The Pathology of Hypertensive Pulmonary Vascular Disease

A Description of Six Grades of Structural Changes in the Pulmonary Arteries with Special Reference to Congenital Cardiac Septal Defects

By Donald Heath, M.D., and Jesse E. Edwards, M.D.

Progressive histologic changes occur in the pulmonary arteries and arterioles, as a complication of chronically elevated pulmonary arterial blood pressure, in patients with congenital septal defects of the heart. This progression is so stereotyped as to allow a division of the structural effects into 6 grades. The histologic features of each grade are described in detail in this communication. These results afford a basis for comparing the magnitude of these changes to the clinical findings.

PROGRESSIVE histologic changes occur in the pulmonary arteries and arterioles, as a complication of chronically elevated pulmonary arterial blood pressure, in patients with congenital septal defects of the heart. The progression is so stereotyped as to allow a division of the structural effects into 6 grades (table 1), although it is recognized that there is a gradual change from one grade to another. This division is of great practical value, since it enables the pathologist to express a whole group of complex changes in a succinct manner as a grade number. In the present communication, based primarily on the study of 67 cases of congenital septal defects of the heart and 2 cases of idiopathic pulmonary hypertension, a detailed description is given of the histologic changes that characterize each grade. In 55 cases pulmonary hypertension was demonstrated at cardiac catheterization or at cardiectomy; in 9 instances elevated pressure in the pulmonary circulation was inferred from the clinical and pathologic findings. In the remaining 5 cases, the pulmonary artery mean blood pressure was less than 30 mm. of mercury; these were all cases of atrial septal defect studied to illustrate the grade-1 changes in this disease. No cases with pulmonary venous obstruction were studied although at least the earlier changes of hypertensive pulmonary vascular disease and pulmonary arteritis occur in this group of patients. In a companion paper,1 the relation between each grade and pulmonary artery blood pressure, flow and resistance, and age is demonstrated. In a third study,2 the relation between each grade and the reversibility of pulmonary hypertension after surgical correction of the cardiac anomaly is considered.

This paper is concerned solely with the changes found in small pulmonary vessels. Structural changes also are found in the intima and media of elastic pulmonary arteries. Atheroma is the characteristic intimal feature related to pulmonary hypertension in these large arteries. The configuration of the elastic tissue of the media of the pulmonary trunk differs in pulmonary hypertension that is acquired from that which is present from birth. These changes in the intima and the media and their relation to pulmonary hypertension are considered in detail elsewhere.3 4

A description is given of the structural changes characteristic of each grade, as found specifically in cases of large ventricular sep-
tal defect, large patent ductus arteriosus, or any other form of congenital heart disease associated with a free communication between the systemic and pulmonary circulations and pulmonary hypertension from birth. This qualification is necessary because the earliest changes seen in the pulmonary vessels in cases of atrial septal defect (or similar diseases associated with acquired pulmonary hypertension following a long period of high pulmonary blood flow) with increased pulmonary artery blood pressure are not identical with, although in some respects they are similar to, those seen in ventricular septal defect. Furthermore, in acquired idiopathic pulmonary hypertension, the early histologic changes associated with the elevation of blood pressure differ from those associated with ventricular septal defect. The histologic changes defined as grade 1 of hypertensive pulmonary vascular disease in the following section refer to changes seen in patients having congenital heart disease associated with pulmonary hypertension from birth. The corresponding grade of change seen in patients having atrial septal defect and acquired idiopathic pulmonary hypertension is dealt with at the end of the paper. It needs to be stressed, however, that, whereas grade-1 changes are simply an integral part of the various structural and functional alterations in large ventricular septal defect, structural changes of grades 2 and 6 occur as a result of the raised pulmonary artery blood pressure. Grades 2 to 6 are present among all forms of hypertensive pulmonary vascular disease, whatever the etiology, and are found in each of the 2 groups of heart disease referred to herein, as well as in idiopathic pulmonary hypertension.

Before the pathologic aspects of hypertensive pulmonary vascular disease are described, it is necessary to present the histologic features of normal pulmonary blood vessels.

