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DEGENERATIVE ARTERIOPATHY WITH PULMONARY HYPERTENSION: A REVISED CONCEPT OF SO-CALLED PRIMARY PULMONARY HYPERTENSION
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The etiology of so-called "primary" pulmonary hypertension is a current medical enigma. It is not enigmatic for lack of attention, for there are a number of current theories, capably reviewed by Dresdale and McGuire. One of the popular theories attributes the arterial histopathology to long-standing arterial spasm, the cause of which is unexplained. Another theory suggests repeated embolization, based on the finding of apparent emboli in the small vessels of the lung at necropsy, but a consistent demonstration of a source for such embolization has not been presented.

Although inexorably downhill, the clinical course of this disease is of considerable interest. One of the features which has attracted study is the frequency of syncope, often as a presenting symptom. Most explanations regarding this syncope have been unsatisfactory, principally because they have failed to account for the infrequency of syncope in patients with equal degrees of pulmonary hypertension secondary to some demonstrable cause.

Following the recent demonstration of vascular lesions in the sinus node and AV node of three patients with "primary pulmonary hypertension," it was postulated that these lesions are the mechanism of both the frequently observed syncope and sudden death. Perhaps more important than a possible explanation of the mechanism of syncope and sudden death in these cases, however, is the fact that the vascular lesions observed in the sinus node and AV node were in systemic arteries. This makes the theory that the similar histopathology in the pulmonary arteries is secondary to pulmonary hypertension less tenable.

An investigation of other systemic arteries in these three necropsied cases of so-called "primary" pulmonary hypertension has confirmed the observation that an unusual process involves the walls of their systemic as well as pulmonary arteries. For this reason the three cases being reported are diagnosed degenerative arteriopathy with pulmonary hypertension, which for the sake of brevity will be referred to as DAPH. The clinical and necropsy findings in all three fulfill the diagnostic criteria of so-called "primary pulmonary hypertension".

CASE REPORTS

Case 1. M. B., a 31 year old white housewife, was admitted to the Henry Ford Hospital on May 22, 1960, because of fainting spells. She was well until syncopal bouts began 6 months prior to admission, progressively increasing in frequency so at the time of admission they were occurring several times daily. All the episodes were preceded by palpitation. The first occurred during an emotional upset, but subsequent ones had followed progressively decreasing amounts of physical exertion. For two weeks prior to admission there was increasing cardiac failure and dyspnea.

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She had had four normal pregnancies, with healthy children aged 12, 10, 8 and 6 years. In 1954 the patient had tubal ligation, and in October of 1957 a hysterectomy. An uncle, aunt and the patient's mother had diabetes. Her father and four siblings were alive and well.

On examination the patient was small, pale and of ectomorphic habitus. There was no cyanosis nor clubbing; peripheral pulses were normal. The lungs were resonant, with good breath sounds and no rales. Cardiac rhythm was regular at 90 per minute; blood pressure was 100/80 mm. Hg. A left parasternal heave was present, with a systolic thrill in the left second intercostal space; the second pulmonic sound was markedly accentuated and split, being followed by a soft blowing diastolic murmur at the left sternal border. The liver edge was palpable at the costal margin and tender, but did not pulsate. There was no peripheral edema.

An electrocardiogram showed right ventricular and right atrial hypertrophy with sinus tachycardia. Other laboratory studies, including blood and urine sugar determinations, were normal. She was treated conservatively, discharged May 23, and requested to return in one month for cardiac catheterization.

On June 26 a right cardiac catheterization was done by Dr. E. H. Drake. Pressures in the pulmonary wedge position, main pulmonary artery and right ventricle were respectively (in mm. Hg) 10 mean, 110/45 and 115/5-20. A small amount of oxygen desaturation in the femoral artery blood was raised to normal when the patient breathed 100% oxygen. Oxygen content of blood from the pulmonary arteries and right heart was normal. A diagnosis of primary pulmonary hypertension was made and the patient was again discharged. Treatment included digitoxin, hydrochlorothiazide and reserpine.

Syncope continued to increase in frequency, and her terminal admission was August 19, at which time a new murmur of tricuspid regurgitation was present. Cardiac rhythm was regular at 100 per minute. On August 20 an examiner noted frequent premature beats, and that evening there was bigeminal rhythm; no electrocardiogram was made then but the one of August 19 showed normal sinus rhythm and was unchanged from the one of May. During the night of August 21 the patient was found dead in bed.

At necropsy both the right atrium and ventricle were dilated and hypertrophied. There were no cardiac septal defects nor extracardiac shunts. The cardiac valves were normal. A moderate degree of sclerosis was present in all arteries, including the coronary arteries (Fig. 6). The sinus node artery and AV node artery both arose from the right coronary artery at the usual sites.25,26 There were no obvious mural thrombi on gross inspection (see below). There were no gross pulmonary emboli and no apparent peripheral sources for emboli.

Histology of the pulmonary arteries is shown in Figs. 1-5; it is characteristic of "primary pulmonary hypertension". Notice the similarity to the arteriopathy of the systemic arteries shown from the heart and the adrenal gland (Figs. 7-15). The same arteriopathy was less frequently seen in the kidney, spleen, and liver.
Involvement of the sinus node artery was characterized by a focal granular degeneration of the tunica media, with some cyst formation and frequent hemorrhage (Fig. 7). An identical lesion was present in the AV node artery and some of the pulmonary arteries of this case (Figs. 3 and 10), and has also been described by others (Case 4 of Kuida, et al.\textsuperscript{27}). Note the resemblance of the arteriopathy in the AV node and a larger ventricular artery (Figs. 6 and 12) to the prevalent lesion in Case 2 (Figs. 17-22, 25-30).

A variety of stains were employed in an effort to identify the amorphous material in the degenerated portion of the wall of the sinus node artery. It did not stain as collagen with the Goldner trichrome stain. It was not metachromatic with toluidine blue nor Alcian blue and was Schiff negative. It did not stain with Oil Red O. It had no affinity for iron. On staining with acridine orange the rim of the degenerating area fluoresced bright yellow under ultraviolet (Fig. 15), but the majority of the material did not fluoresce; there was no fluorescence with acriflavine, nor with any of the non-fluorochromatic stains. The material was not basophilic for hematoxylin.

Similar histochemical analysis of the intimal proliferation in the pulmonary arteries demonstrated that this process was Schiff positive, stained with Alcian blue and with the Rinehart-Abul Haj colloidal iron stain, was not fluorescent with any of the above stains, was not metachromatic with toluidine blue, and had no basophilic character. This material was likely an acid mucopolysaccharide. The endothelial proliferative process did not contain elastic fibers.

The old organized mural thrombus shown in Fig. 16 is directly underneath the sinus node and occupies the antrum atrii dextri of the crista terminalis, a site which Söderström\textsuperscript{28} has indicated is a frequent one for atrial thrombosis. It is not difficult to see how such a thrombus may be overlooked, as it was in the gross study of this case.

![Figure 1](image-url)

**Figure 1**
Small pulmonary artery from Case 1; note the remarkable intimal endothelial proliferation and the hypoplastic tunica media. Verhoeff-Van Gieson stain with magnification in A X64 and in B (same artery) X160.
Figure 2
Another small pulmonary artery from Case 1, with the smudgy degeneration of the tunica media well shown under high power (A and B). Goldner trichrome stain with magnification in A X102 and in B (same artery) X256. C shows a similar artery; acridine orange stain, UV light, BG-12 filter, X64.

Figure 3
Small pulmonary artery from Case 1, demonstrating intramural degeneration and hemorrhage identical to that seen in the sinus node artery (Fig. 7) and AV node artery (Fig. 10). Goldner stain with magnification in A X40 and in B (same artery) X102.
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Figure 4
Two small pulmonary arteries of Case 1 with emboli. Note the distention of the vessels and the absence of attachment of the emboli to the wall or of any cellular reaction in the wall. A is stained with toluidine blue, X160; B is stained with Verhoeff-Van Gieson, X64.

