per cent Diodrast, revealed no evidence of an overriding aorta, apparent recirculation of the contrast media in the pulmonary artery after its appearance in the aorta and the presence of a small "ductus diverticulum" directed anteriorly from the first part of the descending aorta. On May 31, 1949, cardiac catheterization studies were performed under Pentothal anesthesia. A number 6 cardiac catheter was guided without difficulty into the right ventricle, pulmonary artery and through a patent ductus into the descending aorta. The essential findings are summarized in table 5. On March 27, 1951, cardiac catheterization was repeated by Dr. Sidney Sobin with essentially similar results, the catheter again passing from the pulmonary artery through the ductus and into the aorta.

Subsequently at operation a large patent ductus was ligated and divided. A follow-up report obtained through the courtesy of Dr. Louis Martin indicated that there has been marked clinical improvement but that a somewhat less intense systolic murmur is still present at the fourth intercostal space along the left sternal border.

Comment. This patient possibly also had an interventricular septal defect as evidenced by: (a) catheterization studies indicating a rise of 0.8 volume per cent in oxygen from right auricle (average oxygen 8.8) to right ventricle; (b) the persistence of the loud precordial systolic murmur and thrill after ligation and division of the ductus.

Case 7, E. B. This 33 year old white American housewife entered the hospital on March 25, 1952. Her mother had developed rubella during the third or fourth month of pregnancy. A heart murmur was first noted at the age of two years. Growth was slow

<table>
<thead>
<tr>
<th>Location</th>
<th>O2 Content cc./100 cc.</th>
<th>% Saturation</th>
<th>Pressure mm. Hg</th>
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<tr>
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</tr>
<tr>
<td>Rt. at.</td>
<td>9.9</td>
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<tr>
<td>Rt. at.</td>
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<tr>
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<td></td>
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<tr>
<td>P.A.</td>
<td>11.1</td>
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<tr>
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<tr>
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<td>13.7 (89)</td>
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<tr>
<td>O2 cap.</td>
<td>15.3</td>
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</tbody>
</table>

Desc. = descending.

and the patient had always been slender and under normal weight. She had developed frequent bouts of pneumonia as a child and also had pneumonia and a prolonged convalescence following a cesarean section at the age of 27. In the past two years she had noted slight exertional dyspnea.

Physical examination revealed a thin woman with a blood pressure on several occasions varying from 135/65 to 150/80. There was an accentuation of visible carotid pulsations in the neck. A distinct bulge of the rib cage over the left precordium was noted. There was a prominent heave to the left of the sternum, and at the second intercostal space along the left sternal border a systolic thrill and a palpable pulmonic shock was present. A loud grade IV systolic murmur was present along the left sternal border and in midsystole a prominent click was noted which was louder during expiration. The second pulmonic sound was accentuated and followed by a high pitched, faint, blowing diastolic murmur heard only just beneath the pulmonic area.
The hemoglobin was 13 Gm. and the packed cell volume was 40 per cent. The electrocardiogram (fig. 1) showed changes compatible with both left and right ventricular hypertrophy. A phonocardiogram (fig. 2) confirmed the presence of the murmurs and sounds noted clinically. X-ray studies, including fluoroscopy, revealed enlargement of both right and left ventricles, a normal sized aorta and prominence of the pulmonary arteries which pulsed vigorously (fig. 3). On March 27, 1952, cardiac catheterization studies were performed with the results indicated in table 6.

**Table 6.—Findings on Catheterization in Case 7**

<table>
<thead>
<tr>
<th>Location</th>
<th>O2 Content cc./100 cc. and % Saturation</th>
<th>Pressure mm. Hg s/d/mean</th>
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</thead>
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<tr>
<td>Av. both v.c.</td>
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</tr>
<tr>
<td>Rt. at.</td>
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</tr>
<tr>
<td>Low rt. vent.</td>
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</tr>
<tr>
<td>High rt. vent.</td>
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<td>100/10</td>
</tr>
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<td>Right P.A.</td>
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<td>Main P.A.</td>
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<td>Br. art. (rest)</td>
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<td>136/55/91</td>
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<td>Av. both v.c.</td>
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<td>Rt. at.</td>
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<td>P.A. (exer.)</td>
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<td>130/92</td>
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<tr>
<td>O2 cap.</td>
<td>14.0</td>
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On May 15, 1952, surgery was performed and a large patent ductus 1.5 cm. long and 1.6 cm. in outside diameter was found connecting the aorta and the left pulmonary artery near the origin from the main pulmonary artery.