**Histologic Features of Normal Pulmonary Blood Vessels**

The walls of the pulmonary arterioles consist of a single elastic lamina except proximally at their origin from a muscular artery where serial sections demonstrate their walls to consist of a thin media sandwiched between internal and external elastic laminae. In the majority of patients beyond adolescence studied in this series and in groups of controls studied previously, fine acellular intimal fibrosis was found in arterioles as a normal age change. As already stated, the vast majority of pulmonary arterioles do not have a muscular media beyond their immediate origin from a muscular pulmonary artery, but vessels as small as 80 μ in diameter with a thin but distinct muscular media, bounded by internal and external elastic laminae, can be found after careful search of sections of the normal lung. These tiny vessels, which look like small muscular pulmonary arteries, are found predominantly in the lingula pulmonis. Arterioles arise either as branches, at right angles to the parent stem, which is related to the respective alveolar duct, or as terminations, at an oblique angle, of small muscular pulmonary arteries. Branches of the former type also may arise from quite large muscular arteries near small bronchi and much more proximally in the pulmonary vascular tree than the arterioles that arise as terminations of muscular pulmonary arteries. They have a thin wall with a lumen-to-wall ratio of about 8:1. Brenner defined pulmonary arterioles as arterial vessels in the lung less than 100 μ in diameter, but obviously this is only an approximation. The main criteria employed in the recognition of arterioles apart from size are the structure of their walls and their origin from small muscular arteries.

The muscular pulmonary arteries, usually defined as arterial vessels between 100 and 1,000 μ in diameter, consist of a thin media bounded by internal and external elastic laminae. The media is composed predominantly of smooth muscle with occasional collagenous and elastic fibrils. In small muscular arteries less than 300 μ in diameter the media has a thickness equivalent to 2.8 to 3.1 per cent of the external diameter of the vessel in the upper and lower lobes and 5.5 to 6.8 per cent in the region of the lingula. These figures have been confirmed previously by mensuration of medial thickness in this class.
of vessel in series of controls. As in the case of arteries and veins, acellular intimal fibrosis is found as a normal age change beyond adolescence. The adventitia is thin. These vessels are associated with the bronchioles, the respiratory bronchioles, and the alveolar ducts.

The elastic pulmonary arteries, defined as vessels greater than 1,000 μ in diameter, differ from muscular pulmonary arteries in that the elastic arteries show a specific pattern of elastic fibrils that predominate in the media. The media of elastic pulmonary arteries is relatively thicker than that of the muscular pulmonary arteries, so that in normal persons it may account for 10 per cent of the external diameter of the vessel. The thickness of the media of the pulmonary trunk and the configuration of its elastic fibrils in control patients of various ages, in patients with pulmonary hypertension present at birth, and in patients with pulmonary hypertension acquired in adult life are considered in detail elsewhere. Intimal age changes occur less frequently in the pulmonary trunk than in the small pulmonary blood vessels.

The media of the normal venule and small vein up to about 200 μ in diameter consists of a single elastic lamina, and that of the vein, greater than 200 or 300 μ, consists of collagen and smooth muscle fibers with admixed elastic laminae that tend to lie centrically around the walls of the vein. The clear differentiation of media and inner and outer elastic laminae, so characteristic of arteries, is lacking. Venules move away from the air spaces of their respective units to the interlobular septum to form venous trunks. This location is of great importance in distinguishing them from distended thin-walled veinlike arterial vessels found near small bronchi and bronchioles in the severer forms of hypertensive pulmonary vascular disease. Brenner demonstrated that intimal fibrosis occurs universally in adults in all classes of pulmonary blood vessels, especially veins, as a normal age change.

**Histologic Features of Grades of Hypertensive Pulmonary Vascular Disease (Table 1)**

**Grade 1. The Stage of Retention of Fetal-Type Pulmonary Vessels.** The definitive histologic features lie in the pulmonary arterioles and the muscular pulmonary arteries. This grade is the earliest ever found in large ventricular septal defect, wide patent ductus arteriosus, or any other congenital cardiac anomaly that allows the pulmonary vascular bed to be subjected to systemic systolic blood pressures from birth.

