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THE EFFECT OF PATENT DUCTUS ARTERIOSUS AND OF INTERAURICULAR AND INTERVENTRICULAR SEPTAL DEFECTS ON THE DEVELOPMENT OF PULMONARY VASCULAR LESIONS *

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During the past several years there has been increasing interest in the diagnosis and surgical treatment of congenital heart disease. No systematic study has been made of the possible changes in the pulmonary circulation in cardiac anomalies in which there is a left to right shunt. This matter now assumes greater importance as the result of operations recently introduced in which a systemic vessel is anastomosed to the pulmonary artery. For this reason, representative groups of cases of congenital heart disease in which there was a left to right shunt were studied. The histologic changes in the lungs were evaluated and an attempt was made to correlate these findings with known physiologic facts regarding the pulmonary circulation in similar groups of cases.

Material was gathered from the autopsy files of the Beth Israel (BIH), the Children's (CH), the Mallory Institute of Pathology at the Boston City (BCH), the Massachusetts General (MGH), and the Peter Bent Brigham (PBBH) Hospitals. This represented an autopsy population of 44,220. From this group, 67 cases of congenital heart disease, considered to be suitable for this study, were selected.

Only cases which were significant from a clinical as well as a pathologic viewpoint were used. Cases in which there were multiple defects were discarded unless the associated lesions might be expected to increase the degree of left to right shunt. Three main groups were studied: (1), patent ductus arteriosus; (2), interauricular septal de-

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fects; and (3), interventricular septal defects. A fourth but smaller group in which there was a combination of lesions giving a left to right shunt also were included in the study.

Control groups of 10 cases from each of the first 7 decades of life were studied also to give a baseline of pulmonary vascular change resulting from age alone. Care was taken to avoid, so far as possible, any condition which would predispose to secondary pulmonary vascular change. Special care was taken to eliminate cases in which there was chronic pulmonary disease, *i.e.*, emphysema, extensive fibrosis, obliterating pleuritis, tuberculosis, neoplasm, or thoracic deformity. Cases with cardiovascular-renal disease of any type also were discarded.

Methods

It was necessary to depend upon autopsy protocols for the description of lesions of the large branches of the pulmonary artery. This represented the work of a large number of prosectors with consequent variation in reliability. Routine sections of lung were used for microscopic study. These usually were taken at random from unspecified portions. Two to eight blocks from each case were studied. Sections were fixed in either Zenker's acetic or 10 per cent formalin solutions. They were stained with hematoxylin and eosin, a combination of van Gieson's and Weigert's elastic tissue method on the same section, and Masson's trichrome light green stain.

Because of the confusion in terminology regarding the divisions of the pulmonary artery, the vessels were arbitrarily divided by size into four groups. External diameters of the arteries were computed from the external elastic lamellae. Group I consisted of vessels greater than 1 mm. in diameter; group II, 250 to 500 μ; group III, 100 to 250 μ; and group IV, 25 to 100 μ. These were studied to determine the type, location, and extent of any vascular lesions present.

The sections were pooled and then examined objectively without knowledge of the age of the patient or the extent and nature of the cardiac lesions.

The changes were graded from 1 plus to 4 plus depending upon the severity of the lesion. The lesions in each group were classified under three general headings: intimal proliferative changes, hyaline changes, and medial changes (Table I).

The intimal proliferative lesion consisted of an increase in subendothelial connective tissue and was frequently associated with splitting and reduplication of the elastica interna. This change ranged from

asymmetric plaques involving a small segment of the circumference of a vessel in mild lesions to a total obliterating endarteritis in severe lesions. There was considerable variation in the cellularity of the lesions, and occasionally vacuolar degeneration was found. There appeared to be a transition stage between intimal proliferative and intimal hyaline lesions with loss of cellularity and increasing evidence of collagen deposition.