Figure 5
A longitudinal section of a small pulmonary artery from Case 1, demonstrating the intimal proliferation and thin tunica media; Verhoeff-Van Gieson, X64.

Figure 6
A left ventricular coronary artery from Case 1, exhibiting an "atheroma"; Goldner stain. Magnification in A is X40 and B (same artery) X160. Cystic degeneration of the tunica media is apparent at the higher power.
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Figure 7
The sinus node artery from Case 1, with some extravasation of blood into the node. The granular compartmented degeneration with hemorrhage is well seen at the higher power. Goldner stain with magnification in A X64 and in B (same artery) X160.

Figure 8
A section through the sinus node artery of Case 1 taken 16 mm. from the section in Fig. 7. The degeneration in the tunica media is discernible at this magnification (X160) but is less apparent at lower power. Goldner trichrome stain.

Figure 9
A section through the sinus node artery of Case 1 taken 4 mm. from the one in Fig. 7. The internal and external laminae are intact, but the degeneration of the tunica media is obvious. Verhoeff-Van Gieson stain with magnification in A X64 and in B (same artery) X160.
Figure 10
Artery to the AV node from Case 1, showing focal intramural hemorrhage and degeneration similar to that of the sinus node artery (Fig. 7) and a pulmonary artery (Fig. 3). Goldner stain with magnification in A X64 and in B (same artery) X160.

Figure 11
Two views of another portion of the AV node artery in Case 1, showing cystic degeneration of the tunica media. Goldner trichrome stain magnification in both A and B X160.

Figure 12
A third section through the AV node artery of Case 1, showing still a different arteriopathy (although the same artery) from Figs. 10 and 11; the lesion here is primarily intimal proliferation and is identical to the predominant lesion in Case 2. Note the process here begins to comprise the lumen of the artery. Goldner stain, X64.
Figure 13
Three other abnormal myocardial arteries from Case 1. A is from the right atrium, showing an obliterator mixed intimal and medial proliferation; Goldner, X256. B is also from the right atrium, with primarily medial degeneration; acridine orange stain with ultraviolet light and BG-12 filter, X160. C is from the right ventricle, showing cystic medial degeneration; Goldner, X160.

Figure 14
The wall of an adrenal artery from Case 1, showing granular and cystic degeneration; Goldner trichrome, X160.

Figure 15
A section of the sinus node artery from Case 1 taken near that in Fig. 7; note the fluorescent rim in the area of maximal mural degeneration. Acridine orange stain with ultraviolet light and BG-12 filter; A X82, B (same artery) X160.
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Figure 16
Comparable sections of sinus nodes showing the vacant antrum atrii dextri of the crista terminalis in the normal (A) but the presence of an old organized mural thrombus in Case 1 (B). Both Goldner stain, X4. The sinus node can be seen about the artery in the upper left corner of each photomicrograph, near the epicardium; in B a focus of hemorrhage is visible in the wall of the artery, but the extensive infarction of the node which was present is not visible at this power.

Case 2. E. B., a 35 year old white unmarried schoolteacher, was delivered at the Henry Ford Hospital October 31, 1924; her mother's pregnancy and the delivery were uncomplicated. Except for one examination for a minor feeding problem in infancy, the patient was next seen July 6, 1950, complaining of weakness of both legs present 4 months. She also described coldness and numbness of the fingers on contact with cold for 3 years. Following hospitalization and extensive study, the final diagnoses were post-influenzal asthenia and mild Raynaud's phenomenon. In the review of symptoms she incidentally mentioned that she had been fainting about 3 or 4 times a year, usually in church, for the past 4 years. She had no other cardiac complaints and physical examination of the heart was normal. Erythrocytic sedimentation rate was 45 mm./hr., but other laboratory studies were normal. No electrocardiogram was made.

In January of 1958 she again complained of weakness beginning after "flu," followed by exertional dyspnea, orthopnea and the development of visible pulsations in the neck. After being ill for one month she was admitted to another hospital for two weeks, where she was told her heart was enlarged and sent home to rest. When her condition continued to deteriorate she returned to the Henry Ford Hospital and was admitted April 2, 1958.

On this terminal admission peripheral cyanosis and orthopnea were noted. The blood pressure was 105/60 mm. Hg but the sounds were faint. The femoral pulse was regular at 120 per minute; the radial pulses were difficult to palpate. The lungs were resonant and there were no rales. There was a left parasternal heave and the second pulmonic sound was accentuated. No murmurs were audible. Pulsations were present in the jugular veins; the liver was enlarged but not tender; there was moderate pretibial edema.
Except for a slight neutrophilia the blood studies were normal; repeated LE cell preparations were negative. There were some granular casts and 2+ albumin in the urine. At fluoroscopy there was marked cardiac enlargement and cardiac pulsations were virtually absent. An electrocardiogram on several occasions revealed right ventricular hypertrophy and sinus rhythm.

The patient remained afebrile throughout her hospital course. Two aspirations from the pericardium yielded 80 cc. of clear fluid and 165 cc. of serosanguinous fluid; these were negative for LE cells, and cultures were sterile. Despite conventional therapy for cardiac failure, this continued to increase, with the exception of pulmonary edema, from which she remained free. Ascites appeared and increased. On the 21st hospital day (April 23, 1958) she became more cyanotic, apprehensive, and expired quietly.

At necropsy there was a small amount of serosanguinous pericardial fluid. The right ventricle and right atrium were dilated and hypertrophied. Near the apex of the right ventricle there was a mural thrombus with central liquefaction. The arteries to the sinus node and AV node both arose from the right coronary artery. The cardiac valves and septa were normal and there was no arteriovenous shunt. No peripheral thrombi were found and no atrial thrombi were recognized on gross examination (see below).

The histologic appearance of the pulmonary arteries was characteristic of "primary pulmonary hypertension" (Figs. 17, 18). Note their resemblance to the arteriopathy present in the adrenals, brain, spleen, liver, kidneys and heart (Figs. 19-30). Prevalence of the systemic arterial lesions was marked in the adrenals, where virtually all the arteries were involved, and in the heart, especially the right atrium and sinus and AV nodes; in other organs the lesions had to be sought. The special similarity of the lesions in the adrenals, the heart and lungs is impressive. Hemorrhage in the tunica media is seen in Fig. 24, similar to that of the sinus node artery and some pulmonary arteries of Case 1. Histochemical studies in this arteriopathy gave the same negative results as in Case 1. There was no significant fluorescence with any of the stains studied.

As in Case 1 an antemortem thrombus was present underneath the sinus node (Fig. 31), and was not recognized on gross inspection. In discussing such thrombi, Söderström indicated that even though the portion of damaged atrial myocardium bordering on these sinuses in the crista terminalis was very small, the ensuing thrombosis usually filled most of the sinuses. The possible role of emboli from such thrombi relative to both pulmonary hypertension and pulmonary arteriopathy in DAPH is the subject of later discussion.
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Figure 17
Two views of the same pulmonary arteriole from Case 2, showing the typical intimal proliferation and the hypoplastic tunica media, visibly degenerated at the higher magnification. Goldner trichrome; A X64 and B X160.

Figure 18
Another small pulmonary artery from Case 2, showing the same intimal proliferation and medial degeneration as Fig. 17, plus the intact internal and external laminae. Verhoeff-Van Gieson, X160.

Figure 19
An adrenal artery from Case 2, with obliterative intimal proliferation. Hematoxylin and eosin, X64.

Figure 20
Another adrenal artery from Case 2, showing the same pathology as the pulmonary arteries in Figs. 17 and 18. The basic similarity of the arteriopathy in all the organs of each of the three cases soon becomes apparent. Verhoeff-Van Gieson; A X64, B (same artery) X160.
Figure 21
Adrenal artery from Case 2; note the similarity of this artery to those from the liver (Fig. 25) and kidney (Fig. 26). Hematoxylin and eosin, X64.