In the arterioles that normally have a distinct muscular media with internal and external elastic laminae only in the immediate

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**Table 1.** Basis of Grades of Hypertensive Pulmonary Vascular Disease Found in Association with Large Ventricular Septal Defects and Functionally Related Diseases

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<th>Type of intimal reaction</th>
<th>Grade of hypertensive pulmonary vascular disease</th>
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<td>None</td>
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<th>State of media of arteries and arterioles</th>
<th>Grade of hypertensive pulmonary vascular disease</th>
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* Pulmonary hemosiderosis associated with distended, thin-walled, arterial vessels throughout the lung.
† Necrotizing arteritis.
vicinity of their origins, there is distal extension of muscle. In this way, even arterioles as small as 30 \( \mu \) look like small muscular pulmonary arteries instead of like veins as they do in the normal lung (fig. 1a). The media is relatively thicker than that found in muscular arteries and may be as thick as 25 per cent of the external diameter of the vessel. There is no intimal fibrosis. The adventitia is thick and fibrous. The thickened arterioles also bear a striking resemblance to the intralobular pulmonary arteries of the fetus. It is worthy of comment at this point that comparable classes of vessels differ greatly in size in the fetus and in the adult.

The media of the muscular pulmonary arteries is thickened and may be as thick as 25 per cent of the external diameter (fig. 1b). Intimal fibrosis is not present, but the adventitia is thick and fibrous. The medial thickness gradually increases from grade 1 to grade 3, generally speaking, with great variation in the thickness of the individual muscular pulmonary arteries in any one case.

As has been suggested previously in a study of the small vessels of the lung in mitral stenosis, this study confirms that there is no clear-cut relation between medial thickness of any one vessel and pulmonary artery blood pressure. The pulmonary veins are normal in ventricular septal defect associated with pulmonary hypertension.

**Grade 2. Stage of Medial Hypertrophy with Cellular Intimal Reaction.** There is cellular intimal proliferation in the smaller muscular pulmonary arteries, less than about 300 \( \mu \) in diameter, and the pulmonary arterioles and the lesion may be so marked as to occlude the vessels. There is no intimal reaction elsewhere in the pulmonary arterial tree. Plump endothelial cells that stain brown with van Gieson's stain form only an unduly prominent vascular lining in some arterioles (fig. 2a). In other vessels they have proliferated to the extent of forming characteristic eccentric masses with underlying material staining brown with van Gieson's stain (fig. 2b). This proliferated intimal material may coalesce...
and lead to vascular occlusion. In some cases the proliferated endothelium and material staining brown with van Gieson’s stain may form a concentric rim around the circumference (fig. 2c). In time, fibrous tissue, recognizable by its property of staining red with van Gieson’s stain, forms beneath the endothelium and this constitutes the earliest stage of grade 3.

Grade 3. Stage of Progressive Fibrous Vascular Occlusion. In this grade there is progressive intimal fibrosis in the smaller (300 µ) muscular pulmonary arteries and pulmonary arterioles with a change in the nature of the intimal proliferation and an extension of it into medium-sized (300 to 500 µ) arteries. The intimal proliferation seen in early lesions of grade 3 represents a change from the predominantly cellular endothelial reaction seen in grade 2 to one that consists of cellular fibrous tissue as judged by its tinctorial properties (fig. 3a). Later lesions are characterized by concentric or eccentric masses of less cellular fibrous tissue that stains bright red with van Gieson’s stain. Old intimal fibrotic lesions show an admixture of fine or even coarse elastic fibrils and some splitting or elastosis of the internal elastic lamina, while the fibrous tissue may be relatively acellular. Running parallel with these characteristic changes in the histologic structure of the intimal fibrous tissue is its equally characteristic extension.

Most of the intimal lesions are first found in the arterioles and smaller muscular pulmonary arteries and extend back around the mouths of origin of the vessels and involve the parent muscular arteries (fig. 3b). In many instances, however, heaped up intimal fibrotic lesions are found early in a muscular pulmonary artery in proximity to the origin of an arteriole. It has already been pointed out that arterioles may rise at a proximal point in the pulmonary vascular tree as right-angled branches of fairly large muscular arteries. They also may arise distally as terminations of the arteries. Intimal fibrosis is found first in both sites. Only in severer cases of pulmonary hypertensive change is widespread intimal fibrosis found in the medium-sized muscular pulmonary arteries.

