Primary Pulmonary Hypertension

Review of Literature and Results of Cardiac Catheterization in Ten Patients

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A brief historical review of primary pulmonary arteriosclerosis and hypertension has been given. Ten additional cases with detailed laboratory, roentgenographic, electrocardiographic, cardiac catheterization, and angiocardiographic studies are presented. The findings on 4 necropsied cases are also included. Progressive exertional shortness of breath, syncope, left chest pain, right ventricular hypertrophy, and pulmonary arterial dilatation, combined with high right ventricular and pulmonary arterial pressure and normal pulmonary capillary pressure in the absence of pulmonary disease, should be extremely suggestive of primary pulmonary hypertension. An unrelenting downhill course of right ventricular failure is usually seen.

Primary pulmonary hypertension has been considered a rare disease. This paper is presented for the purpose of adding 10 cases to the literature and discussing the differential diagnosis and pathology. An attempt will be made to discuss the outstanding features of the cases presented with regard to similarities and differences in the literature. The patients in this series have been studied by clinical evaluation, routine laboratory procedures, electrocardiographic tracings, roentgenograms, cardiac catheterization, lung biopsy in 1 case, necropsy examination in 4 cases, angiocardiography in 2 cases, and miscellaneous clinical procedures such as circulation times, venous pressures, and pulmonary function studies.

Because of sharp conflicts of opinion in the literature, it is very difficult to know the frequency with which the disease occurs. As with many rare diseases, the discrepancy in reporting has been due in part to the numerous synonyms and variance in the criteria for diagnosis. Ayerza’s disease, Ayerza’s syndrome, idiopathic pulmonary hypertension, arteriosclerosis of the lesser circulation, idiopathic right ventricular hypertrophy, cardiacos negros, “black cardiac disease,” pulmonary Raynaud’s disease, and many other names have been applied to the disease.