Figure 22
Two other adrenal arteries from Case 2, showing the basic pattern of intimal proliferation and medial degeneration or hypoplasia. Verhoeff-Van Gieson, X160 in both A and B.

Figure 23
Two small arteries from the brain of Case 2, with granular focal degeneration in the tunica media. Both A and B with Goldner stain at X160.
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Figure 24
Small artery in the spleen of Case 2, with mural hemorrhage. Goldner, X160.

Figure 25
Intimal proliferation and medial hypoplasia in a small artery in the liver in Case 2. Goldner, X160.

Figure 26
The same basic arteriopathy as in the other organs, shown here in the kidney of Case 2. Goldner, X64.

Figure 27
Two views of a section of the left coronary artery in Case 2, with an "atheroma." Goldner stain; A X10, B (same artery) X64.
Figure 28
Two other coronary arteries from Case 2, A showing remarkable intimal proliferation and B smudgy medial degeneration. A is a branch of the right coronary artery in the eustachian ridge of the right atrium. Goldner, X64; B is a branch of the left coronary artery in the obtuse margin of the left ventricle. Goldner, X160.

Figure 29
The artery to the AV node in Case 2, with the lumen virtually occluded by intimal proliferation. Goldner, X82.

Figure 30
The sinus node artery from Case 2, showing the same arteriopathy as the artery to the AV node. All 3 views are of the same artery, Verhoeff-Van Gieson stain with A X40, B X64 and C X160. In B there is a gross defect in the tunica media which has been replaced by the intimal proliferative process; see text for a discussion of this relationship, and its applicability to the pathogenesis of systemic atherosclerosis. In C the moth-eaten appearance of the degenerating tunica media is well shown.
Case 3. J. M., a 29 year old white married housewife and mother of two children (ages 4 and 7) was referred to the Henry Ford Hospital from Grand Rapids by Dr. Noyes L. Avery, Jr. She was admitted May 9, 1958, with complaints of dyspnea and syncope which began 8 months previously. In October of 1957 she had been catheterized by Dr. Avery and the pressures in the wedged (pulmonary) position, the pulmonary arteries and right ventricle were respectively (in mm. Hg) 4 mean, 120/50 and 120/12. Right atrial pressure was 16/8 and the pulse contour suggested tricuspid valvular regurgitation. Oxygen contents were all normal. The diagnosis of primary pulmonary hypertension was made.

On admission to Henry Ford Hospital the patient was weak, orthopneic and slightly cyanotic. Blood pressure was 124/90 mm. Hg and cardiac rhythm was regular. There was a left parasternal heave and a blowing diastolic murmur along the left sternal border, with a loud systolic murmur and thrill in the same area. The second pulmonic sound was loud and split. There were no rales, but resonance and breath sounds were diminished at the right lung base. The neck veins were full and pulsating. Ascites was present.

NPN on admission was 70 mg. percent; there were granular casts and albumin in the urine. Repeated LE cell tests were negative. Other blood studies were normal. An electrocardiogram showed right ventricular hypertrophy and sinus rhythm.

Her course in the hospital was marked by increasing weakness, oliguria and increasing right heart failure. She expired quietly on the fourth hospital day.

At necropsy there was dilatation and hypertrophy of the right atrium and right ventricle; the valves and septa were normal; mural thrombi were adherent to the endocardium of the right atrium near the sinus node, and the left ventricle. No arteriovenous shunt and no peripheral thrombi were found. There was marked gross atherosclerosis of the pulmonary arteries. The sinus node artery arose from the left circumflex coronary artery while the AV node artery arose from the right coronary artery. Congestion was present in the lungs and all the abdominal viscera.
Histology of the pulmonary arteries was characteristic of "primary pulmonary hypertension" (Fig. 32). In addition to the typical intimal endothelial proliferation and hypoplasia of the tunica media of the pulmonary arteries, there was an unusual number of emboli present in the small arteries, though none were grossly identified. Hemorrhage in the tunica media similar to that of Cases 1 and 2 is seen in Fig. 32 C.

Although the primary feature of the arteriopathy in the sinus node was a non-specific proliferation of the tunica media (Fig. 33), focal degeneration and hemorrhage of the media, similar to that of Case 1, was also seen in other portions of the sinus node artery (Fig. 34). Other examples of the systemic arteriopathy are shown from the AV node, left and right ventricles, spleen and adrenal glands (Figs. 35-40). Similar but much less frequent lesions were seen in the kidney and liver. The medial hypertrophic process in the sinus node artery stained as collagen rather than muscle on the Goldner trichrome stain.

The antemortem thrombus in the right atrium was recognized at gross inspection in this case. As in the other two cases it was attached to the endocardium beneath the sinus node and filled the anterior sinuses of the crista terminalis (Fig. 41). It is the logical source for the emboli observed in the pulmonary arteries.

Figure 32
Pathology of the small pulmonary arteries of Case 3. A (Goldner trichrome, X64) shows the classical intimal proliferation with thin tunica media. B (Verhoeff-Van Gieson, X160) shows a small pulmonary artery distended by an embolus; note the intimal hyperplasia in addition. C (Goldner, X160) shows intramural hemorrhage in a small pulmonary artery.
Three views of a section through the sinus node artery of Case 3. The predominant pathology here is a bizarre medial hyperplasia which virtually obliterates the lumen of the artery; there is some superimposed intimal proliferation visible inside the internal elastic lamina. This type of process sometimes occurs in the lungs, where it might be interpreted as "medial hypertrophy". It is clear from the higher power view in C that this is not a normal smooth muscle hypertrophy. Verhoeff-Van Gieson; A X40, B X82 and C X205.

Figure 34
An oblique section through the sinus node artery of Case 3, taken 12 mm. from the section of the same artery shown in Fig. 33. Here there is intramural degeneration and hemorrhage very similar to that in the sinus node artery of Case 1. Goldner trichrome stain; A X64 and B (same artery) X319.
Figure 35
AV node artery of Case 3, showing intimal proliferation in which the nuclei are plump; the lumen of the artery is compromised. Goldner, X160.

Figure 36
The left coronary artery of Case 3, showing an "atheroma" which is very similar to the coronary arteries of Cases 1 and 2. Goldner trichrome stain, X10.

Figure 37
The main right coronary artery (A) and a right ventricular branch (B) from Case 3; note the "atheroma" with medial thinning in A. There is cystic medial degeneration in the right ventricular branch. Goldner stain; A X10 and B X160.

Figure 38
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Figure 39
Adrenal arteriopathy in Case 3. A shows a bizarre intimal hyperplasia with a disorganized tunica media; Verhoeff-Van Gieson, X64. B shows granular degeneration and fragmenting of the tunica media; Goldner, X160.

Figure 40
Another adrenal artery in Case 3, showing pathology similar to Fig. 39B. Goldner trichrome stain; A X160 and B (same artery) X319.

Figure 41
Two views of the antemortem mural thrombus of Case 3, attached to the endocardium directly under the sinus node. A Goldner stain, X10; B Verhoeff-Van Gieson, X25.

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CRITERIA FOR THE DIAGNOSIS OF DEGENERATIVE ARTERIOPATHY WITH PULMONARY HYPERTENSION

There is little question that the cases of "primary pulmonary hypertension" recorded in the literature represent a heterogenous group etiologically, a point emphasized by others7,39,40. A number of experienced observers have been impressed, however, with the frequency of similarities in one particular group, characterized as being represented by a young multiparous female with frequent bouts of syncope, clinical and laboratory evidence of marked pulmonary hypertension, absence of an arteriovenous shunt inside or outside the heart, absence of an apparent peripheral source for pulmonary emboli, and ultimately a relentless downhill course due to right ventricular failure31,41. It seems likely that this is a "pure" group, although as will be discussed later there are undoubtedly closely related and overlapping groups.