The following mean pressure measurements were recorded:

1. Ductus open
   - Aorta: 73 mm. Hg
   - Pulmonary artery: 65 mm. Hg

2. Ductus closed
   - Aorta: 83 mm. Hg
   - Pulmonary artery: 55 mm. Hg

The ductus was clamped, divided and the ends were sutured with silk. The patient's convalescence was uneventful and she left the hospital on the tenth postoperative day. At that time her blood pressure was 160/80 and a rough grade III systolic murmur was present at the third intercostal space along the left sternal border with accentuation of the pulmonic second sound. No diastolic murmur was heard. A lung biopsy was made during surgery. Histologic examination revealed one small artery, the lumen of which was nearly filled with a mass of connective tissue in which there were several irregular endothelial-lined spaces containing a few red blood cells. The appearance suggested thrombosis with recanalization (fig. 5).

On June 24, 1952, the patient was again studied in the hospital. She had noted no dyspnea or orthopnea since her operation and was doing all her housework and shopping without symptoms. Physical examination revealed only a faint grade I systolic murmur over the pulmonic area and only moderate accentuation of the pulmonic second sound. The systolic click noted prior to surgery was no longer audible. The blood pressure was 120/80. The electrocardiogram was unchanged but x-ray films revealed a distinct decrease in heart size and in the degree of pulmonary congestion. Cardiac catheterization studies were performed with the results summarized in table 6.

**Comment.** The catheterization studies indicated the presence of a fairly large left to right shunt through a patent ductus, pulmonary hypertension and probably a small right to left shunt through the ductus in part of the cardiac cycle as evidenced by a lower oxygen saturation in the femoral artery than in the brachial artery. Exercise did not increase the magnitude of this "reversed shunt." Because of this fact and also because of the large magnitude of the left to right shunt, operation was advised in the hope that a decrease in the total pulmonary flow would result in a lowering of the pulmonary artery pressure. That this occurred is indicated in the table. However the pulmonary vascular resistance is still elevated above normal, probably due to vascular occlusions of the type encountered in the lung biopsy. Whether these will regress in the course of time remains to be seen. The rise in femoral artery diastolic pressure following surgery is striking and emphasizes the importance of a low diastolic pressure as an indication of a patent ductus with a left to right shunt.

**Case 8, D. P.** This 48 year old white American cook and laborer entered the San Francisco Hospital for the first time on Dec. 22, 1941. At the age of 7, a heart murmur was heard. In subsequent years he was told he had an enlarged heart and a "leaky valve." In December 1941, following a period of overwork, he developed severe dyspnea, orthopnea, palpitation, weakness and a sharp, non-radiating precordial pain of 24 hours duration and entered the hospital.
Physical examination revealed a dyspneic, orthopneic man whose blood pressure varied from 142/64 to 136/70. The neck veins were distended and there was a distinct bulge of the rib cage over the left precordium. There was a visibly exaggerated pulsation of the carotid arteries. The chest was of an emphysematous contour and many moist rales were present at the bases. A diffuse precordial heave was easily felt and a loud systolic murmur was heard over the entire precordium, being loudest at the apex. Following a loud second pulmonic sound, a faint blowing diastolic murmur was heard along the left sternal border.

The erythrocytes were 4.9 million and the hemoglobin 15.8 Gm. The packed cell volume was 43 per cent. The Wassermann and Mazzini tests for syphilis were negative. An electrocardiogram (fig. 1) revealed diphasic T waves and depressed S-T segments in the limb leads, a prominent S wave in lead I and a diphasic T wave with a depressed S-T segment in CR4. X-ray films (fig. 3) and fluoroscopy revealed a prominent "hilar dance," moderate enlargement of the right ventricle and pulmonary arteries and prominent pulmonary vascular shadows. The patient improved and was discharged a month after entry.