Review of Literature

Sclerotic plaques in the pulmonary arteries were noted by Vieussens in 1709, but their presence is not necessarily diagnostic of primary pulmonary arteriosclerosis in view of present concepts of the disease. Brenner reported in 1935 that 23 of 31 routine autopsies showed some pulmonary vascular sclerosis, but only 1 case showed right ventricular hypertrophy and had circulatory symptoms. Moschowitz reported varying degrees of pulmonary arteriosclerosis in 6.5 per cent of 770 consecutive necropsies. Ayerza, in 1901, described a patient with severe cyanosis who at autopsy had right ventricular hypertrophy and chronic bronchitis, but he did not mention any pathology in the pulmonary vessels. It was because of a doctoral thesis by Marty in 1912, and subsequent articles by Arrillaga, and Escudero that the term “Ayerza’s disease” became popular. These 3 men were former students of Ayerza, and besides popularizing that term, they focused attention on obliteratorive disease of the pulmonary vessels, which they attributed to syphilis. In 1891 and 1892, Romberg and Aust described the clinical picture of pulmonary hypertension and ascribed it to pulmonary sclerosis found grossly at necropsy. However, they did not demonstrate obliteratorive changes in the vessels. In 1908, Posselt discussed the use of the electrocardiogram and
<table>
<thead>
<tr>
<th>Name, age and sex</th>
<th>First symptom</th>
<th>Presenting complaint</th>
<th>Shortness of breath</th>
<th>Cyanosis</th>
<th>Syncope</th>
<th>Cough</th>
<th>Hemoptysis</th>
<th>Chest pain</th>
<th>Orthopnea</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR, 13, M</td>
<td>Cyanosis</td>
<td>Hemoptysis?</td>
<td>Ex. SOB when first able to walk, squat to get breath</td>
<td>At 18 mo.</td>
<td>None</td>
<td>Upper respiratory infection</td>
<td>Gross, at 12 yrs.</td>
<td>None</td>
<td>None</td>
<td>Was known to have heart murmur as infant; can walk a block and a half at present.</td>
</tr>
<tr>
<td>JS, 17, F</td>
<td>Ex. SOB, weakness gradual</td>
<td>Hemoptysis</td>
<td>Became SOB after s.l. exertion for 4 yrs.; marked for 8 mo. before death</td>
<td>Terminally, at 17 yrs.</td>
<td>At 14 yrs.</td>
<td>At 14 yrs.</td>
<td>Gross at 14 yrs.; several times</td>
<td>None</td>
<td>None</td>
<td>Expired after minor operative procedure at 17 yrs.</td>
</tr>
<tr>
<td>SW, 24, F</td>
<td>Ex. SOB</td>
<td>SOB; ? fainting</td>
<td>Ex. SOB, rather sudden onset at 20 years</td>
<td>None</td>
<td>At 20 yrs.</td>
<td>At 20 yrs.</td>
<td>None</td>
<td>At 24 yrs.</td>
<td>None</td>
<td>Still living; many syncopeal spells associated with SOB; has had dependent edema.</td>
</tr>
<tr>
<td>JS, 30, F</td>
<td>Ex. SOB, paroxysmal tachycardia</td>
<td>Tachycardia</td>
<td>Ex. SOB began with 2nd pregnancy at age 25</td>
<td>At 30 yrs.</td>
<td>At 30 yrs.</td>
<td>Occas.</td>
<td>Streaks, at 29 yrs.</td>
<td>At 30 yrs.</td>
<td>None</td>
<td>Known murmur at 2½ yrs.; onset of symptoms with 2nd pregnancy; dyspnea &amp; syncope outstanding features; pt. still living.</td>
</tr>
<tr>
<td>RG, 34, F</td>
<td>Cough, fatigue</td>
<td>Cough</td>
<td>First noted Ex. SOB a few days before admission</td>
<td>At 34 yrs., Terminally</td>
<td>None</td>
<td>None</td>
<td>Streaks, at 34 yrs.</td>
<td>None</td>
<td>None</td>
<td>Pt. died May 1951; cough and fatigue outstanding features; cyanosis terminal.</td>
</tr>
<tr>
<td>PJ, 8, F</td>
<td>Asymptomatic</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Murmur first noted at 3 months; patient has gotten along well.</td>
</tr>
<tr>
<td>GF, 29, F</td>
<td>Hemoptysis</td>
<td>SOB</td>
<td>Ex. SOB is chief complaint since 27</td>
<td>None</td>
<td>None</td>
<td>Occas. Non-prod. at 27 yrs.</td>
<td>Streaks at 26, gross at 27 yrs.</td>
<td>None</td>
<td>At 29 yrs.</td>
<td>Still living; gravida IX, para IV, aborta IV.</td>
</tr>
<tr>
<td>AG, 29, M</td>
<td>Ex. SOB</td>
<td>Chest pain</td>
<td>Ex. SOB age 28</td>
<td>None</td>
<td>At 29 yrs. with effort</td>
<td>None</td>
<td>None</td>
<td>Subternal &amp; left arm, exertional</td>
<td>None</td>
<td>Died after minor surgical procedure.</td>
</tr>
<tr>
<td>PH, 38, M</td>
<td>Ex. SOB</td>
<td>SOB</td>
<td>Ex. SOB</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Left chest</td>
<td>None</td>
<td>None</td>
<td>Still living but in chronic right heart failure.</td>
</tr>
</tbody>
</table>

Ex. SOB—Exertional shortness of breath
the teleroentgenogram in the diagnosis of pulmonary hypertension. Sanders,10 in 1904, reviewed the autopsy material in 7 cases and found thickened intimal changes in the pulmonary arterial segment along with right-sided heart failure. Monckeberg,12 in 1907, presented what may be the first authenticated case of primary pulmonary arteriosclerosis with clinical and microscopic confirmation. Moschowitz,3 in 1927, believed that all sclerosis of the pulmonary vascular tree was secondary to pulmonary hypertension of various causes. Brenner,2 in 1935, clarified the concept of primary pulmonary arteriosclerosis. He defined the disease as "a rare condition in which there is sclerosis of the pulmonary arteries for no obvious reason (such as cardiac or pulmonary disease) as well as hypertrophy of the right but not of the left side of the heart." He made the statement that primary pulmonary arteriosclerosis is not one pathologic entity, but several different conditions with certain clinical and pathologic characteristics. Brenner thought that most of the cases in the literature were not adequately documented or that some other reason existed to account for the clinical and pathologic findings.