The conventional clinical and antemortem laboratory criteria for diagnosis of "primary pulmonary hypertension" (or DAPH), briefly summarized below, have been the subject of extensive description1-3, 16-34 and do not therefore require fuller development here. They are as follows:

1. The patient is characteristically a young multiparous female.
2. Syncope is a frequent presenting symptom and usually becomes an increasing problem as the disease progresses; as a corollary, death is often sudden.
3. It is unusual to see cyanosis and peripheral edema early in the disease but these may appear in later stages.
4. Syncope, chest pain, and dyspnea commonly follow exertion, and as the disease progresses they occur with less and less stress.
5. Physical findings vary with the stage of the disease; early they are limited to evidence of right ventricular enlargement and a pulmonary ejection type murmur, with right ventricular failure minimal or absent. Later, right ventricular failure progressively increases, and eventually regurgitant murmurs appear at both the pulmonic and tricuspid areas. Pulmonary congestion is rare.
6. Electrocardiograms demonstrate right ventricular and right atrial hypertrophy, which are also apparent radiographically; radiographs show no pulmonary congestion and no left atrial enlargement, but the central pulmonary arteries are enlarged.
7. On cardiac catheterization the pulmonary wedge pressure is normal but the pressure in the pulmonary arteries and right ventricle markedly elevated. There is no evidence of arteriovenous shunting and, until late in the disease, no peripheral oxygen desaturation. The increased hazard associated with cardiac catheterization in these patients has been well documented27,28.
8. There is no evidence of a peripheral source for pulmonary emboli, no intrinsic non-vascular pulmonary disease, and no evidence of systemic
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diseases known to be associated with arteriopathy, such as lupus erythematosus or scleroderma.

Gross findings at necropsy consist of right ventricular and right atrial hypertrophy and dilatation, and frequently grossly visible sclerosis of the larger pulmonary arteries. Thickened smaller arteries may be visible on the cut surface of the lung. Small emboli in the pulmonary arteries are commonly found, but larger emboli are not. There are no cardiac septal defects nor any valvular lesions, though the pulmonic and tricuspid valve rings may measure as slightly dilated. No peripheral thrombi are present. Though intracardiac thrombi have only seldom been reported, small intertrabecular thrombi in the right atrium and ventricle can easily be missed. Their presence in all three of the present cases, as well as their potential role in the pathogenesis of the pulmonary hypertension makes a careful gross and microscopic search for them in future cases important.

Microscopic findings reported in the past have been limited almost exclusively to those of the lungs. With few exceptions histology of other arteries has not been reported, except in general terms as “negative”. The frequency of emboli or thrombi in the smaller pulmonary arteries varies considerably in reported cases. Most of the pathological changes previously described in the smaller pulmonary arteries differ little in DAPH from those found in secondary pulmonary hypertension, but the extent of these changes is different. In DAPH remarkable intimal endothelial proliferation (Figs. 1, 2, 17, 18, 32A) is more frequent and more striking. Some consider a capillary proliferative (“glomeroid”) lesion highly suggestive. But the really significant changes occur in the tunica media.

Bredt was among the first to be impressed by the medial degeneration seen in the pulmonary arteries in “primary pulmonary hypertension”. Later, Gilmour and Evans called attention to “aplasia or hypoplasia” of the media. Though Bredt as well as Gilmour and Evans postulated that the medial degeneration was the primary lesion and that pulmonary hypertension developed as a consequence, this postulate remained speculative and the prevailing current interpretation has been that the pulmonary arteriopathy is the consequence of the hypertension and not the cause of it. The present demonstration of a similar arteriopathy in normotensive systemic arteries of three patients with “primary pulmonary hypertension” now makes re-evaluation of this question necessary.

Instead of extensive hypertrophy of the smooth muscle of the tunica media of the pulmonary arteries, which is characteristic of most states associated with pulmonary hypertension, the arteries of the lungs of patients with DAPH show a singular lack of such response. When one searches carefully enough, a few vessels with medial hypertrophy may be found in DAPH, but these are exceptional and by far the prevalent lesion is the medial degeneration and hypoplasia. Conversely, on careful search of the lungs from cases of secondary pulmonary hypertension medial degeneration or hypoplasia is occasionally encountered, but again this is the exceptional lesion.
The medial degenerative changes are characteristic. Though these sometimes show small cyst formation, somewhat similar to Erdheims' cystic medial necrosis, they are more typically a ground-glass or finely granular degeneration of the smooth muscle fibers (Figs. 2B, 7B, 8, 9B, 30C). Significantly, there is no associated inflammatory cellular response. In other arteries a pyknotic degeneration of the nuclei of arterial smooth muscle occurs, perhaps as an earlier stage. Intimal hyperplasia or proliferation is usually associated with underlying medial atrophy or hypoplasia. In most areas both the internal and external elastic membranes remain intact, but occasionally the former becomes slightly frayed. All these lesions are segmental or focal, and serial sectioning demonstrates that the same artery may appear normal in one area but diseased further on.

Since the specific arteriopathy in the three present patients differs in some arteries from others, one may consider whether the three patients all represent the same disease. For example some arteries show recent medial degeneration with hemorrhage while others show intimal proliferation and hyperplasia. Since all these lesions were present in one artery or another in all three patients, it is probable that they all are the same disease and that these variations in arteriopathy are more apparent than real.

In general the arteries with recent medial degeneration showed little intimal response, while those with extensive intimal response showed no recent disease in the tunica media, which was, however, usually atrophic or hypoplastic. It is reasonable to believe, therefore, that the medial changes are the initial ones and that the intimal response is secondary to this, the difference in histologic appearance thus depending on the time of examination in the natural course of the arteriopathy. Presuming the basic pathology is a generalized degenerative arteriopathy, one is still faced with the need for explaining the higher prevalence of the lesion in the lungs. This is the subject of later discussion.

One type of arterial medial response in DAPH may be confused with conventional medial hypertrophy seen in secondary pulmonary hypertension. The sinus node artery of Case 3 illustrates this process: note whereas the tunica media is tremendously "hypertrophied", this hypertrophic process does not include normal smooth muscle but is formed of relatively non-specific cells (Fig. 33). Contrast this to the hypertrophy of smooth muscle seen in the pulmonary arteries in secondary pulmonary hypertension (Fig. 42). Thus though a sort of medial proliferative process may be seen in arteries in DAPH, it is not a normal smooth muscle response to increased work. Possibly it is a non-specific fibroblastic reparative response to smooth muscle degeneration in the tunica media. That it is not an unusual smooth muscle hypertrophy (e.g. longitudinal fibers) responding to the increased work demands of pulmonary hypertension is suggested by the presence of an identical process involving systemic arteries.
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Figure 42
Smooth muscle hypertrophy in small pulmonary arteries of two patients with secondary pulmonary hypertension. A and B are from a 19 year old male with severe pulmonary hypertension and reversed flow in a patent ductus arteriosus; C is from a 29 year old female with severe pulmonary hypertension due to an interatrial septal defect. Contrast the relatively orderly smooth muscle hypertrophy here with the bizarre medial proliferation in Fig. 33. A Verhoeff-Van Gieson, X32. B Goldner, X82. C Goldner X82.

Of considerable importance in differentiating the arterial lesion of DAPH from other arteriopathies is the absence of any inflammatory cellular response to the degeneration. There are no giant cells nor a leukocytic response, which helps to distinguish it from most of the arteriopathies associated with the "collagen" diseases. In Case 3 there were a large number of mast cells around the arterial lesions of the lung, but not about the systemic arterial lesions; in the other two cases there were no more mast cells than normally seen in relation to blood vessels.

SIGNIFICANCE OF SYSTEMIC ARTERY INVOLVEMENT

Involvement of the arteries to the sinus node and AV node, which are systemic arteries, explains the syncope and sudden death which are commonly observed in "primary pulmonary hypertension". Others have occasionally noted involvement of various systemic arteries of patients dying with this disease, but have either interpreted it vaguely or could not be certain they were not coincidental lesions. This particular arteriopathy in the cardiac nodes must be accepted as an integral part of the basic disease process, since the clinical features it produces are accepted as an integral part of the basic clinical picture of "primary pulmonary hypertension".