Eighteen months after leaving the hospital he noted the presence of tarry and bloody stools for two weeks and entered obviously anemic and in congestive failure again. The erythrocytes were 2.0 million and the hemoglobin was 6.9 Gm. Auricular fibrillation was present. A gastrointestinal x-ray study including a barium enema was not remarkable. Despite careful therapy his congestive failure became more severe and he expired five months after entry.

Autopsy revealed a large heart weighing 660 Gm. and marked hypertrophy of the right ventricle. When dissected free of the septum the right ventricle weighed 250 Gm. and the left ventricle 200 Gm. The right ventricular myocardium was 14 mm. thick and the left ventricular myocardium was 12 mm. thick. The leaflets of the aortic valve were thickened and fused at their margins up to 1 cm. from the base of the leaflets. A moderate amount of calcium was present in the thickened valves but there was no appreciable narrowing of the valve orifice. The pulmonary artery was dilated and its wall was equal in thickness to the wall of the aorta. Both the pulmonary artery and the aorta contained numerous longitudinal intimal striae and wrinkles strongly suggestive of syphilis and there were frequent calcified plaques measuring up to 2 cm. in diameter. The dilatation and thickening of the pulmonary artery extended out into the finer branches. No emboli or thrombi were seen. About 2 cm. above the aortic valve ring and on the inferior aspect of the arch of the aorta opposite the origin of the left subclavian artery was a patent ductus arteriosus opening into the left main branch of the pulmonary artery just beyond its origin. The ductus was 1 cm. in diameter and the edges were smooth. Since the walls of the aorta and pulmonary artery were closely approximated at this point the ductus was very short (fig. 4). No other congenital anomalies were noted. The atrial and ventricular septa were intact. The right lung weighed 860 Gm. and the left lung 560 Gm. Both lungs were markedly congested in the basal portions and readily oozed fluid upon compression. No infarcts were seen. The liver weighed 1500 Gm. and the appearance of the cut surface was suggestive of passive congestion. The remainder of the examination was not remarkable.

Microscopic examination of the lungs revealed an extensive bronchopneumonia and pulmonary congestion with edema. The larger branches of the pulmonary artery adjacent to the aortic-pulmonary communication were markedly thickened by medial hypertrophy and intimal fibrosis with atheroma formation (fig. 5). Several discrete scars were present in which the medial elastic tissue was replaced by collagenous tissue containing small blood vessels. These scars were similar to those also found in the media of the aorta. Occasional small focal collections of lymphocytes were present in the adventitia. The smaller branches of the pulmonary artery, and particularly the arterioles, showed a striking narrowing of their lumina by concentric intimal fibrous proliferation and reduplication of the elastic layers (fig. 5). No evidence of arteritis or thrombosis with recanalization was seen. Sections of thoracic aorta revealed intimal thickening with atheroma formation, vascular fibrous tissue scars and rare focal collections of lymphocytes in the adventitia. Sections of the right ventricle revealed hypertrophy of myocardial fibers and a moderate amount of fibrous tissue diffusely distributed throughout the muscle fibers in somewhat long strands but occasionally near vessels in fairly dense masses.

Similar scars were also present in sections of the left ventricle. Sections of liver showed central congestion and thinning of central hepatic cell cords with some areas of central necrosis.

Comment. The ductus in this case was very short, the wall of the aorta and pulmonary artery being closely approximated at that point. The gross and histologic evidence of syphilis in the aorta and pulmonary artery must be evaluated. The ductus was probably not a perforated aortic aneurysm since it was in the usual location for a ductus and no ductal remnant was found elsewhere. Further enlargement of the orifice could have been caused by syphilis. There was no histologic evidence that the narrowing of the smaller arterioles was syphilitic in origin. The aortic stenosis was mild and probably produced little functional disturbance.