Serial sections demonstrate the plaques of intimal fibrous tissue in muscular arteries are focal (fig. 3a). In some instances these foci of intimal fibrous tissue are continuous with the fibrous tissue in the smallest muscular
Fig. 3. a. Grade 3. Transverse section of a small muscular pulmonary artery with an oblique section of an arteriolar branch. There is medial hypertrophy in the artery. Cellular fibrous tissue forms eccentric masses in the artery and occludes the arteriole. From a 9 year old boy having cor triloculare biventriculatum without pulmonary stenosis. X 160.  

b. Grade 3. Transverse section of a medium-sized muscular pulmonary artery and oblique sections of 2 of its branches. The parent artery shows hypertrophy of the media but no intimal reaction. The smaller branch shows some dilatation with thinning of the media and acellular intimal fibrosis. From a 6 year old girl with ventricular septal defect. X 30.  
c. Grade 3. Transverse section of a medium-sized muscular pulmonary artery. There are medial hypertrophy and severe intimal fibrosis so that only a small eccentric endothelium-lined channel remains patent. There is elastosis of the internal elastic lamina. From a girl, aged 6½ years, with ventricular septal defect and patent ductus arteriosus, X 175.  
d. Portion of wall of large muscular pulmonary artery showing fasciculi of longitudinal muscle in close apposition to the external elastic lamina. This case had grade-5 structural changes in the small pulmonary vessels, but the appearances are equally characteristic of any of the grades from 3 to 6. From a 27 year old woman with atrial septal defect. X 200.

arteries and the arterioles but in others there is no connection. Finally, the concentric or eccentric masses of avascular fibrous tissue in the muscular arteries and pulmonary arterioles may completely occlude the vessel, but a small endothelium-lined channel with an irregular course frequently remains patent (fig. 3c). Thus the characteristic feature of
severe hypertensive pulmonary vascular disease, grade 3, is the widespread occlusion of muscular pulmonary arteries less than about 500 μm in diameter and of arterioles by acellular fibrous tissue admixed with fine elastic fibrils. The large muscular arteries more than about 600 μm in external diameter rarely show intimal fibrosis even when the smallest and medium-sized arteries and arterioles show foci of complete occlusion. Atheroma rather than intimal fibrosis is found in the large muscular and elastic pulmonary arteries in the presence of severe pulmonary hypertension.3

In grade 3 the media reaches the limit of its capacity for hypertrophy, so that its thickness may be up to 30 per cent of the external diameter of the vessel. The media of the arteriole is similarly much thickened. In the medium-sized and large muscular arteries the increase in medial thickness is brought about partly by the development of fasciculi of longitudinal muscle which usually lie in close apposition to the internal or external elastic lamina and which are bounded by elastic laminae as shown in figure 3d. Occasionally increased numbers of longitudinal muscle fibers, not in distinct fasciculi delineated by elastic fibrils, may be seen in the media itself.

Although the characteristic feature of grade 3 is medial hypertrophy, some thinning of the media is seen also in the severer, later stages of this grade. This dilatation occurs in patent vessels (fig. 4a) and those showing focal areas of occlusion (fig. 4b). In the latter case, the dilatation of vessels with thinning of the media is found in smaller muscular arteries and arterioles either at or distal to a focus of fibrotic occlusion of a parent muscular artery, and in medium-sized arteries, proximal to the foci of occlusion. In the former site the thinning is probably a type of disuse atrophy subsequent to the lowering of blood pressure distal to the fibrotic occlusion and is analogous to the thinning of pulmonary arteries in pulmonary stenosis. In the latter site the dilatation is an expression of decompensation to the severely elevated pulmonary resistance.