Brenner believed that the disease could be diagnosed clinically. He said that the symptoms were chiefly those of right ventricular failure, for which no adequate cause could be found. He was impressed with the minimal dyspnea and the absence of orthopnea in patients with intense cyanosis. In the cases that he reviewed, syncope, hemoptysis, and chest pain were uncommon. Edema, sometimes associated with ascites and pleural effusion, was a prominent symptom in most cases. He said that it is possible to diagnose the condition by the following points: (1) severe cyanosis and edema with comparatively little dyspnea; (2) clinical and electrocardiographic evidence of hypertrophy of the right ventricle but not of the left; (3) an accentuated pulmonary second sound, perhaps with a pulmonary diastolic murmur, without murmurs indicative of valvular or congenital cardiac disease; (4) clinical or roentgenographic evidence of enlargement of the right heart with prominence of the pulmonary artery and conus of the right ventricle, but with a normal shadow of the left atrium; and (6) no evidence of syphilis.

Brill and Krygier13 described the pathology as consisting of intimal proliferation in the pulmonary arterioles resulting in marked narrowing or occlusion of the lumen in many of the vessels and some recanalization. The larger and medium-sized arteries revealed little or no change from normal. There was associated right ventricular hypertrophy and no evidence of valvular damage or left atrial hypertrophy. Cross and Kobayashi14 found similar pathologic changes with marked hyperplasia of the intimal endothelium in the arterioles, venules, and small veins. These changes were seen with right ventricular hypertrophy and rightsided cardiac failure.

Dresdale and co-workers,15 in 1954, described the characteristic lesion as occurring predominantly proximal to the capillaries, which is consistent with our physiologic findings of a normal pulmonary capillary pressure in 3 patients.

Parmley and Jones16 divided the clinical picture into 2 phases, respiratory insufficiency and cardiac insufficiency. The respiratory phase is predominantly characterized by dyspnea. In the second phase, the patient may develop venous distention, progressive peripheral edema, passive congestion, and effusions in the pleural, peritoneal, and pericardial cavities. They believed that syncopal attacks were rare and could be ascribed to cerebral hypoxia.