Discussion

The occasional association of an isolated patent ductus arteriosus with marked right ventricular hypertrophy and an atypical clinical picture has been noted previously. In 1924
Holman\textsuperscript{13} discussed the problem and presented 16 cases he had collected from the literature in which right ventricular hypertrophy was present. He pointed out the possibility of a right to left shunt occurring through the ductus and in six of his collected cases there appeared to be clear postmortem evidence that such reversal of flow had been present during life. Since then several reports of similar cases have appeared.\textsuperscript{12-18 (case 1)} None of these cases, however, exhibited any clear evidence of a reversal of flow through the ductus. In 1944 Chapman and Robbins\textsuperscript{20} reported in detail the case of a 37 year old taxi driver who exhibited chronic cyanosis, polycythemia with a packed cell volume varying from 60 to 74 per cent, right axis deviation in the electrocardiogram, right ventricular and pulmonary artery enlargement by x-ray study and an inconstant pulmonary diastolic murmur. The arterial oxygen saturation was 75 per cent. Although not stated in the report, the determination was probably on a femoral arterial sample. Autopsy revealed a huge right ventricle, enlargement and grossly visible arteriosclerosis of the pulmonary artery and a very short ductus 1.2 cm. in diameter. Histologic studies revealed luminal narrowing of the smaller pulmonary vessels which were suggestive of recanalization of vascular thrombi.\textsuperscript{20 (Figs. 3, 4, 6 and 8)} Five subsequent reports\textsuperscript{21-25} have been made of cases in which a right-to-left shunt through the ductus was present but complete physiologic data are available in only one report\textsuperscript{23} and in that instance the magnitude of the shunt was small.

It is possible that the number of patients reported in the past do not give a true picture of the actual incidence of these cases, which may be relatively high. Dammann and Sell\textsuperscript{19} encountered 15 cases at the John Hopkins Hospital, all of which came to surgery in one year. The examination of reports of large numbers of patients studied by cardiac catheterization reveals several instances of marked pulmonary hypertension associated with patency of the ductus arteriosus.\textsuperscript{15, 26, 57, 28, 32} It is possible also that many cases, particularly those with reversal of blood flow, are unrecognized and are erroneously diagnosed as cases of Eisenmenger’s syndrome\textsuperscript{23 (case 0261), 25} atrial septal defects with pulmonary hypertension and primary pulmonary hypertension. The eight cases reported in this paper were seen in the space of four years in a hospital where, during the same period of time, six cases of Eisenmenger’s syndrome were found so that the incidence of these two conditions may be comparable. For these reasons it is important to examine the clinical manifestations of this syndrome so that its correct recognition can be made more frequently.

\textbf{Clinical Features}

\textbf{Symptoms.} The most frequent symptom noted by all patients was the presence of dyspnea on exertion. This was not associated with orthopnea or nocturnal dyspnea except in terminal heart failure. In addition four patients noted a sensation of abnormal weakness or fatigue on exertion described in one instance as “a feeling as if my legs were going to fold up under me.” Three patients complained of attacks of substernal pain made worse by exertion and two patients noted episodes of vomiting or nausea.

\textbf{Physical Findings.} In none of these cases was the typical continuous murmur of a patent ductus present nor was there any evidence that it had been present in the past. In all patients the pulmonic second sound was loud and at times accompanied by a palpable shock. In four patients a blowing diastolic murmur was present along the left sternal border which was probably a Graham Steele murmur. In one case (J. J.) the murmur was very loud and accompanied by a palpable thrill. In four cases a loud systolic murmur was present over the pulmonic area and in three of these cases the murmur was accompanied by a palpable thrill. It is of interest that one patient (G. F.) had no audible murmurs and that one patient (J. W.) had only a grade II systolic murmur along the left sternal border.

In the four patients with right to left shunts the arterial blood pressure was normal with a decreased pulse pressure in one case (100/96, 100/70, 120/80, 110/80). No abnormal carotid artery pulsations were noted. In contrast, in the four patients with predominant left to right
shunts, the pulse pressure was distinctly increased (100/60, 95/35, 135/65, 142/64) and prominent pulsations of the carotid arteries were noted in the neck.

X-ray examination revealed in every case a prominence of the pulmonary artery and its branches and enlargement of the right ventricle. Increased pulmonary artery pulsations producing a "hilar dance" was noted in three of the noncyanotic cases and distinct x-ray evidence of left ventricular enlargement was present in two of these cases.

Each of the cyanotic and one of the noncyanotic patients had electrocardiograms which were compatible with marked right ventricular hypertrophy. The other noncyanotic patients had electrocardiograms suggesting hypertrophy of both right and left ventricles.