Hyaline lesions consisted of a deposition of acellular, homogeneous, subendothelial hyalin. In the mild lesions, small asymmetric deposits were present, while in severe lesions a thick hyaline ring was found with marked reduction of the lumen of the vessel. The location of the

TABLE I

Grading of Lesions

	+	++	+++	++++
Intimal proliferation	Occasionally present and asymmetric	Consistently present but asymmetric	Consistently present and uniform	Marked reduction to obliteration of lumen
Hyalin	Occasionally present and asymmetric	Consistently present but asymmetric	Consistently present and uniform	Marked reduction to obliteration of lumen
Medial thickening	Occasional asymmetric thickening	Consistent asymmetric thickening	Uniform thickening	Marked hypertrophy or hyalinization

hyaline material in relation to the internal elastic lamella varied considerably. Usually the hyalin was between the internal elastic layer and the lining endothelium. In some instances it enveloped the elastic lamella, while less commonly it extended for variable distances into the media. This material took an acidophilic stain with hematoxylin and eosin and with the combined Weigert elastic tissue and van Gieson method. With Masson's trichrome stain the hyalin appeared pale green.

The medial layers were examined for evidence of hypertrophy or an increase in number of smooth muscle cells, and for an increase in intercellular collagen. The lesions graded as 1 plus were those in which thickening was asymmetric and present in an occasional vessel, while the lesions regarded as 4 plus were those in which there was marked and consistent concentric hypertrophy or hyalinization of the arteries.

The capillaries and veins were examined to determine the presence or absence of thickening or scarring.

TABLE II

Control Group

Decade	Case	Pulmonary vascular lesions Microscopic											
		1 mm.			250–500 μ			100–250 μ			25–100 μ		
		I*	H†	M‡	I	H	M	I	H	M	I	H	M
1st	1	.	.	.	.	.	.	.	.	.	.	.	.
	2	.	.	.	.	.	.	.	.	.	.	.	.
	3	.	.	.	.	.	.	.	.	.	.	.	.
	4	.	.	.	.	.	.	.	.	.	.	.	.
	5	.	.	.	.	.	.	.	.	.	.	.	.
	6	.	.	.	.	.	.	.	.	.	.	.	.
	7	.	.	.	.	.	.	.	.	.	.	.	.
	8	.	.	.	.	.	.	.	.	.	.	.	.
	9	.	.	.	.	.	.	.	.	.	.	.	.
	10	.	.	.	.	.	.	.	.	.	.	+	.
2nd	11	.	.	.	.	.	.	.	.	.	.	.	.
	12	.	.	.	.	.	.	.	.	.	.	.	.
	13	.	.	.	.	.	.	.	.	.	.	.	.
	14	.	.	.	.	.	.	++	++	.	++	+	.
	15	.	.	.	.	.	.	.	.	.	.	.	.
	16	.	.	.	.	.	.	.	.	.	.	.	.
	17	.	.	.	.	.	.	.	.	.	.	.	.
	18	.	.	.	.	.	.	.	.	.	.	+	.
	19	.	.	.	.	.	.	+	.	.	.	.	.
	20	.	.	.	.	.	.	+	.	.	+	.	.
3rd	21	—	—	—	.	.	.	+	.	.	+	+	.
	22	+	.	.	+	.	.	+	++	.	.	+++	.
	23	+	.	.	+	.	.	+	+	.	.	+++	.
	24	.	.	.	.	.	.	.	.	.	.	.	.
	25	.	.	.	+	.	.	+	.	.	.	+	.
	26	.	.	.	.	.	.	.	.	.	.	+	.
	27	.	.	.	.	.	.	+	.	.	.	++	.
	28	.	.	.	.	.	.	.	.	.	.	+	.
	29	.	.	.	.	.	.	.	+	.	.	++	.
	30	.	.	.	.	.	.	.	.	.	.	+	.
4th	31	.	.	.	+	.	.	++	++	.	+	+	.
	32	.	.	.	.	.	.	.	+	.	.	++	.
	33	.	.	.	+	+	.	+	+	.	.	+	.
	34	++	.	.	++	+	.	++	+	.	.	+	.
	35	.	.	.	.	.	.	.	+	.	.	+	.
	36	.	.	.	.	.	.	+	+	.	.	+	.
	37	.	.	.	.	.	.	.	+	.	.	+	.
	38	.	.	.	.	.	.	.	++	.	.	+	.
	39	.	.	.	++	.	.	++	++	.	+	++	.
	40	.	.	.	+	.	.	++	+	.	+	++	.
5th	41	+	.	.	+	.	.	++	+	.	.	++	.
	42	.	.	.	+	.	.	+	.	.	.	+	.
	43	+	.	.	++	.	.	+++	+	.	.	++	.
	44	.	.	.	+	+	.	+	++	.	.	+++	.
	45	+	.	.	.	.	.	.	+	.	.	++	.
	46	.	.	.	+	.	.	+	+	.	.	+	.
	47	.	.	.	.	.	.	+	.	.	+	+	.
	48	.	.	.	.	.	.	.	++	.	.	+	.
	49	.	.	.	.	.	.	+	+	.	.	.	.
	50	+	.	.	+	.	.	.	++	.	.	++	.