**Review of Present Series of Patients**

In our series exertional shortness of breath was present in every case and is probably the most distressing symptom that these patients have (table 1). Dyspnea at rest is a late symptom. More importance must be attributed to this symptom than in most other types of pulmonary congestion. Only 1 of our patients had had orthopnea. Six of our patients have had at least 1 episode of hemoptysis; 3 of them on more than 1 occasion. Six patients have been cyanotic, though none severely so. One patient was cyanotic shortly before death. Cyanosis was noted by the parents of 1 of these patients at 18 months of age and another at 3 years of age. They are now 13 years and 18 years old, respectively. Four of our patients complained of syncope related to exertion, and 1 patient had numerous "weak spells" with exertion but no loss of consciousness. Coughing was noted in all but 1 of our cases. It varied in severity,
| Name, age, sex | Blood pressure | Respiratory rate | Lungs and thorax | Chamber overactivity | Heart size | Thrill | Rhythm | As/Ps | Murmurs | Cyanosis | Clubbing | Abdomen | Habitus |
|----------------|----------------|-----------------|------------------|---------------------|------------|--------|--------|-------|---------|----------|----------|----------|---------|---------|
| RR, 19 F      | 150/100        | 15               | Clear; left chest prominent | Right | AAL, retrosternal | None | Not known | Gr. 3 systol. pulmon. | Tips | None | Negative | Asthenic |
| JS, 20 F      | 150/100        | 20               | Clear; left chest prominent | Right | AAL, RSB 1+ | None | Gallop | Gr. 2 pulm. syst. disappeared in upright position | Terminal | None | Liver down 2 cm. tender | Sthenic |
| SW, 24 F      | 100/70         | 20               | Moist rales right base posteriorly | Right | Enlarged to L & R: 1+ AAL 2-3+ RSB | None | SR | Gr. 4 syst. mit., Gr. 1 mit. preysyst. | Marked in nails | None | Liver down 2 FB tender | Asthenic |
| JS, 30 F      | 120/80         | 22, no distress | Clear | Right, marked | AAL RB retrosternal | None | SR | Gr. 3 syst. | None | None | Negative | |
| RG, 34 F      | 100/70         | 116              | 32, marked distress with coughing | Right | AAL 1+ RSB 2+ | None | SR | Gr. 3 pulm. syst., Gr. 1-2 mitral systolic | Present lips and nails | None | Liver down 3 cm. tender | Asthenic |
| PJ, 36 F      | 120/80         | 60               | Clear | Right, marked; left, slight | AAL retrosternal | None | Not known | No | None | Liver down 1 FB | Asthenic |
| GF, 29 F (Negro) | 100/60       | 20                | No distress | Clear | MCL 1+ RSB 2+ | None | SR, occ. gallop | P1 = P2 | None | P2 > P1 | None | Liver down 3 FB, tender | Asthenic |
| AF, 29 M (Negro) | 100/60       | 20                | No distress | Clear | MCL 1+ RSB 2+ | None | SR, occ. gallop | P2 > P1 | None | Terminal only | None | Negative | Sthenic |
| PH, 36 M      | 120/80         | 60               | Clear | Right | AAL | None | SR | P2 > P1 | Gr 3 mit. syst., Gr. 2 mit. preysystolic | During marked exercise | None | Liver down 3 FB | Sthenic |

AAL—anterior axillary line, FB—fingerbreadths, RSB—right sternal border, MCL—mideclavicular line, SR—sinus rhythm
however, from an occasional dry cough to severe episodic bouts productive of frothy, purulent, or bloody sputum. Chest pain was present in 4 of our patients and was severe in 2 of them. Chest pain was predominantly substernal in character, and, in some, with radiation down both arms on exertion. The pain was at times relieved by nitroglycerin. In some, "catching" chest pain with respiration between these episodes was present. The substernal pain may in part be due to pulmonary hypertension and also to coronary insufficiency.

All except 2 of our patients were slender and undernourished (table 2). Systemic hypertension was not present in any of them. Three were cyanotic when first seen, and 3 others were cyanotic shortly before death. Minimal clubbing of the fingers was present in 1 patient. The lungs were usually clear to physical examination, though bilateral crepitant rales were noted in 1 case, and evidence of pleural effusion in 1 case. Right ventricular overactivity was present in all cases. The heart was enlarged to the left of the midclavicular line by percussion in all but 1 case and to the right of the sternum in 5. Thrills were palpable along the left sternal border in the third and fourth interspaces in 2 patients. All of our patients had a regular sinus rhythm with a pulse rate of between 70 and 130/min. P1 was loud and greater than A2 in all except 1 case. Eight of our 10 patients had murmurs. These were predominantly pulmonary systolic murmurs, though pulmonary diastolic murmurs were noted in 2 instances. Two patients had an apical systolic murmur, and 2 patients had a questionable apical presystolic murmur. In 6 cases the liver was moderately enlarged and tender.

Teleroentgenograms and fluoroscopy revealed right ventricular hypertrophy, prominent pulmonary arterial segments, and frequently dilated pulmonary trees well out into the lung parenchyma (table 3). In some, marked pulsations were seen in the pulmonary hilar vessels. In addition, uniform lack of parenchymal lesions and failure of the left
atrium to show enlargement helped complete the picture (fig. 1).