The catheterization findings are characteristic in the noncyanotic cases and should clearly establish the correct diagnosis. In cases with a reversal of the shunt the diagnosis by cardiac catheterization may be more difficult. The difference in oxygen contents between the right ventricle and the pulmonary artery may be small. In the presence of a prominent degree of functional pulmonic insufficiency the oxygen content of blood samples removed from the outflow tract of the right ventricle may be high and incorrectly suggest the presence of an interventricular septal defect. If, in addition, only femoral blood samples are obtained, the erroneous diagnosis of an Eisenmenger's syndrome may be made. The simultaneous withdrawal of samples from brachial and femoral arteries before and after exercise will prevent this error.

It is of interest that angiocardiography in one cyanotic case (C. P.) failed to demonstrate the right to left shunt through the ductus which was clearly established by the arterial oxygen studies. The volume of the right to left shunt in this case was probably not large enough to enable the contrast media to be seen in the aorta. In G. F. contrast media was seen in the aorta but it was not sufficiently concentrated to demonstrate the ductus. Apparently contrast media may fill the aorta just proximal to the point of insertion of the ductus and in the anterior-posterior projection falsely suggest the presence of an over-riding aorta.

Physiology and Pathology. In the usual patent ductus there is a relatively large flow of blood from the aorta to the pulmonary artery ranging from 2 to 10 liters per minute. This results in an increase of total pulmonary blood flow to levels of 6 to 15 liters per minute. In these cases there is either a normal or only moderately elevated pulmonary artery pressure, the degree of elevation being roughly related to the magnitude of the shunt. This capacity of tolerating even fairly large flows with only slight elevations in pressure is a characteristic of the pulmonary vascular bed and is due to its low resistance to flow.

The most important common physiologic feature of the cases presented in this paper is the presence of a marked elevation of pulmonary artery pressure. This may be due to either an elevation of total pulmonary flow or to an increase in the pulmonary vascular resistance. Inspection of figure 6 reveals no relation between total pulmonary flow and pulmonary artery pressure in these cases. The noncyanotic cases had pulmonary flows no greater than those encountered in the usual patent ductus yet the pressures were markedly elevated. The cyanotic cases had the highest pulmonary artery pressure of the group with the lowest calculated pulmonary blood flows. The uncomplicated patent ductus had relatively normal pressures and demonstrated a roughly linear relationship between pulmonary flow and pressure. The ligation of the ductus in patient E. B., while it lowered moderately the pulmonary artery pressure by decreasing the total pulmonary flow, did not reduce the peripheral resistance of the pulmonary vascular bed, and after surgery the pulmonary artery pressure was still abnormally high. This indicates that the major cause of the pulmonary hypertension is an increase in the vascular resistance of the lung. Calculation of the pulmonary peripheral resistances in these cases indicates that this increase is striking (table 7). Further confirmation of increased pulmonary vascular resistance was obtained by the data on postmortem studies in J. J. in which the kerosene perfusibility was greatly impaired.
and the injected specimen revealed a striking obliteration of the smaller branches of the pulmonary artery. In addition histologic studies have revealed marked alterations in the structure of the smaller pulmonary arteries which would obstruct easy flow of blood through these vessels. These data also suggest that this vascular narrowing is anatomic and probably largely irreversible instead of being functional and related to a sustained arterial hypertonus as has been postulated to exist in other varieties of pulmonary hypertension.\(^{31}\)

It is important to examine briefly the cause of this vascular narrowing. Four general possibilities exist: (1) It is the result of a prolonged increase in total pulmonary blood flow and represents a late complication of the usual patent ductus arteriosus. (2) It is the result of multiple pulmonary emboli probably of small size and occurring in repeated episodes or over long periods of time. (3) It is due to an antecedent acute pulmonary arteritis with subsequent healing and vascular occlusion. (4) It is due to the persistence of the high pulmonary vascular resistance of the fetus into postnatal life.