Dilatation Lesions. In addition to the generalized dilatation that occurs in severe examples of grade 3 and in grades 4, 5, and 6, excessive dilatation occurs in some of the smallest muscular pulmonary arteries and the arterioles to form distended sacs. In many of these microaneurysms there is endothelial proliferation and at times superadded throm-
Fig 5. a. Grade 5. Section of a muscular pulmonary artery showing hypertrophy of the media and excessive dilatation of an arteriolar branch to form a plexiform lesion. The intimal proliferation in the distended sac is cellular indicating the dilatation lesion to be of recent formation. From a 27 year old woman with atrial septal defect. X 150. b. Grade 5. Section of a muscular pulmonary artery showing hypertrophy of the media, with the development of longitudinal muscle, and a plexiform lesion. The cellular proliferation in the dilatation lesion is partially replaced by fibrous tissue indicating that it is older.

(Continued on opposite page)
bosis. These complex vascular formations consisting of severely dilated vessels with internal cellular proliferations we term "dilatation lesions," and they are to be distinguished from the generalized dilatation that occurs throughout the pulmonary vasculature in some stages of pulmonary hypertension. These dilatation lesions are seen in 4 main forms: (1) plexiform lesions, (2) veinlike branches of hypertrophied, usually occluded, muscular pulmonary arteries, (3) angiomatoid lesions, and (4) cavernous lesions.

1. The Plexiform Lesion. The pulmonary arterioles and smallest muscular pulmonary arteries are greatly distended to form saes whose walls are fragile, consisting of a single elastic lamina or an exceedingly thin layer of muscle between 2 ill-defined elastic laminae (fig. 5a). Large similarly thin-walled channels leave these dilated saes and terminate as capillaries that pass to the alveolar walls. In some instances vessels of capillary size leave the saes and pass directly to the alveolar capillaries. As a result of endothelial proliferation and thrombosis in these dilated vessels, 3 zones, frequently well defined, may be seen in them. Proximally there is fibrous tissue continuous with that in the intima of the patent muscular pulmonary artery. In early lesions this fibrous tissue is cellular; in late lesions it is acellular. There is a central zone of proliferative cellular endothelial tissue which often assumes a characteristic plexiform pattern in the sae so that this lesion might conveniently be termed the "plexiform lesion." It is the hallmark of grade 4. Distally, in the distended sae, there is frequently a thrombus, stimulated probably by the papilliferous endothelial proliferation. As the lesion ages, the fibrosis spreads through it and finally replaces it (fig. 5b and c).

2. Veinlike Branches of Hypertrophied Muscular Pulmonary Arteries (fig. 6a and b). Muscular pulmonary arteries, which show medial hypertrophy and gross intimal fibroelastosis, give rise to thin-walled branches resembling veins, and these end as capillaries in the alveolar walls. Such veinlike structures usually emerge from the parent muscular pulmonary artery proximal to the point of obstruction and have been considered to represent a collateral pulmonary blood flow to the alveolar walls. In the present cases, however, some of these dilated branches were found to arise from vessels with patent lumens.

3. The Angiomatoid Lesion (fig. 6c). In this instance muscular pulmonary arteries showing intimal fibrosis give rise to thin-walled vessels. The latter show peculiar vascular formations within their lumens. Cross sections of these formations show them to be composed of a series of thin blood vascular structures having walls of simple elastic tissue. These intraluminal vessels leave the arteries containing them to form a surrounding angiomatoid mass. Since the angiomatoid structure surrounds the dilated vessel it lies somewhat removed from the muscular artery that gave rise to the dilated branch. The angiomatoid lesion itself gives rise to many thin-walled vessels which ramify in all directions in the pulmonary substance to supply capillaries to the air spaces. If the intimate connection between parent muscular pulmonary artery, thin-walled branch, and angiomatoid lesion is not established by examination of serial sections, one may mistakenly consider the angiomatoid mass to be an independ-
Fig. 6. a. Grade 5. Transverse section of a muscular pulmonary artery, showing hypertrophy of the media and obliteration of its lumen by fibrous tissue, and its veinlike, thin-walled branches which cluster characteristically around the parent vessel. From a 24 year old woman with patent ductus arteriosus. X 75.  b. Grade 5. Transverse section of a muscular pulmonary artery, showing obliteration of its lumen by dense acellular fibrous tissue. There are gross thickening and elastosis of the internal elastic lamina. The media is largely replaced by fibrous tissue. Clustering near the artery are its thin-walled, veinlike branches. From a 24 year old woman with patent ductus arteriosus. X 75.  c. Grade 5. Transverse section of the angiomatoid form of dilatation lesion. The thin-walled, veinlike branches of a hypertrophied muscular pulmonary artery form an angiomatoid mass in the lungs. From a 32 year old woman with ventricular septal defect. X 100.  d. Grade 5. Section of lung showing a cavernous dilatation lesion. Cavernous thin-walled branches, one showing endothelial proliferation, are seen clustered around the hypertrophied parent muscular pulmonary artery. From a 24 year old woman with patent ductus arteriosus. X 75.
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ent separate entity in the pulmonary substance. The diameter of this structure approaches 1 mm.