The electrocardiographic tracings indicated right ventricular hypertrophy in 9 of 10 cases. In 2 of the far-advanced cases ischemic T wave changes were also noted. No excessive P wave changes were noted (fig. 2).

One of the autopsied cases revealed right ventricular hypertrophy with a normal electrocardiogram.

Routine laboratory procedures were of little diagnostic importance in our cases. An elevated erythrocyte count and hemoglobin were found in 2 of our patients. The serologic tests for syphilis were negative in all cases.

**Review of Cardiac Catheterization Data in Other Cases**

Dresdale’s group\(^1\)\(^5\) catheterized 3 patients, and all revealed greatly increased pulmonary, right ventricular, and right atrial pressures. In the 1 patient in whom the pulmonary capillary pressure was obtained, it was found to be normal. In all 3, the resting arterial oxygen saturations were normal, and it was only slightly decreased in 1 patient after exercise.

Soothill\(^7\) reported a cardiac catheterization of a 22-year-old woman with greatly elevated pressures in the right atrium (26/12 mm. Hg), right ventricle (54/17 mm. Hg), and pulmonary artery (128/83 mm. Hg), and a decreased cardiac output of 1.3 L./M.\(^2\)/min.

**Table 4. Cardiac Catheterization Findings**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Right atrium</th>
<th>Right ventricle</th>
<th>Main pulmonary artery</th>
<th>Pulmonary capillary pressure</th>
<th>Cardiac index L./min./M.(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>3/-1</td>
<td>130/30</td>
<td>110/70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>JS</td>
<td>2/-2</td>
<td>87/6</td>
<td>80/40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BJ</td>
<td>10/0</td>
<td>60/0</td>
<td>60/30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SW</td>
<td>5/2</td>
<td>100/5</td>
<td>98/78 (88)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>JS</td>
<td></td>
<td>75/15</td>
<td>65/35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RG†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PJ</td>
<td>5/1</td>
<td>95/25</td>
<td>97/75 (82)</td>
<td>12</td>
<td>Resting cardiac index 2.01</td>
</tr>
<tr>
<td>GF</td>
<td>5/2</td>
<td>100/5</td>
<td>98/78 (88)</td>
<td>11</td>
<td>Resting cardiac index 1.8; Exercise cardiac index 1.7</td>
</tr>
<tr>
<td>AG</td>
<td>10/3</td>
<td>155/5</td>
<td>160/90 (115)</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>PH</td>
<td>5/2</td>
<td>85/10</td>
<td>85/25</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Oxygen levels were within normal limits on all these patients, with no evidence of left-to-right shunt.
† Angiography revealed right ventricular hypertrophy, prominent pulmonary vascular tree, and no evidence of shunt. Catheterization not done.
‡ Figures in parentheses are mean pressures.

**Table 5. Necropsy Findings**

<table>
<thead>
<tr>
<th>Name, age, sex</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>AG 29 F</td>
<td>Right ventricular hypertrophy; pulmonary arteriosclerosis; small atherotic plaque; pulmonary artery; valve areas normal and no left atrial enlargement; pleural effusion, bilaterally</td>
</tr>
<tr>
<td>RG 34 F</td>
<td>Right ventricular hypertrophy; pulmonary arteriosclerosis; bilateral pleural effusion and ascites, peripheral edema; valve areas normal</td>
</tr>
<tr>
<td>BJ 20 F</td>
<td>Right ventricular hypertrophy; pulmonary arteriosclerosis; pulmonary arteriosclerosis with one plaque; peripheral edema; valve areas normal</td>
</tr>
<tr>
<td>JS 17 F</td>
<td>Right ventricular hypertrophy; pulmonary arteriosclerosis; normal valve areas; small peripheral pulmonary infarction; small area of bronchopneumonia</td>
</tr>
</tbody>
</table>
Dressler\textsuperscript{18} stressed the diagnostic importance of high pulmonary arterial pressures in the disease and no change in the arterial oxygen saturation with exercise.