The first possibility seems unlikely since in none of the cases presented was there a history of a continuous murmur being present at an earlier age and in one case, G. F., cyanosis, and presumably a right to left shunt, had early been present since infancy. Pulmonary vascular lesions are not present in cases of the usual patent ductus\(^{36}\) and in animals with experimentally produced aortic-pulmonary fistulae, no pulmonary hypertension appears even after several years of observation.\(^{22}\) Recent reports of patency of the ductus arteriosus persisting into old age have indicated no unusual degree of pulmonary hypertension.\(^{29, 38}\) The lack of correlation between pulmonary blood flow and pulmonary artery pressure in the patients presented in this paper is evident (fig. 6).

The second possibility seems a good one since it is clear that multiple pulmonary emboli can cause pulmonary hypertension in the absence of congenital heart disease.\(^{41}\) Experimentally, pulmonary hypertension has been produced by intravenous injection of various substances such as seeds, spores, starch grains, amniotic fluid and finely divided thrombi obtained from the animal's own blood.\(^{42-46}\) Histologically an immediate acute arteritis appears with subsequent vascular thromboses and recanalization.\(^{42}\) The lesions thus produced resemble very closely those encountered in cases of the variety reported in this paper as well as in numerous reported cases of "primary" pulmonary hypertension. The pulmonary vessels in cases D. P., E. B. and J. J. show histologic evidence of recanalization of organized intraluminal thrombi which could have resulted from embolization. The same lesions are described or illustrated in several reports of

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**Table 7.** Oxygen Consumption, Blood Flow, Cardiac Output, Pulmonary Artery Pressure and Pulmonary Peripheral Resistance in the Six Patients

<table>
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<tr>
<th>Patient</th>
<th>Plateau area, M(^2)</th>
<th>O(_2) cons., cc./min.</th>
<th>Pulm. flow L/min.</th>
<th>Ductus flow L/min.</th>
<th>RV output L/min.</th>
<th>LV output L/min.</th>
<th>Mean Press. PA mm. Hg</th>
<th>Pulm. PR* deter dynes/cm(^2)/sec.</th>
<th>Pulm. PR pred dynes/cm(^2)/sec.</th>
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<tbody>
<tr>
<td>V. M.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G. F.</td>
<td>1.72</td>
<td>222 (c)</td>
<td>4.8</td>
<td>2.3</td>
<td>0</td>
<td>2.5</td>
<td>4.8</td>
<td>62</td>
<td>1032 (245)</td>
</tr>
<tr>
<td>E. B.</td>
<td>1.41</td>
<td>326 (d)</td>
<td>4.8</td>
<td>1.9</td>
<td>2.0</td>
<td>4.9</td>
<td>4.8</td>
<td>72</td>
<td>1200 (155)</td>
</tr>
<tr>
<td>C. P.</td>
<td>1.65</td>
<td>251 (d)</td>
<td>3.5</td>
<td>1.4</td>
<td>1.7</td>
<td>3.8</td>
<td>3.5</td>
<td>100</td>
<td>2240 (161)</td>
</tr>
<tr>
<td>W. H.</td>
<td>1.60</td>
<td>110 (c)</td>
<td>4.9</td>
<td>2.6</td>
<td>0</td>
<td>2.3</td>
<td>4.9</td>
<td>86</td>
<td>1405 (160)</td>
</tr>
<tr>
<td>J. W., rest</td>
<td>1.90</td>
<td>269 (d)</td>
<td>3.7</td>
<td>2.6</td>
<td>0</td>
<td>2.3</td>
<td>3.7</td>
<td>106</td>
<td>2240 (140)</td>
</tr>
<tr>
<td>J. W., ex.</td>
<td>1.90</td>
<td>592 (d)</td>
<td>3.9</td>
<td>2.6</td>
<td>0</td>
<td>2.3</td>
<td>4.9</td>
<td>86</td>
<td>1405 (160)</td>
</tr>
<tr>
<td>E. B., Postop. rest</td>
<td>1.40</td>
<td>180 (d)</td>
<td>3.9</td>
<td>0</td>
<td>0</td>
<td>3.9</td>
<td>3.9</td>
<td>106</td>
<td>1615 (190)</td>
</tr>
<tr>
<td>E. B., Postop. ex.</td>
<td>1.40</td>
<td>205 (d)</td>
<td>4.5</td>
<td>0</td>
<td>0</td>
<td>4.5</td>
<td>4.5</td>
<td>1012</td>
<td>1900 (190)</td>
</tr>
</tbody>
</table>

* PR = peripheral resistance.