4. The Cavernous Lesion (fig. 6d). Intermediate between the 2 forms previously described, this form of lesion is composed of cavernous vessels that arise from a thin-walled branch of a muscular pulmonary artery.

All 4 types of dilatation lesions are simply severer and more complex expressions, in the pulmonary arterioles and the smallest pulmonary arteries, of the generalized dilatation that occurs throughout the pulmonary vasculature as a result of the chronically high vascular resistance. Early generalized dilatation is seen in association with the predominantly hypertrophied vessels in a late stage of grade 3, but the appearance of the plexiform lesion is the hallmark of grade 4. In severer examples of grade 4 and in grade 5, the generalized dilatation of pulmonary arteries also proceeds. Grade 5 is characterized by the appearance of many veinlike branches of hypertrophied arteries and the angiomatoid and cavernous lesions, all of which give rise to sinusoid-like vessels throughout the pulmonary substance. The angiomatoid lesion is rare and was not seen in the Mayo Clinic series reported herein. The case included for the sake of completion was one of ventricular septal defect with pulmonary hypertension studied by one of us (D.H.) in association with Dr. D. B. Brewer at the University of Birmingham, England.

Grade 4. Stage of Progressive Generalized Arterial Dilatation with the Formation of Complex Dilatation Lesions (Plexiform Lesions). In grade 4 the emphasis in the histologic picture shifts from predominant signs of hypertrophy to those of dilatation. Both the muscular pulmonary arteries and the arterioles show progression in the dilatation that was seen to originate in the late stages of grade 3. The hallmark of grade 4 is the appearance of the plexiform type of dilatation lesions described in the previous section (fig. 5a, b, and c). In addition, segments of branches of hypertrophied arteries dilate (fig. 5d).

A distended sac is formed but the wall consists of a thin but still recognizable arterial structure with a distinct media and internal and external elastic laminae. In such dilated arteries intimal thickening may occur. The intimal tissue is fibrous and the fibers and nuclei tend to be arranged concentrically to give a so-called onion-layering appearance (fig. 5d). Beyond the distended segment of the artery, the normal arterial structure is resumed with superadded intimal fibrosis. Many muscular arteries and arterioles in grades 4 to 6 still show marked increase in medial thickness with gross intimal fibroelastosis.

Grade 5. Stage of Chronic Dilatation with Formation of Numerous Dilatation Lesions and Pulmonary Hemosiderosis. This is the stage of dilatation in which the vessels show medial as well as intimal fibrosis and look rigidly dilated. The media of the muscular pulmonary arteries and the arterioles is thinned and fibrosed and in many cases, the intimal fibrous tissue is acellular or even hyaline. In grades 3 and 4, as previously mentioned, arteries with intimal fibrosis show small endothelium-lined channels as the remainder of a lumen all but obliterated by fibrous tissue. In grade 5, however, some of such central channels are widely dilated and surrounded by what appears to be a rigid tube consisting largely of acellular fibrous tissue and a thin, fibrosed media. The arterioles show similar dilatation with fibrosis.

All 4 types of dilatation lesions, that is, the simple veinlike branch of the hypertensive muscular pulmonary artery, the plexiform lesion, the angiomatoid lesion, and the cavernous lesion, are commonly found and give rise to thin-walled, dilated vessels which ramify throughout the lung rendering it highly vascular and filled with sinusoid-like vessels (fig. 7a). It would seem that these are fragile and either burst or allow diapedesis of blood, for foci of hemosiderin-containing macrophages are scattered throughout the lung in grade 5 (fig. 7b).