TABLE II (cont'd.)

Decade	Case	Pulmonary vascular lesions Microscopic											
		1 mm.			250–500 μ			100–250 μ			25–100 μ		
		I*	H†	M‡	I	H	M	I	H	M	I	H	M
6th	51	++	.	.	+	+	.	+	+++	.	.	+	.
	52	.	.	.	+	+	.	+	+	.	.	.	.
	53	.	.	.	+	.	.	+	+	.	+	++	.
	54	—	—	—	.	.	.	.	+	.	.	++	.
	55	++	.	.	++	+	.	+++	++	.	++	+++	.
	56	—	—	—	++	.	.	++	++	.	+	++	.
	57	.	.	.	++	+	.	+	++	.	+	++	.
	58	+	.	.	+	+	.	++	++	.	.	+	.
	59	+	.	.	+	.	.	++	++	.	.	+++	.
	60	+	.	.	++	.	.	+	++	.	+	+	.
7th	61	—	—	—	+++	+	.	+++	++	.	+	+++	.
	62	.	.	.	+	.	.	+	+	.	.	+	.
	63	.	.	.	+	.	.	++	+	.	.	+	.
	64	.	.	.	+	.	.	++	++	.	.	+	.
	65	+	.	.	+	+	.	.	+++	.	.	+	.
	66	+	.	.	+	+	.	+++	++	.	++	+++	.
	67	+	.	.	++	+	.	+++	++	.	++	+++	.
	68	.	.	.	+	+	.	++	+++	.	.	++	.
	69	.	.	.	++	+	.	.	++	.	.	++	.
	70	+	.	.	+	.	.	++	+	.	++	+++	.

* Intimal proliferation.
† Hyalin.
‡ Medial thickening.

Vascular Changes in Normal Lungs

Vascular changes in the lungs of the control groups were graded according to the criteria used for the groups in which there was congenital heart disease.

A study of Table II, in which the pulmonary vascular lesions in the control group are summarized, indicates that in the first decade of life only one case had a recognizable lesion. In the second decade only scattered minimal lesions were found. In the third decade one case had no lesions, 7 had minimal lesions, and 3 plus lesions were found in the precapillary vessels in 2 cases. It was not until the fourth decade of life that consistent vascular changes were encountered, and these changes, for the most part, were mild. Lesions from this period on were more pronounced, and by the seventh decade 2 plus and 3 plus lesions were encountered consistently in arteries measuring from 25 to 500 μ in diameter.

No changes were found in the capillaries or veins in any of the cases in the control group. No thickening of the capillary basement membrane or change in the alveolar lining cells was observed. Such changes were described by Parker and Weiss [1] in patients having severe mitral stenosis.

The incidence of arteriosclerosis of the pulmonary arteries is remarkably high. In this series some degree of change was found in every case in which the subject was over the age of 40 years and in 9 of 10 cases from the third decade of life. It should be noted again that these cases were carefully selected so as to conform as closely as possible to the normal. It is obvious that any lesions found in the lungs in cases of congenital heart disease must be judged in the light of changes associated merely with ageing.

These findings are in accord with a survey by Brenner [2] who reviewed 100 consecutive autopsies and found macroscopic evidence of pulmonary vascular sclerosis in 70 per cent. On microscopic study this incidence increased to 97 per cent. In but 3 cases, all under 10 years of age, were no sclerotic changes found in the pulmonary vascular bed.

Patent Ductus Arteriosus

Twenty-five cases of patent ductus arteriosus, considered suitable for this study, were selected from the autopsy material available. Only those cases were used in which the internal diameter of the ductus was greater than 3 mm. The size of the defects ranged from 3 to 15 mm. and 7 measured 10 mm. or more in diameter. Twenty-three of these cases were not complicated by any significant cardiac or vascular anomalies. One case was associated with moderate coarctation of the aorta, and there was marked hypoplasia of the aorta distal to the ductus in the other case. The ages of the patients varied from 2 months to 65 years, with 13 over 20 years of age. There were 9 females and 16 males. The classical clinical picture with a typical "machinery" murmur was present in 17 patients. These cases are summarized in Table III.