\(\dagger\) c = O\(_2\) consumption calculated.

\(\ddagger\) d = O\(_2\) consumption determined.
similar cases.¹³, ²¹, ²³, ²⁴ The case reported
by Campbell and Hudson²⁴ is of particular
interest since it appeared that a typical con-
tinuous murmur with a wide pulse pressure
had been present nine years previously and
both these features had disappeared at the
time of the study three weeks before death. It
is a well known fact that pulmonary emboli
may occur without striking clinical manifesta-
tions, especially if the embolus is small and the
lungs are not congested. Certain points, how-
ever, are against this attractive theory.
Autopsy studies in 13 cases, including reported
cases and the three cases in this paper, have
revealed only one instance of pulmonary in-
fection with a grossly demonstrable embolus,
and that was of recent origin and occurred
during terminal congestive failure.¹³ If multiple
pulmonary embolization was the basis of the
elevation of pulmonary arterial pressure, one
would expect some history suggestive of such
a process. Such a history is not present either
in the eight cases in this paper or in the other
reported cases. In several cases it is quite pos-
sible that the pulmonary hypertension had
been present since infancy, a period of life in
which multiple pulmonary emboli would not
seem likely to occur. The mere demonstration
of recanalization of an organized intravascular
thrombus does not establish the diagnosis of
embolic vascular occlusion since the throm-
bosis may be secondary to other processes
such as inflammation, for example.

It is possible that in some instances a pul-
monary arteritis may be the initial lesion with
thromboses and vascular alterations playing a
secondary role. The presence of an acute arte-
ritis in case V. M. supports this viewpoint and
other cases have been reported with an acute
inflammatory process limited to the branches
of the pulmonary artery.⁷⁷-⁷⁹ Illustrations of
the pulmonary vascular lesions in one report of
a patent ductus with pulmonary hyperten-
sion show what appears to be a healed arteritis,
although this is not mentioned in the text.²³, ²⁵
Fig. ⁷⁵ In many cases, however, the arteritis
may be the initial reaction to multiple emboli
since this apparently occurred in the exper-
imental studies of Muirhead and others,⁴² or
the arteritis may be caused by the elevation of
intravascular pressure.

Finally one has to consider the possibility
that due to a maladjustment during the neo-
natal period the equal resistances in the sys-
temic and pulmonary circulations during fetal
life persist into postnatal life. It is thought that
under certain circumstances the physiologic
fall in pulmonary vascular resistance which
should take place after birth does not occur,
and a persistent elevation of the pulmonary
arterial pressure results from it, leading
eventually to organic changes in the pulmonary
vascular tree. Such a mechanism, initiated by
as yet undetermined factors, has been postu-
lated as a condition for survival in certain
genital malformations of the cardiovascular
system, such as the Eisenmenger complex,⁵¹ the
monoventricular trilocular heart⁵² and the
syndrome of patent ductus arteriosus with
infantile coarctation of the aorta.⁵³ This mech-
anism possibly operates in some cases of “pri-
mary” pulmonary hypertension occurring in
infancy⁵⁴, ⁵⁵ and could well be responsible for
some or most cases of patent ductus arteriosus
with pulmonary hypertension presented in
this report. One could even suggest the possi-
bility that such pulmonary hypertension developing early enough in neonatal life could interfere with the closure of the ductus and thus be the cause rather than the result of patency of the ductus arteriosus.

The striking increase in pulmonary vascular resistance and pulmonary artery pressure is responsible for most of the clinical signs of these cases. The decrease in pressure gradient between the aorta and the pulmonary artery may extinguish the diastolic phase of the continuous murmur and leave only a systolic murmur. In patients with more severe pulmonary hypertension both systolic and diastolic pressures in the aorta and pulmonary artery become equal and no murmur at all may be present.