Grade 6. Stage of Necrotizing Arteritis. Few patients with hypertensive pulmonary vascular disease ever show the vascular
cardiac disease; a few cases have been reported in mitral stenosis associated with pulmonary hypertension and in idiopathic pulmonary hypertension.

In necrotizing arteritis some of the muscular pulmonary arteries show acute fibrinoid necrosis. In sections stained with hematoxylin and eosin the muscle has a glassy appearance with loss of nuclei or has smudgy staining. The typical staining reactions for fibrinoid are given. Vessels show complete necrosis of muscle with a surrounding inflammatory reaction consisting predominantly of polymorphonuclear leukocytes with a few eosinophils.

Many arteries exhibit the subacute or healing phase of arteritis with masses of young basophilic cellular fibrous tissue replacing the dead muscle and forming masses in proximity to it in the intima and adventitia. The masses of fibrous tissue in the intima appear to be reactive to the underlying medial necrosis and, being basophilic and cellular, form a striking contrast to the pre-existing intimal fibrous tissue, which is eosinophilic and relatively acellular. Thrombosis is found in some arteries, many of which show gross hypertrophy. The granulation tissue may replace as much as a third of the media (fig. 8a) and in exceptional circumstances, the entire vessel may be replaced by granulation tissue, only the elastic laminae retaining partial integrity (fig. 8b). In other cases, only a small arc of the media is replaced by fibrous tissue so that, lying between the bulbous expansions in the intima and adventitia, this gives the lesion a dumbbell shape. In the connecting bar of fibrous tissue in the media, the long axes of the fibroblast nuclei are radial.

The adventitial masses of granulation tissue lie around branches of arteriolar size, and endothelium-lined channels of this magnitude enter the fibrotic region but become lost therein. Many small capillaries, lined by plump endothelium and containing erythrocytes, ramify throughout the basophilic fibrous tissue and a few thin-walled vessels leave this tissue to lie between the old acellular collagen fibers of the adventitia (fig. 8a to d).

![Image](http://circ.ahajournals.org/)

**Fig. 7.** a. Transverse section of a lung showing one of the numerous thin-walled, sinusoid-like vessels which are branches of hypertrophied muscular arteries and which characterize grade 5. From a 21 year old man with ventricular septal defect. ×100. b. Grade 5. Transverse section of lung showing the pulmonary hemosiderosis which results from bleeding from thin-walled vessels as shown in figure 7a. From a 23 year old man with idiopathic pulmonary hypertension. ×100.

Changes in the lung that we include in grade 6. In fact, the only patient of the present series who had this group of histologic features characterized by necrotizing arteritis in its acute and subacute forms was suffering from an unusual form of atrial septal defect associated with pulmonary hypertension from birth. There is justification for including this case at this point to illustrate this grade of hypertensive pulmonary vascular disease, for necrotizing arteritis has been observed in ventricular septal defect with pulmonary hypertension. It is at the same time necessary to point out that necrotizing arteritis is uncommonly reported with any type of
This imparts a characteristic picture of many dilated veinlike structures lying scattered throughout the adventitia of the larger muscular pulmonary arteries (fig. 8c).

The site of masses of adventitial fibrous tissue lying around branches of the muscular pulmonary arteries again suggests that the junction of artery and arteriole is a site of predilection for arteritis just as has been found for intimal fibrosis and the so-called dilatation lesions (fig. 8d).

**Grade 1 in Atrial Septal Defect.** In atrial septal defect, and those other forms of congenital heart disease characterized by the presence of high pulmonary blood flow over a prolonged period prior to the onset of pulmonary hypertension, the structural changes in grade 1 differ from those seen in ventricular septal defect. Initially, before the onset of pulmonary hypertension, the pulmonary arterioles are lined by a single elastic lamina as in the normal person.

Both they and the small muscular pulmonary arteries are widely dilated. Even at this stage where the pulmonary arterial blood pressure is normal or only slightly elevated, the pulmonary veins are the site of pronounced, intimal acellular fibrosis. This
venous intimal change remains characteristic of atrial septal defect with all grades of changes in the pulmonary arteries (fig. 9a).