Examination of Table III shows that with but one exception the changes in the pulmonary vascular system were no greater than the changes found in the control group in comparable ages. It should be emphasized that no medial changes were found in any of the vessels examined. There were severe intimal proliferative and hyaline changes in one case (BCH no. A-43-64), that of a 37-year-old male who had a ductus with an internal diameter of 12 mm. Four plus intimal proliferative and 3 plus hyaline changes were encountered in vessels measuring from 25 to 100 μ, while in vessels of other sizes the changes were no greater than those found in the control group. This case has been reported in detail by Chapman and Robbins.[3] A similar case has been reviewed by Keys and Shapiro.[4] Their patient was a 48-year-old woman who had a ductus measuring 15 mm. in diameter. The heart weighed 700 gm. and there was marked right ventricular hypertrophy.

The large branches of the pulmonary artery were dilated and microscopically there was marked intimal atherosclerosis of the large and small branches of the pulmonary artery. Other reports of pulmonary atherosclerosis in patients with a patent ductus either have described changes limited to the immediate vicinity of the ductus, have included significant associated cardiac defects, or were difficult to evaluate because of inadequate pathologic study. Isolated reports have noted macroscopic changes but failed to give detailed microscopic descriptions of the nature, distribution, and severity of the pulmonary vascular lesions.

The rarity of reports of cases of patent ductus with pulmonary atherosclerosis and the fact that only one of 25 cases in this series had excessive pulmonary atherosclerosis indicate that such findings are unusual. It should be noted, however, that in both of the reported cases there appeared to be a significant pulmonary vascular block with subsequent right heart failure.

In contrast to the above was case PBBH no. A-44-102, a woman of 27 years with a ductus having an internal diameter of 15 mm. together with a severe diffuse hypoplasia of the aorta beyond the ductus. Evidence that this hypoplasia produced a considerable resistance in the systemic circuit is offered by the fact that immediately after the ductus was divided the left heart dilated and the patient expired on the table. This combination of lesions would necessarily result in a tremendous volume flow through the pulmonary circuit. The lungs showed no vascular lesions.

It has been postulated frequently that there is a significant elevation of pulmonary arterial pressure in cases of patent ductus. Dexter and his group [5] have measured the pulmonary arterial pressure by means of the venous catheter in 12 patients having patent ductus arteriosus. In 9 cases it was not significantly elevated in the absence of congestive failure. In 3 patients the pressure was elevated despite the absence of clinical manifestations of cardiac failure. However, each had decreased exercise tolerance. The volume flow through the pulmonary artery in these patients was 16.9, 14.2, and 8.8 liters per minute, respectively. Cournand [6] has recently reported the case of a 3-year-old girl with a patent ductus, who had a pulmonary flow of 5 liters per minute and a systemic flow of 2 liters per minute. Her pulmonary arterial pressure was 55/39 mm. of Hg, which Cournand considered three times normal for the age. In 9 of the 12 cases studied by Dexter the internal diameter of the ductus was greater than 7 mm. One patient, a man of 38 years, had a ductus with a diameter of 13 mm. and a volume flow of 9 liters per minute, yet the pulmonary arterial pres-