When the pulmonary artery pressure reaches such levels, a right to left shunt may occur through the ductus, resulting in a reduced femoral arterial oxygen saturation. Exercise appears to increase the difference between the oxygen contents of arterial blood from the upper and lower extremities in the presence of a "reversed shunt" and this may be a useful diagnostic method in cases whose resting femoral arterial saturation is only questionably decreased. Whether the decrease in femoral arterial saturation occurring during exercise is due to an increase in the volume of the right to left shunt or to a fall in the oxygen content of pulmonary artery blood is not known, but it seems likely that both factors may be involved. In J. W., for example, exercise produced a fall of (19.1 to 11.5) 7.6 volumes per cent in the oxygen content of pulmonary artery blood. At the same time brachial arterial pressure rose from 128/76 to 171/86 while the pulmonary artery pressure rose from 130/82 to 168/106, resulting in only a slight increase in the pressure gradient from pulmonary artery to aorta (6 to 10 mm. Hg), and that occurred during diastole only. Here the most important factor causing unsaturation of femoral artery blood during exercise appeared to be the fall in oxygen content of mixed venous blood. Whether this occurs in the similar cases remains to be determined.

The determination of the presence of a right to left shunt through the ductus is important because in the presence of such a shunt surgery appears to be contraindicated. The ductus in such cases may be serving as a "safety valve" keeping pulmonary artery pressure from rising to excessive levels during exercise, or the postoperative deaths that have occurred may be related to the acute pulmonary hypertension resulting from a greatly hypertrophied right ventricle pushing the entire cardiac output through the narrowed pulmonary vascular bed instead of a portion of the flow going through the ductus. It seems clear, however, that in the absence of any demonstrable reversed shunt the ductus can be ligated in the presence of pulmonary hypertension, with gratifying results. The return to normal of an elevated pulmonary flow will lower the pulmonary artery pressure, reduce the work of the right and left ventricles and result in marked clinical improvement. Some pulmonary hypertension will remain, however, since the pulmonary vascular disease has not been affected, as illustrated by the postoperative values obtained in E. B. Whether further gradual improvement will occur remains to be determined.

**Summary**

1. Eight cases of patent ductus arteriosus associated with pulmonary hypertension have been presented with clinical studies in all cases, cardiac catheterization studies in six cases and autopsy studies in three cases.

2. Four of the patients had conclusive evidence of a right to left or "reversed" shunt through the ductus, and three of these cases presented the clinical picture of chronic cyanotic congenital heart disease.

3. Four cases had no evidence of a right to left shunt but presented an atypical clinical picture with absence of the characteristic continuous murmur and evidence of enlargement of the right ventricle in the electrocardiogram and x-ray. Two of these cases were greatly improved following ligation of the ductus.

4. This study suggests that the basis of this syndrome is an elevation of the anatomic re-
sistance of the pulmonary vascular bed with a resultant increase in pulmonary artery pres-

ture. The cause of this increased resistance is not apparent, but thrombosis with recanaliza-
tion, and in one instance a diffuse arteritis, has been demonstrated. Clinical evidence suggests that in some cases the disease has been present since birth. No evidence was found suggesting that it was the result of a prolonged elevation of pulmonary blood flow.

5. It appears that surgery is indicated in those cases in which a right to left shunt is not present but that ligation may be dangerous or fatal in instances where a right to left or “reversed” shunt is present.

6. The most important single diagnostic study which will detect the presence of a ductus with a reversed shunt consists of the determination of the oxygen content of simultaneously drawn blood samples from the right brachial and femoral artery at rest and during exercise.

7. Cardiac catheterization is necessary to detect accurately the “atypical” ductus without a right to left shunt, which may be erroneously diagnosed clinically as an atrial septal defect with pulmonary hypertension or “primary” pulmonary hypertension.

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SUMARIO Español

Ocho casos de conducto arterioso patente asociado con hipertensión pulmonar marcada son presentados con estudios completos de catarización cardíaca en seis pacientes y estudios de autopsia en tres. Cuatro pacientes tenían evidencia clara de una desviación inversa a través del conducto, tres de ellos presentaban el cuadro clínico de enfermedad congénita cianótica del corazón. Los autores discuten la naturaleza del aumento en resistencia de la red vascular pulmonar que es la base de los cambios circulatorios en estos casos.

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