In their discussion of the etiologic factors involved in "so-called primary pulmonary hypertension", Rawson and Woske described one case in whom extrapulmonary arterial lesions were found; these consisted primarily of a perivascular cellular reaction and no details are given of the histology of the walls of these arteries. On the basis of this and the clinical symptoms of 3 other cases, plus a review of the symptoms of reported cases in the literature, they suggested that "primary pulmonary hypertension" may be related to the "collagen" group of diseases.
Although the arguments of Rawson and Woske are consonant with the concept of "primary pulmonary hypertension" as a systemic disease, the systemic arterial histopathology in their case was somewhat different from that observed in the three present cases. The similarity of the medial involvement in these three cases in both the systemic and pulmonary arteries, as well as its similarity to the process in pulmonary arteries described by Gilmour and Evans\textsuperscript{45}, Bredt\textsuperscript{46}, Wade and Ball\textsuperscript{47}, Kuida et al\textsuperscript{34}, and Berthrong and Cochran\textsuperscript{48}, suggests that this is a specific arteriopathy. There are probably cases of atypical collagen diseases with somewhat similar changes; these may represent intermediary or overlapping forms inevitably found in virtually all arteriopathies.\textsuperscript{47-49}

There is little question that severe hypertension is often associated with necrosis of the tunica media, and the frequency of this phenomenon in malignant systemic arterial hypertension makes the previous presumption that such changes in the pulmonary arteries were also the consequence of abnormally elevated pressure plausible. Some of the changes observed in the media still quite likely are the consequence of hypertension, but the presence of similar changes in non-hypertensive systemic arteries makes it unlikely that hypertension is the only cause. It is possible that some of the arteriopathy in the lung involves bronchial (systemic) arteries rather than hypertensive pulmonary arteries.

**PATHOGENESIS OF THE PULMONARY HYPERTENSION**

Some substance present in the venous blood returning to the right heart and lungs has long been postulated as a possible cause of pulmonary arterial and arteriolar spasm eventually leading to irreversible vascular damage and right heart failure. The basic flaw in this theory has been the inability to identify such a substance in patients with the disease. The present findings do not refute this possibility, but they do indicate several previously unrecognized factors at least contributing to the hypertension.

One of these factors is the demonstration of a source for embolism to the lung. All three of the present patients had mural thrombi in the right atrium (Figs. 16, 31, 41); in two of the three cases the thrombus was not detected at the time of gross examination, but was demonstrated microscopically. Since various stages of injury were present in the sinus node of all three cases, varying from old fibrosis to recent hemorrhage, it seems reasonable to believe that this area is the site of repeated small infarctions and associated mural thrombosis. Repeated embolization of small fragments from these thrombi would be unlikely to produce clinically recognizable bouts of pulmonary embolism, but in association with a pulmonary arterial bed already diseased it could readily lead to a vicious cycle of events (Fig. 43). Repeated attacks of transient arrhythmias during the syncopal attacks could further contribute to right atrial stasis and thrombus formation.
GENESIS OF PULMONARY HYPERTENSION IN DAPH

1. SINUS NODE INFARCTS → MURAL THROMBUS
   ARRHYTHMIAS
   MECHANICAL OBSTRUCTION
   PLUS
   REFLEX VASOSPASM
   REPEATED SMALL PULMONARY EMBOLI

2. MEDIAL INERTIA OR WEAKNESS → INTIMAL PROLIFERATION

3. ATEROMA FORMATION OVER MEDIAL DEGENERATIVE FOCI → LUMINAL COMPROMISE

4. NOXIOUS HUMOR (THEORETICAL)
   VASOSPASM
   INTIMAL EDEMA AND PROLIFERATION

A schematic indication of the factors involved in production of pulmonary hypertension in DAPH.

Emboli from the endocardium beneath the sinus node may produce pulmonary hypertension in three ways. Mechanical obstruction is the first of these, but it is improbable it is a major factor because of the relatively small size of the initial mural thrombus as well as the lack of recognition of clinical episodes suggesting pulmonary embolism in these patients. More likely the small emboli have a more chronic effect by stimulating an arterial proliferative process demonstrable experimentally. The third effect involves the possible release of serotonin from the mural thrombus as well as the small emboli from it; this substance has been demonstrated to be a powerful stimulator of pulmonary vasoconstriction. The latter effect is likely operative only while active thrombosis is present and capable of releasing serotonin from disintegrating platelets, but how often in the course of DAPH active mural thrombosis is occurring is unknown.

The seeming inadequacy or inertia of the pulmonary arterial media, as expressed by its failure to hypertrophy under the hypertensive stimulus, suggests another interesting hypothesis. If the tunica media which is later seen to degenerate is at an earlier stage simply weak, arteriolar dilatation may be expected to occur. According to Laplace's law, the pressure in a hollow chamber (in this case the artery) is directly proportional to the tension in the chamber wall and inversely proportional to the radius of the chamber. Thus if the tension in the arterial wall decreased, in order
to maintain the same pressure the radius of the artery would have to decrease. Since the weakened media is incapable of doing this via spasm, the usual physiologic means, one may reason teleologically that the body takes another recourse by intimal endothelial proliferation. That the intimal proliferation corresponds to points of medial hypoplasia, as observed by Gilmour and Evans and also in the three present cases, may mean that the body has attempted to heal a point of medial weakness. The beautiful concentric intimal proliferation so characteristic of DAPH may thus be the consequence of evenly distributed concentric medial weakness, and the focal “atheroma” the consequence of focal medial weakness. The possible relationship of the same hypothesis to pathogenesis of systemic atherosclerosis will be discussed later.

Demonstration that priscoline and acetylcholine are capable of transiently lowering the pressure in the pulmonary arteries of patients with “primary pulmonary hypertension” suggests vasospasm is present, but it has not defined the cause of the vasospasm. Because of consideration regarding a neurogenic cause thoracic sympathectomy has been attempted as treatment, but the patient did not improve. More recently attention has been directed to the possible effect of serotonin, and its ability to produce a type of arteriopathy; this seems an unlikely major factor because of the absence of other findings due to increased circulating serotonin seen in malignant carcinoid. Perhaps more suspicion should be directed at epinephrine and norepinephrin, particularly in view of the presence of adrenal arteriopathy in all 3 of the current cases. Though relatively weak pulmonary vasoconstrictors, these catecholamines potentially have other effects on the pulmonary arterial wall which may lead to luminal obstruction; this will be developed more fully subsequently.

Whether vasospasm is due to some substance circulating in the blood or due to a neurogenic reflex, perhaps related to repeated small embolisms, there is no doubt that organic obstructive lesions are present in the majority of authentic cases of “primary pulmonary hypertension”. One cause for these lesions is embolism, but for a more complete understanding of the disease it is necessary to define the nature of the primary degenerative changes in the arterial wall.

**ETIOLOGIC POSSIBILITIES REGARDING THE DEGENERATIVE ARTERIOPATHY**

Although the present findings do not exclude the role of a noxious venous substance in the pathogenesis of DAPH, it is not necessary to explain the disease on this basis. The pulmonary hypertension and clinical course can all be explained on the basis of the degenerative arteriopathy without the presence of such a substance. The medial weakness as a possible cause of intimal proliferation has already been discussed, and the manner in which this would contribute to hypertension if unchecked is apparent; the additional occurrence of repeated small emboli from recurring mural thrombosis near the sinus node would aggravate and accelerate this process, ultimately causing it to become self-propagating: the pulmonary hypertension producing more

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*A lucid differentiation of intimal elastic hyperplasia, commonly seen in atheroma, and intimal endothelial proliferation, which is uncommon except in “primary pulmonary hypertension,” is made by Brenner. Both processes are seen in DAPH.*

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arterial medial damage which through intimal proliferation would in turn lead to more hypertension (Fig. 43).