TABLE III

Patent Ductus Arteriosus

Autopsy	Age	Sex	Internal diameter of ductus	Heart weight	Thickness of ventricle		Significant associated cardiac defects	Gross
					Right	Left		
	years		*mm.*	*gm.*	*mm.*	*mm.*		
CH A-35-4	2/12	M	3	22	4	6	None	Normal
CH A-36-11	3/12	F	3	20	2	6	None	Normal
CH A-39-31	4/12	F	15	Not given	6	10	None	Agenesis of right pulmonary vessels
CH A-31-74	9/12	M	Patent	29	3	8	None	Normal
CH A-39-117	10/12	M	5	47	3	9	None	Normal
CH A-46-131	2 11/12	M	5	88	3	10	None	Normal
CH A-35-104	7 2/12	M	3	180	4	13	None	Normal
CH A-30-132	7 7/12	M	3	129	2	9	None	Normal
CH A-43-187	10 10/12	M	10	Normal	4	16	Mycotic aneurysm of pulmonary conus proximal to ductus	Plaques only in vicinity of ductus
PBBH A-43-98	13	M	12	"Slight cardiac enlargement"	10	24	None	Normal
PBBH A-42-142	14	F	4	400	7	20	S.b.e.§ of ductus, aortic and mitral valves	Normal
PBBH A-39-187	15	F	10	Not given	8	18	S.b.e. of ductus	Normal
PBBH A-44-127	20	M	5	730	4	19	S.b.e. of mitral and aortic valves	Plaques opposite opening of ductus
PBBH A-45-74	21	F	Patent	520	6	19	S.b.e. of ductus	Pulmonary artery markedly dilated
MGH 9237	21	M	5	550	5	15	S.b.e. of pulmonary artery, pulmonary and mitral valves, and ductus	Normal
MGH 8789	21	F	3	380	3-5	14	Slight coarctation and s.b.e. of aortic and mitral valves	Normal

Pulmonary vascular lesions														
Microscopic														
1 mm.			250–500μ			100–250μ			25–100μ			Blood pressure	Signs and symptoms referable to ductus	Cause of death
I*	H†	M‡	I	H	M	I	H	M	I	H	M			
												mm. Hg		
.	.	.	.	.	.	.	.	.	.	.	.	Not taken	Terminal cyanosis	Bronchopneumonia
.	.	.	.	.	.	.	.	.	.	.	.	Not taken	Murmur	Dehydration and infection
.	.	.	.	.	.	.	.	.	.	.	.	Not taken	Cyanosis on effort	Pneumonia
.	.	.	.	.	.	.	.	.	.	.	.	Not taken	None	Hydrocephalus (postoperative)
.	.	.	.	.	.	.	.	.	.	.	.	Not taken	Murmur	Meningitis and pneumonia
.	.	.	+	.	.	.	.	.	.	.	.	98/70	None	Lead poisoning and medullary compression
.	.	.	.	.	.	.	.	.	.	.	.	Not taken	None	Bulbar poliomyelitis
.	.	.	.	.	.	.	.	.	.	.	.	Not taken	None	Meningitis
.	.	.	.	.	.	.	.	.	+	.	.	95/55	Murmur	Cardiac tamponade and rupture of mycotic aneurysm
.	.	.	+	.	.	.	+	.	.	+	.	118/70	Murmur	Hemopericardium of 1200 cc. following division of ductus
+	.	.	+	.	.	+	++	.	.	++	.	110/56	Murmur	Died during operation
.	.	.	.	.	.	+	++	.	+	++	.	142–162 / 40–0	Murmur	Died following operation
.	.	.	.	.	.	+	+	.	.	+	.	105/40	Murmur	S.b.e.
+	.	.	.	.	.	.	+	.	.	+	.	104/54	Murmur; dyspnea, 8 yrs.	Hemorrhage due to silver clip in left pulmonary artery with erosion
.	.	.	.	.	.	+	.	.	.	.	.	112/60	Murmur	S.b.e. and congestive heart failure
.	.	.	+	.	.	.	+	.	+	++	.	90/30	Murmur	S.b.e. and congestive heart failure; pulmonary embolus

TABLE III (cont'd.)

Autopsy	Age	Sex	Internal diameter of ductus	Heart weight	Thickness of ventricle		Significant associated cardiac defects	Gross
					Right	Left		
PBBH A-41-127	*years* 25	M	*mm.* 4	*gm.* 400	*mm.* 7	*mm.* 15	Healed s.b.e. of ductus	Normal
MGH 10,884	26	F	10	400	4	16	None	Plaque opposite ductus
PBBH A-44-102	27	F	15	560	5	18	Diffuse hypoplasia of aorta distal to ductus	Normal
BCH A-99-85	30	M	4	510	5-8	18	None	Calcification and thrombus in region of ductus
PBBH A-43-102	31	M	Aorta, 5; pulmonary artery, 4	"Moderate hypertrophy"	7	23	S.b.e. of mitral valve and left auricle	Normal
BCH A-43-64	37	M	12	680	18-22	14	Healed pulmonic endocarditis	Marked atherosclerosis of large branches; pulmonary artery, 12 cm. in circumference
BCH A-41-580	44	M	Patent	380	5	18	None	Endarteritis in vicinity of ductus
PBBH A-32-136	47	M	Aorta, 15; pulmonary artery, 5	480	4-6	15-18	S.b.e. of mitral valve and left auricle	Normal
PBBH A-36-173	65	F	3	440	6	17	Calcified annulus fibrosus of mitral and aortic valves	Atherosclerosis of large branches

* Intimal proliferation.
† Hyalin.
‡ Medial thickening.
§ Subacute bacterial endocarditis.

sure was normal. It would appear that there is no constant relation between either the diameter of the ductus or the calculated volume flow and the degree of pulmonary hypertension.