Dexter\textsuperscript{19} reported 4 cases in which venous catheterization of the heart was performed. The cardiac index was reduced in 3 and the stroke output was reduced in all 4. The arterial oxygen saturations were 77, 89, 94, and 93 per cent. The pulmonary arterial pressures were reported as 110/50 mm., 110/60, and 80/65 Hg, and the right ventricular pressures were elevated in patients with failure. The pulmonary capillary pressures were reported as 10 in the 2 instances in which it was done. The total pulmonary resistance and pulmonary vascular resistance were markedly increased.

In all of our 9 patients that were catheterized, high right ventricular and pulmonary arterial pressures were uniformly found (table 4). The 3 pulmonary capillary pressures that were obtained were within normal limits. This may be a very important diagnostic point in the differentiation from secondary pulmonary hypertension in which the so-called "wedge pressure" is frequently elevated. This suggests a high resistance in the pulmonary arterioles prior to the pulmonary capillary

\textbf{Fig. 2. Electrocardiographic tracing revealing right ventricular hypertrophy}
Fig. 3. Heart and lungs, revealing marked right ventricular hypertrophy, small yellow atheromatous plaques in main pulmonary artery, and 2 small hemorrhagic infarcts in the lungs.

area. Cardiac outputs were reduced in the 2 patients in whom they were obtained.

Cross and Kobayashi reported that a 20-month-old infant who received 75 ml. of saline and 25 ml. of plasma suddenly became cyanotic, collapsed, and died almost instantaneously. In 1 patient in whom all the catheterization procedures had been successfully completed, a final 25 ml. of Diodrast was injected into the pulmonary artery; the patient almost immediately developed a convulsive seizure, became cyanotic, and died. These experiences emphasize the relative rigidity of the pulmonary vascular tree and the possible high degree of "precapillary block" in such patients, and suggest the need for extreme caution in carrying out catheterizations. Unless the case is quite unusual, we believe that catheterization should not be performed.

Dresdale and co-workers noted that the ventilatory capacity was reduced at rest, and the rise with exercise was less than expected. In 2 of our patients with extensive pulmonary function studies, the only abnormality noted was a slight diminution in the timed vital capacity.

The most characteristic findings of primary pulmonary arteriosclerosis were those in the lung microscopically and in the heart grossly. The heart was enlarged as a result of right ventricular hypertrophy (fig. 3). The right ventricle measured up to 4 times its normal thickness, while the left ventricle was either normal or less than normal. The right ventricle varied in thickness from 10 to 30 mm., having a homogeneous red-brown appearance. Areas of focal fibrosis were seen grossly. The endocardial surfaces were smooth and glistening, and the valves showed no deformities. There was little coronary or generalized arteriosclerosis. This latter finding, however, depended to a great degree upon the age of the
patient, but characteristically no arteriosclerosis was present within the coronary system. In all 4 of our patients, the pulmonary artery was larger in total circumference than the combined circumference of the pulmonary veins. This is the reverse of the normal findings.

The gross examination of the lungs revealed little pathologic change. These patients were more susceptible to infectious diseases, and at the time of autopsy areas of bronchopneumonia were discernible in 1 of the patients. One case here reported showed multiple small infarcts, which several other authors have reported as a frequent finding. The infarcts appeared as wedge-shaped airless portions of lung located in the periphery, and were quite small.