What then are the possible causes of the degeneration in the tunica media? There is a resemblance to the medial lesions of Marfan's syndrome and many other heritable disorders of connective tissue. In both diseases sudden death is a common phenomenon, and the possibility that it is sometimes due to involvement of the nodal arteries in Marfan's syndrome as well as in DAPH is now being investigated. Cystic medial degeneration occurs in the pulmonary artery in both diseases and ruptured dissecting aneurysm of the main pulmonary artery has been described in "primary pulmonary hypertension". The histology of the media of the aorta in the three present cases was normal, but this needs to be studied further in other cases of DAPH. Similarly the histology of the smaller pulmonary arteries needs to be examined in Marfan's syndrome, as well as in experimental lathyrism. Recently vascular lesions were produced in swine fed a copper-deficient diet, an observation which deserves further study.

If a specific degenerative process of the tunica media of certain arteries is the primary pathology in DAPH, this may be either congenital or acquired. Much the same analysis regarding these possibilities may be applied to DAPH as to Marfan's syndrome. Since a familial incidence of "primary pulmonary hypertension" has been observed, it will be important to determine if any relatives of patients with heritable disorders of connective tissue develop DAPH. Berthrong and Cochran suggested unexplained pulmonary hypertension in children may be associated with an increased incidence of congenital cardiovascular malformations (themselves not producing the pulmonary hypertension). If it is an acquired lesion, there has so far been no explanation of how it becomes acquired. It is possible there is a hereditary predisposition which, in combination with some process which would otherwise be innocuous, results in arterial medial degeneration in these susceptible patients.

One possible means of acquisition of the arteriopathy which has impressed numerous observers is pregnancy. The primary problem with accepting pregnancy as the only process responsible for DAPH is the observation of the disease in women who have never been pregnant (Case 2, e.g.), as well as some acceptable cases in males. The placenta or the gravid uterus as the possible source of a substance aggravating or even producing DAPH can only be accepted if there are also other causes. A number of other cardiovascular diseases seem equally obscurely related to menstruation and pregnancy.

That pregnancy and breeding have an influence on arteries is well documented. It has been demonstrated that experimental animals repeatedly bred are more susceptible to atherosclerosis than non-bred controls. The occurrence of dissecting aortic aneurysm in pregnancy has been reported numerous times, and its possible relationship to hormonal derangements of pregnancy have been the subject of study. Aortic dissection in experimental lathyrism is reported to be more frequent.
in male than female animals\(^4\), but the histology of the pulmonary arteries in these animals has not been reported.

Among endocrine secretions possibly responsible, one which has some experimental and clinical observations to support it is the thyroid stimulating hormone (TSH). It has recently been reported that the administration of high levels of TSH produces certain degenerative myxomatous changes in muscle\(^5\) somewhat suggestive of the lesion in the tunica media of DAPH. These changes did not occur in control animals treated with thyroid hormone alone. Some years ago Kountz and Hempelmann reported the occurrence of dissecting aortic aneurysm in three consecutive patients with severe systemic hypertension treated with thyroidectomy\(^6\), and convincingly argued that the thyroidectomy and dissection were related; these patients presumably developed elevated levels of TSH. Myxomatous degenerative changes in the heart and in the coronary arteries have long been recognized as commonly occurring in myxedema\(^7\)\^-\(^9\) and have been presumed to be related partly to elevated cholesterol levels; perhaps the TSH level in these patients is equally important.

Also deserving consideration in the etiology of the degenerative arteriopathy are epinephrin and norepinephrin, which are capable of producing arterial lesions experimentally\(^10\)-\(^12\). A very similar change is sometimes seen in the pulmonary arterioles of patients with pheochromocytoma (Fig. 44, 45). In all three of the present patients there was arteriopathy present in the adrenal glands, involving occasional arteries in Cases 1 and 3, but virtually all the adrenal arteries in Case 2 (Figs. 14, 19-22, 39, 40). Furthermore the process in the adrenal arteries was the same as the process in other systemic arteries and the pulmonary arteries in each case, as well as characteristic of lesions generally described in "primary pulmonary hypertension" in the lungs by others.

![Figure 44](image)

Two small pulmonary arteries from the lungs of a young woman who died of pheochromocytoma. Note the similarity of the arteriopathy to many of the arteries in Cases 1, 2 and 3. A (Goldner, X64) shows intimal proliferation with a thin tunica media. B (Goldner, X64) shows focal intimal proliferation over an area of medial thinning.
Pulmonary arteriopathy in another case of fatal pheochromocytoma, this in a middle-aged male. A and B are the same artery, Goldner stain, at X64 and X160; there is a small amount of intimal proliferation, with edematous endothelial cells overlying it, and with a disorganized and degenerate tunica media underlying it. Another artery with a similar process is shown in C (Goldner, X160), with the cystic changes in the tunica media clearly seen.

How often there is extensive adrenal arteriopathy in DAPH cannot be stated from observations in 3 cases. Since it was extensive in one of the three, however, the possible role of adrenal ischemia must be considered. During right heart failure which is common in DAPH, right atrial and peripheral venous pressure rises, and this must include pressures in the inferior vena cava and adrenal veins. Such venous hypertension coupled with the fall in aortic pressure which occurs would be further aggravated by luminal lesions in the adrenal arteries, thus suggesting that a disproportionate ischemia must occur in the adrenal glands, similar to that affecting the cardiac nodes, where the arteries are similarly involved. That adrenal ischemia is associated with increased elaboration of pressor agents has been suggested from experiments. It is reasonable to presume, therefore, that an excessive amount of epinephrin or norepinephrin (or both) will reach the pulmonary arteries in patients with DAPH at least intermittently.

Since epinephrin and norepinephrin have been shown to be only weak pulmonary vasoconstrictors in animals and normal man, the presence of pulmonary arteriopathy in patients with pheochromocytoma is puzzling. The lesion illustrated in Fig. 45 suggests edema or slight proliferation of the intimal endothelium; there were in addition arteries with a moderate degree of smooth muscle hypertrophy and some cystic degeneration; occasional arteries resembling those of DAPH were also found (Fig. 44). Others have described extensive smooth muscle hypertrophy, as well as degenerative changes of various types in the tunica media of the pulmonary arteries of patients with pheochromocytoma. The pressure in the pulmonary arteries of such patients has not been measured, so it is improper to presume that it is not elevated because of experimental observations in animals or in man without pheochro-
mocytoma. It is not known what the response of the arteries in “primary pulmonary hypertension” is to epinephrin and norepinephrin, though their hypotensive response to adrenolytic agents has been repeatedly observed.\(^2^4^2\,4^3\)

Regarding the sexual predilection of DAPH, it has been shown that women’s conjunctival arterioles become exquisitely sensitive to epinephrin during menstruation. Conceivably the preponderance of DAPH in women in the child-bearing age is related to this observation. It may be well to study the response of the conjunctival arterioles to various pressor agents in patients with DAPH.

Despite these intriguing implications, it is unlikely epinephrin or norepinephrin is the major factor in DAPH. Absence of systemic hypertension indicates there is no increase in total circulating catecholamines. Presence of systemic arterial lesions indicate the arteriopathy probably occurs without abnormal blood pressure elevation. The evidence suggests that epinephrine or norepinephrin may contribute intermittently to the pulmonary hypertension and arteriopathy, however, and this possibility deserves further investigation.

Recently attention has been directed to serotonin as a possible etiologic factor in “primary pulmonary hypertension”, its powerful vasospastic effect on the pulmonary circulation being well known. Administration of serotonin has produced a pulmonary arteriopathy in rabbits but failed to do so in rats.\(^6^8\) Since nature has provided a specific human example of the effect of excessive secretion of serotonin in the malignant carcinoid syndrome, and since its clinical and pathologic characteristics\(^1^0^0\,1^0^1\) are considerably different from those of DAPH, it seems unlikely that serotonin is a significant factor in the latter. Resemblance of pulmonary arteriopathy in one case of malignant carcinoid syndrome to DAPH (Fig. 46), however, suggests further study of this question.