Associated with the onset of pulmonary hypertension is a pronounced cellular endothelial reaction in the arterioles and the smallest muscular pulmonary arteries, so that vascular occlusion by intimal proliferation appears to be the origin of the increased pulmonary vascular resistance (fig. 9b). Once pulmonary hypertension is established, a distinct muscular media forms in the arterioles and there is hypertrophy of the media of the muscular pulmonary arteries. These histologic features are the same as those seen in hypertensive pulmonary vascular disease, grade 2, associated with ventricular septal defect, and from this point the progression of structural changes is identical with that already described.

**Summary**

Progressive histologic changes occur in the media and intima of pulmonary arteries and arterioles in the presence of chronic elevation of pulmonary artery blood pressure complicating congenital septal defects. This progression is so stereotyped as to allow a division of the structural effects of the hypertension into 6 grades. The classification is based on the study of lungs from 67 patients having congenital heart disease, and 2 having idiopathic pulmonary hypertension. Pulmonary arterial hypertension was demonstrated at cardiac catheterization in 55 instances and was inferred from the clinical and pathologic features in 9 others. The classification is as follows:

**Grade 1.** In large ventricular septal defect and wide patent ductus arteriosus: medial hypertrophy in arteries and arterioles; no intimal changes. In atrial septal defect: cellular, intimal proliferation in the smallest muscular arteries and the arterioles; intimal fibrosis in pulmonary veins.

**Grade 2.** Medial hypertrophy; cellular intimal proliferation.

**Grade 3.** Medial hypertrophy; intimal fibrosis; early generalized vascular dilatation in severe instances.

**Grade 4.** Progressive generalized vascular dilatation and occlusion by intimal fibrosis and fibroelastosis. Appearance of the plexiform lesions, which are one form of the complex dilatation lesions that occur in the pulmonary arterioles and the smaller muscular pulmonary arteries.

**Grade 5.** Appearance of the other “dilatation lesions,” including veinlike branches of hypertrophied muscular arteries, cavernous lesions, and angiomatoid lesions; highly vascular lung due to veinlike arterial branches; pulmonary hemosiderosis.

**Grade 6.** Necrotizing arteritis.
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Summary in Interlingua

Progressive alterationes histologic occurre in le tunicas mediae e intime del arterias e arteriolas pulmonar in le presentia de elevacion chronic del pression de sanguine pulmone-arterial que complica congenite defectos septal. Iste phenomeno es si stereotype que nos pote divider le effectos structural del hypertension in 6 grados successive. Lor definition es basate super le studio del pulmones de 67 patientes con congenite morbo cardiac e de 2 con idiopathic hypertension pulmonar. Hypertension pulmono-arterial esseva demonstrate per catheterisation cardiae in 55 casos e esseva presumite super le base de observationes clinic e pathologic in 9 alteres. Le classification es le sequente:

Grado 1. In casos de grande defectos ventriculo-septal e de marcate patente ducto arteriose: Hypertrophia medial in le arterias e arteriolas; nulle alterationes del intima.—In casos de defecto atrio-septal: Proliferation cellular del intima in le plus miere arterias muscular e in le arteriolas; fibrose intimal in le venas pulmonar.

Grado 2. Hypertrophia medial; proliferation cellular del intima.

Grado 3. Hypertrophia medial; fibrose intimal; precoce generalisate dilatation vascular in casos grave.

Grado 4. Progressive dilatation vascular generalisate e occlusion per fibrose e fibroelastose intimal. Apparition del lesiones plexiforme, le quales representa un del formae del complexe lesiones de dilatation occurrente in le arteriolas pulmonar e in le minor arterias pulmonar muscular.

Grado 5. Apparition del altere „lesiones de dilatation,” incluse brancas venoide de hypertrophiatate arterias muscular, lesiones cavernose, e lesiones angiomatoide; pulmon altemente vascularisate in consequentia del venoide brancas arterial; hemosiderosis pulmonar.

Grado 6. Arteritis necrotisante.

References


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DONALD HEATH and JESSE E. EDWARDS

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