Microscopically, the only observations of significance were in the lungs. The lumina of the middle-sized and smaller pulmonary arteries and arterioles were strikingly reduced in size (fig. 4). The capillaries showed no changes. Occasionally, soft, small, yellow, raised atheromatous plaques were found in the major pulmonary arteries; they were noted in 2 of our patients. In the middle-sized and smaller arteries and arterioles, there was a marked increase in the depth of subendothelial space due to numerous lipoid-laden mesothelial cells. Occasionally, cholesterol clefts were present, but calcification was not prominent. This fatty material stained positively with Sudan III. The intima was usually intact but frequently the lumina of these small vessels have been completely obliterated by organized thrombi and subintimal fibrosis.
In some areas, there was evidence of recanalization. Fresh thrombi were not observed in this study. A notable finding was the distinct thickness of the musculature of the smaller arteries and arterioles, which by differential staining technics proved to be an increase in fibrous connective tissue without increase in muscular component. The elastic lamina were usually quite prominent and appeared to be intact by special elastic stains.

In 1 patient, areas of organizing pneumonia and areas of thickened alveolar septa due to old inflammatory reaction were seen. Emphysema was also frequently observed.

Microscopically, the myocardium of the right ventricle showed only evidence of hypertrophy with large “boxcar”-shaped nuclei and large muscle bundles. Frequently, the myocardium showed evidence of focal myocardial fibrosis.

Our 4 necropsied cases all showed evidence of right ventricular hypertrophy. There was marked hypertrophy of the intima in the pulmonary arterioles. In 2 there were atherosclerotic plaques in the pulmonary artery. In 1 there was a questionable malformation of the arterioles and capillaries. The pulmonary parenchyma was normal, and the left atria were normal in all cases. In 1 case multiple small peripheral infarctions were seen.

**Differential Diagnosis**

Eisenmenger’s complex can be differentiated with exercise, according to Dexter,19 because of the much greater increase in pulmonary arterial pressure in primary pulmonary hypertension. He further believed that the pulmonary capillary pressure would be normal, despite the elevated pulmonary arterial pressure, and found it so in 3 of the 4 cases he catheterized. Capillary pressures may also be normal in Eisenmenger’s complex. Right ventricular oxygen step-up, angiocardiograms, and dye-dilution curves aid in making this differentiation.

Interatrial septal defects reveal evidence of a left-to-right shunt on cardiac catheterization and, in some, it may be possible to direct the catheter tip through the septal defect into the left atrium. Electrocardiographic tracings usually show conduction disturbances, most commonly right bundle-branch block or atrioventricular blocks, unlike primary pulmonary hypertension, which shows only right ventricular hypertrophy, with or without ischemic T wave changes.

Mitrail stenosis may present a history of previous active rheumatic fever. The P waves on the electrocardiographic tracings are frequently broadened and notched and right bundle-branch block is frequently seen. The telerentgenogram in the right anterior oblique position usually reveals left atrial hypertrophy. An opening snap or presystolic localized apical murmur helps differentiate the condition, although rarely the presystolic component may occur in association with primary pulmonary hypertension. Congenital mitral stenosis does not always show left atrial enlargement by fluoroscopic examination, and without pulmonary “wedge” pressures may be confused with primary pulmonary hypertension. Endocardial fibroelastosis occasionally must be considered in the pediatric age group, but the electrocardiogram aids in the differentiation. In endocardial fibroelastosis there is usually subendocardial injury and left ventricular hypertrophy. Cor triatriatum must be ruled out by the same method as congenital mitral stenosis, since they cannot be separated clinically.

Pulmonary stenosis with its loud systolic murmur and its diminished or absent second pulmonary second sound must also be ruled out. The post-stenotic dilatation of the pulmonary artery, frequently seen on the left with relatively clear lung fields, combined with high right ventricular pressure and normal or low pulmonary arterial pressure helps to establish its identity.