![Figure 46](image)

**Figure 46**

Two small arteries from the lung of a patient with malignant carcinoid syndrome (other features of this case previously reported from this institution\(^1^0^1\)). Note the intimal proliferation and the thin tunica media. A stained with Verhoeff-Van Gieson, X64; B stained with Goldner trichrome, X160.

On the basis of present evidence it is difficult to determine the cause of the generalized degenerative arteriopathy. An inherited or acquired (or both) defect of the tunica media seems likely, but its cause is unclear. Both the hypertension and...
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and some of the arteriopathy in the lungs is related to recurring small emboli from right atrial thrombi due to sinus node infarction, and in turn some of the arteriopathy is likely due to hypertension. Most of the possible humoral substances which could cause pulmonary hypertension and arteriopathy seem less important in view of systemic arterial involvement with normal systemic arterial pressure; this does not exclude such substances as contributory factors.

What we see in the histopathology of the pulmonary arteries may only be the consequence of chance involvement of certain systemic arteries (those of the cardiac nodes, right atrium and adrenal glands, e.g.) and have relatively little to do with the basic process of a generalized degenerative arteriopathy. In other words it is possible we are being misled by the striking pulmonary arteriopathy which leads to one type of death from a generalized arterial disease, the other possible consequences of which we do not know. In particular we do not know what the natural history of the disease would be in cases where the arteries of the adrenal glands, right atrium and cardiac nodes may be spared.

Even without an adequate explanation for the degenerative arteriopathy, its similarity to systemic atherosclerosis merits some discussion. This is particularly true since all three of these young women had considerable coronary arteriopathy indistinguishable morphologically from atherosclerosis, which is most unusual at their ages in their sex.

CONSIDERATIONS RELATIVE TO ATHEROSCLEROSIS AND ARTERIOSCLEROSIS

In their description of medial hypoplasia in "primary pulmonary hypertension" Gilmour and Evans called attention to the applicability of their observations to systemic atherosclerosis. A better understanding of healing and repair in any arteriopathy may well shed light on the pathogenesis of arterial sclerosis.

From a study of atherosclerotic systemic arteries fixed while being distended by intraluminal fluid under pressure, Crawford and Levene demonstrated that an atheroma in most cases did not protrude into the arterial lumen, the way we are accustomed to seeing it in fixed undistended arteries, but that the lumen retained quite a well-rounded shape and that the atheroma instead bulged into the media. The remaining tunica media beneath the atheroma was considerably thinned out. It was shown that this medial thinning could not be simple pressure atrophy due to the atheroma being pressed into previously normal tunica media, for it is mathematically impossible for the pressure on the media beneath a covering to be higher than that on normal media near by; in fact pressure on media beneath the atheroma is less.

If the tunica media is the site of focal degeneration, two consequences affect normal vascular hemodynamics (Fig. 47). First the focus of weakened tunica media may retain sufficient strength to prevent aneurysmal bulging, but would after atrophy present a cavity toward the lumen of the vessel. It may be expected that this cavity will become filled in order to restore a smooth contour to the inner surface
of the vessel. Whatever the exact filling process, whether by thrombus or by intimal proliferation, or both, the end result will be a “scar” histologically indistinguishable from an atheroma.

The second consequence of a focus of weakened tunica media is an impairment of the efficiency of the unweakened remaining fibers of smooth muscle. For normal function the smooth muscle of the tunica media depends on the maintenance of an intact circle about the vessel. When a segment of this circle is damaged, normal intravascular pressure will force apart the remainder of the circle and thereby increase the diameter of this segment of vessel. A healing of this defect in the tunica media would not only fill in the cavity on the inner surface of the vessel, thus discouraging the aneurysmal centrifugal thrust, but would also link together again the surviving smooth muscle fibers and restore their efficiency in maintenance of “active tension” of the vessel wall. Most discrete atheromata admirably serve both these purposes.

After long-standing or repeated bouts of damage to the tunica media this simple manner of healing must be replaced by a disorderly process in which focal hemorrhage, neighboring degeneration, calcification, and superimposed thrombosis all contribute. By the time most systemic atherosclerosis becomes clinically manifest and by the time opportunity for histological study at necropsy occurs, the simple atheroma with its exquisitely efficient natural reparative process is no longer to be seen.
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If the atheroma is initially an efficient reparative process, why do we then sometimes see arteries which are virtually occluded by simple atheroma? These may of course partly be artefacts seen in collapsed, undistended arteries. They may also be instances of a different process which is only morphologically similar, but they are probably the same process. One explanation may be the body has no efficient checking or suppressing mechanism once atheroma formation has begun. In different patients this may apply to all atheroma formation, or may differ from artery to artery at any one time or at different times. For example, patients with high levels of circulating fat moieties may so fill any developing atheroma with these substances that it gorges and distends it to the point of occluding the arterial lumen.

Another explanation of why the body will construct an atheroma which eventually encroaches on the arterial lumen can be made, however. According to LaPlace's law, which has been shown applicable to normal vascular dynamics by Burton\(^{105}\), pressure is directly proportional to tension and inversely proportional to radius. In application to blood vessels, \(P = \frac{T}{r}\) is interpreted thus: \(P\) is the intravascular pressure, \(T\) is the tension produced by the vessel wall, and \(r\) is the mean radius from the center of a cross-section of the vessel to an average mid-point between endothelium and outer adventitia.

Accepting the applicability of LaPlace's law to the dynamics of blood vessels, it is axiomatic that any decrease in pressure due to failure of tension can only be compensated by a reduction of the vessel's radius. With a small focus of medial damage an atheroma may re-link the undamaged smooth muscle so it may restore normal mural tension, but with a large focus of medial damage this may not be possible and pressure can then be restored only by an intimal proliferative reduction in radius. The consideration of similar variations in these factors (\(P\), \(T\) and \(r\)) as they relate to vascular pathophysiology is beyond the scope of the present discussion, but it is impressive that in all these the applicability of LaPlace's law remains valid.

In DAPH one of the hallmarks of the histopathology is the beautiful concentric reduction of the arterial lumina by radially oriented intimal proliferation (Figs. 1, 2, 17, 18, 32A). Less well recognized previously is the almost universal accompanying medial atrophy which sometimes involves the entire ring of tunica media in that plane. If the entire circumference of the tunica media at this point is weakened, a logical means of restoring local pressure, since the tunica media is unable to do this with constriction, is for the arterial radius to be reduced by concentric intimal proliferation.

Analogy of DAPH and systemic atherosclerosis, including similarities in their pathogenesis, is supported by the amount of coronary atherosclerosis present in the hearts of the three young women in this report. Significant coronary atherosclerosis is singularly uncommon in young women\(^{107-109}\) except in the presence of diabetes, systemic hypertension or other vascular diseases, one of which may be DAPH. Though extensive coronary atherosclerosis has not been considered characteristic of "primary pulmonary hypertension," systemic arteries in this disease have previously seldom been studied with the care given to the pulmonary arteries.
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There is no dearth of possible considerations on the etiology of the damage to the tunica media in any arteriopathy. Cystic medial degeneration can occur as a consequence of impairment of mural blood supply and Schlichter has produced such lesions by coagulating the adventitia of the aorta. The essence of what is being suggested, however, lies in considering the atheroma formation as secondary to such damage rather than responsible for it. This is not to say that intimal proliferation or hyperplasia, once begun, does not aggravate the medial damage, for it probably does. Whatever the initial cause for medial degeneration, thickening of the overlying intima (even for the salutary purpose of strengthening and repair) removes or certainly impairs one possible route of nourishment to at least the inner third of the tunica media. Thus the artery while attempting to heal itself is partially defeating its own purpose.

SIMILARITIES OF DAPH TO COLLAGEN DISEASES, AND SOME IMPORTANT DIFFERENCES

Resemblance of some features of DAPH to collagen diseases is apparent, and it has been suggested that “primary pulmonary hypertension” is a variant form of this group of diseases. Among these, notable similarities exist between DAPH and lupus erythematous, Raynaud’s disease, or scleroderma. In all these diseases a comparison of the typical case of DAPH to a typical case of lupus or scleroderma or Raynaud’s disease allows one to distinguish with ease the striking clinical differences, which are too familiar to require repetition. It is more difficult to separate the atypical cases.