It has been suggested that there is a direct correlation between the size of the ductus, the circumference of the pulmonary artery, and the thickness of the right ventricle. These have been considered to be indices of pulmonary hypertension. In our series there was no correlation between the diameter of the ductus and right ventricular hypertrophy. The right ventricle was of normal thickness in 5 of 8 cases in which the internal diameter of the ductus was 10 mm. or more.

Pulmonary vascular lesions													
Microscopic													
1 mm.			250–500μ			100–250μ			25–100μ			Blood pressure	Signs and symptoms referable to ductus	Cause of death
I*	H†	M‡	I	H	M	I	H	M	I	H	M			
												mm. Hg		
+	.	.	+	.	.	+	.	.	.	.	.	108/68	Murmur	Accidental
.	.	.	.	.	.	.	+	.	.	+	.	105/80	Murmur	Died during operation
.	.	.	.	.	.	.	.	.	.	.	.	136/50	Murmur; dyspnea, 6 yrs.	Died during operation
.	.	.	.	.	.	.	.	.	.	+	.	—	None recorded	S.b.e.
.	.	.	.	.	.	+	++	.	+	++	.	144/72	Murmur	S.b.e.
.	.	.	+	+	.	++++	+++	.	.	+	.	135/85	Murmur	Acute congestive heart failure
.	.	.	.	.	.	+	++	.	.	+	.	126/80	None	Portal cirrhosis
+	.	.	+	.	.	++	+	.	++	+	.	120/80	Murmur; dyspnea, 6 mos.	Bacterial endocarditis
.	.	.	.	.	.	+	.	.	++	++	.	170/70	Murmur	Unknown; autopsy limited to heart and lungs

Conversely, the right ventricle was hypertrophied in 11 cases, yet 6 of these had defects of 5 mm. or less.

The left ventricle was enlarged in 15 of our 25 cases. The diameter of the ductus was 10 mm. or more in 7 and less than 10 mm. in 8 cases. The heart was increased in weight in 16 of the 23 cases in which the weights were given, and yet in only 5 of these were the ducti over 10 mm. In brief, in this series there was no consistent correlation between the size of the ductus and the degree of left ventricular hypertrophy or increase in weight of the heart.

In patent ductus arteriosus there is a marked increase in blood flow

through the pulmonary circuit. Eppinger, Burwell, and Gross [7] have measured the increased blood flow occurring in these cases and have found that 45 to 75 per cent of the blood entering the aorta from the left ventricle passes into the pulmonary artery. Subsequent studies have shown that the normal pulmonary blood flow may be increased up to 300 per cent.[5] The lungs apparently are able to handle this increased volume flow in most cases without any significant elevation of pulmonary arterial pressure until failure of the left ventricle occurs. The reasons for this are manifold. The most important factor probably is the increase in cross sectional area in progressing from the pulmonary artery to the pulmonary capillary bed. This is an approximate increase of from 6 to 38,000 square cm.[8] In addition, the capillary blood volume can be increased by simple distention of the capillaries.[9] This occurs at the expense of vital capacity,[10] yet there is no loss of capillary function in the absence of parenchymatous disease of the lung. While this ability to distend is very valuable in the capillary area, it is equally valuable in the larger branches of the pulmonary arterial tree. Morphologic evidence of this is offered by the loose arrangement of the adventitial coat of these vessels. Experimental proof is afforded by the pressure-volume diagrams of Hochrein [11] and by studies of pulse wave velocity in the pulmonary artery in comparison to the aorta.[12]

Much has been written concerning structural variations and functional differences in the arterioles of the pulmonary and the systemic circulations. Some writers deny the existence of such vessels in the lungs, others claim that there is a simple decrease in the number of smooth muscle cells in the medial layer, while still others describe variations in diameter of a pulmonary arteriole up to four times that found in the systemic group. In this survey there appeared to be an orderly change in caliber in the branches of the pulmonary arteries and appropriate changes in the cellular structure of the layers in descending to the precapillary level.