Because of the syncope Dressler18 emphasized the necessity of ruling out neurosis and hysteria. He believed the mechanism of syncope may be due to decreased cerebral blood flow secondary to decreased cardiac output or to vasovagal reflex. Dressler stressed the importance of effort syncope as an early manifestation of primary pulmonary arteriosclerosis.
He suggested that it is due to a reflex mechanism originating in neuroceptors in the wall of the pulmonary artery, using the vagus nerve as an afferent pathway, and resulting in a fall of the systemic blood pressure and inhibition of the heart beat. Syncope is usually not encountered with mitral stenosis, the congenital heart diseases with which primary pulmonary hypertension might be confused, or chronic cor pulmonale. The syncope of primary pulmonary hypertension must be differentiated from supraventricular or ventricular arrhythmias, carotid sinus and vasovagal syncope, acute left ventricular failure, as seen with advanced aortic stenosis or myocardial infarction, ball-valve thrombi, and venoarterial shunts.

**Course and Prognosis**

Of the original 10 cases followed by us, 4 have already died: 2 who died during minor surgical procedures showed intermittent or no cyanosis, and 2 who died in right-sided cardiac failure showed terminal cyanosis. Of the 6 surviving patients, 5 had exertional shortness of breath, 3 had chronic right heart failure, 3 had cyanosis, and 2 had syncope. There was only 1 patient, aged 8 years, who was relatively asymptomatic. The course, although variable in duration, was ultimately that of fairly intractable and progressive failure of the right ventricle with maintenance of a sinus rhythm and a lack of orthopnea. From the onset of symptomatology to the termination of the disease, De Navasquez\(^2\) observed that the course varied from 5 months to 5 years. This may usually be true, but we have seen 1 patient with symptoms of exertional shortness of breath for 12 years who is still getting along fairly well without right heart failure.

Chess and Yonkman,\(^2\) noted that tolazoline hydrochloride (Priscoline), possibly through its adrenolytic and sympatholytic actions, reduced the pulmonary arterial pressure and increased pulmonary blood flow. The parenteral effects of Priscoline are of short duration, up to 20 to 30 min., and the response to chronic oral administration of the drug was inconclusive. This observation suggested sympathetically as a therapeutic approach to the problem. However, extensive stripping of the sympathetic nerve supply to the pulmonary vascular tree has been very disappointing.\(^2\) In 2 patients in whom we used oral Priscoline, no apparent symptomatic improvement was noted. Because of the occasional tendency to spontaneous pulmonary thrombosis, anticoagulant therapy might be considered, but it has not been used as yet to our knowledge.

**Summary**

A brief historical review of primary pulmonary arteriosclerosis and hypertension has been given. Ten additional cases with detailed laboratory, roentgenographic, electrocardiographic, cardiac catheterization, and angiocardiographic studies are presented. The findings on 4 necropsied cases are also included. Progressive exertional shortness of breath, syncope, and left chest pain with roentgenographic and electrocardiographic evidence of right ventricular hypertrophy, pulmonary arterial dilatation, high right ventricular and pulmonary arterial pressure, and normal pulmonary capillary pressure in the absence of pulmonary disease should be extremely suggestive of primary pulmonary hypertension. An unrelenting downhill course of right ventricular failure is usually seen.

**Summario IN Interlingua**

Es presentate un breve revista historic de primari arteriosclerosis e hypertension pulmonar. Es addite dece nove casos con detaliate studios laboratorial, roentgenographic, electrocardiographic, de catheterisation cardiac, e angiocardiographic. Es etiam includite le constatationes de 4 necropsias. Progressive dyspnea post effortio, syncope, e dolores sinistrothoracic con evidentia roentgenographic e electrocardiographic de hypertrophia dextero-ventricular, dilatation pulmono-arterial, alte presion dextero-ventricular e pulmono-arterial, e normal presion pulmono-capillari in le absentia de morbo pulmonar deberea esser prendite como un forte indication de hypertension pulmonar. Un persistente deterioration del disfallimento dextero-ventricular es usualmente a notar.
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One must be a professional Ulysses in craft and wisdom not sometimes to err in estimating the nature of an attack of severe heart pain. There is no group of cases so calculated to keep one in condition of wholesome humility.—William Osler. Angina Pectoris and Allied States, 1897.
Primary Pulmonary Hypertension: Review of Literature and Results of Cardiac Catheterization in Ten Patients

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