Histologically one of the significant differences is the lack of inflammatory cellular reaction to the degeneration in DAPH, whereas the vasculitis of the collagen diseases is usually associated with a periarterial cellular response. Prevalence of the arterial lesions in various organs is of additional differentiating aid, the vascular pathology of the kidney and spleen in lupus being much more extensive than in DAPH; also in lupus the glomerular capillaries are a prominent site of involvement, whereas in DAPH these seem to be spared. This latter difference between the two diseases applies to other organs as well, lupus tending to spare medium size and larger arteries, whereas DAPH characteristically involves them. Finally, even though the lung and right atrium may be involved in collagen disease, this is an unusual occurrence, whereas these are the site of extensive pathology in DAPH.

Raynaud’s phenomenon, a feature of Case 2, is now considered as etiologically non-specific. It is commonly a feature of the clinical course in the collagen diseases, but is also commonly seen in association with many other diseases. Raynaud’s disease has been reported to involve the pulmonary vessels, but this is unusual. Since it has not previously been appreciated that systemic degenerative arteriopathy occurs in “primary pulmonary hypertension,” it remains to be determined whether some of the reported cases of pulmonary involvement by Raynaud’s disease or by certain collagen diseases may not actually be DAPH.

Undoubtedly this whole group of diseases is closely related, and a too rigid separation of them may be both difficult and undesirable. Shadings of difference exist, and abundant opportunity for misdiagnosis in either direction must occur.
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MECHANISM OF SYNCPE AND SUDDEN DEATH

Although this topic is the subject of a fuller development elsewhere, a brief discussion is appropriate to this report. In the 3 cases reported here the lesions involving the cardiac nodal arteries were of two types. The first was a hemorrhagic and cystic or granular degeneration of the tunica media of the sinus node artery with ultimate rupture into the sinus node (Fig. 7). The second type of lesion was a combination of both intimal and musculoelastic hyperplasia which produced luminal encroachment (Figs. 29, 30, 33, 35). That the second is a likely consequence of the first has already been discussed.

Concomitant with the development of these focal lesions in the nodal arteries in DAPH, the progressive disease in the pulmonary arteries has two effects relative to syncope and sudden death. The first of these is a compromise of the blood flow through the lungs which impairs filling of the left side of the heart and thereby cardiac output into the aorta and coronary arteries. The second, also a consequence of rising pulmonary vascular resistance, is a development of right ventricular hypertension and at least intermittently elevation of right atrial pressure with resistance to coronary sinus flow. The combination of decreased central aortic pressure and elevated right atrial pressure results in a marked reduction in effective coronary perfusion pressure. This reduction in coronary artery flow may be expected to produce generalized myocardial hypoxia, but when it occurs in conjunction with lesions specifically compromising flow in the nodal arteries, an intense focal ischemia of the sinus node and AV node may be anticipated. In DAPH this focal ischemia is most likely the major determinant of the syncope and sudden death.

In addition to focal nodal ischemia, other factors contribute to the pathogenesis of syncope and sudden death. For example, distention of the right atrium is a powerful stimulus for a vagomimetic reflex which may depress function of the sinus node or AV node or both; similarly, ischemia of the nodes as part of a generalized myocardial ischemia, without the selective vascular involvement seen in DAPH, is apparently not sufficient of itself to produce clinical evidence of nodal dysfunction else it should be observed more frequently in any pulmonary hypertension. Analogous observations may be made regarding cerebral anoxia, pulmonary vascular reflexes, retrograde flow of right atrial hypoxemic venous blood into the sinus node and AV node, and other factors which can occur in any pulmonary hypertension. For further details regarding these mechanisms and a consideration of their applicability to the marked increase in hazard of cardiac catheterization in these patients, the reader is referred to the separate communication dealing specifically with them.

Therapeutic Considerations

At present there is no satisfactory treatment for DAPH. On consideration of the various etiologic theories, appropriate therapeutic measures have been suggested and attempted with only modest and inconsistent success. The direct instillation of
acetylcholine or priscoline into the pulmonary artery has been shown to reduce pressure there, but this has been evanescent, the pressure immediately returning to pre-treatment levels when the drug was discontinued. Although this establishes that there is a component of spasm contributing to the pressure elevation in the disease, it is quite likely that the disease would progress even if the element of spasm were removed. One must even give some consideration to the possibility that without spasm (and the consequent high levels of pressure) perfusion of blood through some of the narrowed non-spastic arteries might fail altogether, with subsequent thrombosis and occlusion compounding the pulmonary perfusion problem. In addition, any of the pulmonary vasodilators reaching the systemic circulation may further reduce central aortic pressure and thereby worsen the already lowered effective coronary perfusion pressure.

On the contrary it is perhaps worth considering the employment of systemic vasopressor substances to raise central aortic pressure, especially during a syncopal crisis or similar acute deterioration in patients with DAPH. This would produce an elevation in effective coronary perfusion pressure and could be expected to improve the coronary circulation to the nodes and myocardium. Norepinephrin, which is a profound systemic pressor agent and weak pulmonary pressor agent would be preferable to metaraminol in DAPH, for the latter affects both circulations equally. Against this possible benefit, however, must be weighed the potential risk of rupturing weakened arteries, as in the sinus node or lungs.

Because of the theory that “primary pulmonary hypertension” was due to multiple miliary embolization, use of anticoagulants has been suggested. In consideration of the role of repeated small embolizations from a mural thrombus near the sinus node in DAPH, anticoagulants may be expected to be beneficial. This effect would only eliminate the thromboembolic component of the progressive disease in the pulmonary arteries, however, and would not necessarily alter the medial degeneration and compensatory intimal proliferation. If hemorrhagic cystic lesions of the sinus node artery and pulmonary arteries similar to those observed in Case 1 prove to be frequent in DAPH, the hazard they present in dissection and rupture under the influence of anticoagulants must be considered.

Because of the constant likelihood of sudden dysfunction of the sinus node and AV node in DAPH, the effect of digitalis and quinidine in this regard should be considered when they are chosen for therapy. This is not to imply they should be avoided in DAPH if conventional indications are present, but one should be aware of the potential results of depression of sinus node activity or AV node conduction.

Since the arteriopathy is devoid of inflammatory cellular response, there is no reason to anticipate benefit from adrenal cortical steroids. The possibility of an important role being played by adrenal medullary hormones deserves further investigation, however, and if they are important in the pulmonary hypertension and arteriopathy, certain measures are available to control this factor.

**SUMMARY AND CONCLUSIONS**

Based on observations in 3 cases, evidence is presented that the disease known as...
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as “primary pulmonary hypertension” is a degenerative arteriopathy in which pulmonary hypertension is a devastating but secondary phenomenon. Because of the consistent finding of a pathologic process involving normotensive systemic arteries in these three patients, it is suggested that hypertension can not be the only cause of the degenerative arteriopathy.

Whether all cases presently classified as “primary pulmonary hypertension” prove to be DAPH or not, it seems apparent that DAPH is a distinct disease. In those cases of “primary pulmonary hypertension” in whom syncope or sudden death are features of the clinical course, a careful examination of the arteries to the two nodes of the heart is now important. It must be emphasized that this involvement of the arteries to the nodes is segmental, however, and anything less than a thorough study with sections made at most 2 millimeters apart may miss the diseased segments.

All three patients had adrenal arteriopathy, and in one of these it was extensive. Based on this and certain other considerations it is suggested that the role of the adrenal medullary hormones be further evaluated regarding the pathogenesis and evolution of certain features of DAPH.

In view of the demonstration of systemic arterial involvement in this disease which was previously generally considered to be almost exclusively pulmonary, a number of implications regarding other arteriopathies suggest themselves and have been discussed. Prominent among these is the pathogenesis of systemic atherosclerosis.

The expected benefits and hazards of certain forms of therapy are considered in light of these new observations.

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