However, in approaching this question from the physiologic point of view, Hamilton [13] has shown a difference of pharmacologic response in the arterioles of the two circulations and that the usual vasomotor response of the arteriole is lacking in the pulmonary system. There is at least one protective reflex mechanism present in the pulmonary vascular bed. The exact receptor area has not been accurately defined, but any increase in intravascular tension results in a significant hypotension of the systemic circulation with an associated bradycardia.[14] This mechanism is demonstrated in experimental pulmonary embolism when precapillary vessels are occluded by Lycopodium spores.[15] Here

the pulmonary arterial pressure rises, the femoral arterial pressure falls, and there is a decrease in cardiac output. With this one exception the pulmonary blood flow plays the active rôle and the pulmonary vascular bed a decidedly passive one.

All of the factors mentioned above combine to enable the lungs to care for the increased volume flow when the ductus is patent as long as venous return is unimpeded. In the majority of these cases there is no significant peripheral resistance in the pulmonary vascular bed, and pulmonary hypertension does not develop. Parker and Weiss [1] have postulated three factors that must be present for the production of an abnormal degree of pulmonary arterial and arteriolar sclerosis: High intravascular pressure, stagnation of blood flow, and pericapillary edema. None of these factors is present with a patent ductus until congestive failure supervenes. It is possible that a fourth factor, increase in volume flow, may initiate arteriosclerotic changes in the pulmonary vessels. This would account for the changes in case BCH no. A-43-64 and in the case reported by Keys and Shapiro.[4] Each of these patients had a large ductus (12 and 15 mm., respectively), and each, presumably, had a large increase in volume flow. In addition, they were in the latter part of the fourth decade of life. As will be discussed later, it is in this age group that the patients with large septal defects, in whom there was a marked increase in volume flow, began to show pulmonary vascular lesions in excess of the control group. Unfortunately, in neither of the above cases was there an opportunity to record the pulmonary arterial pressure or the volume flow. Conversely, in the 4 patients having an elevated pulmonary arterial pressure there was no opportunity to examine the pulmonary vasculature. Individual variations in the vulnerability of the pulmonary vessels to atherosclerotic change may also be a factor in these rare cases of marked pulmonary atherosclerosis. It is conceivable that sufficiently severe pulmonary vascular lesions can produce an increase in peripheral resistance in the pulmonary circuit.

Until complete studies can be made, including accurate measurements of pulmonary arterial pressure and volume flow, followed by an opportunity to examine the pulmonary vascular tree, the causal relationship of pulmonary atherosclerosis to pulmonary hypertension in patent ductus arteriosus cannot be answered.

Interauricular Septal Defect

Twenty-five cases were found in which there were significant unguarded interauricular septal defects. Only those cases were chosen in which the defect was greater than 0.8 cm. in diameter. In 17 cases the

TABLE IV

Interauricular Septal Defects

Autopsy	Age	Sex	Measurement of defect	Heart weight	Thickness of ventricle		Significant associated cardiac defects	Gross
					Right	Left		
	years		*cm.*	*gm.*	*mm.*	*mm.*		
CH A-47-23	5/12	M	1.7 x 2.5	66	8	7	None	Dilated 2.5 cm. in diameter
CH A-35-138	9/12	M	2.5	85	5	9	None	Normal
CH A-42-56	1	M	1.5	75	4	8	None	Normal
CH A-30-99	7 1/12	F	2.5 x 2.5	59	6	7	None	Normal
CH A-43-89	9 9/12	F	2.5	140	5	15	R.h.d.§; moderate mitral stenosis and insufficiency	Normal
MGH 11,121	14	F	1.0 x 2.0	380	5-7	17	R.h.d.; mitral and tricuspid stenosis	Normal
PBBH A-46-1	16	F	1.0	460	6	20	Hypertensive heart disease	Normal
BIH A-38-47	17	F	0.9	220	2	8	None	Normal
PBBH A-24-2	29	M	0.8	1000	8	20	Constrictive pericarditis	Normal
BCH 1923-155	34	F	3.5	470	7	11	S.b.e.‖ of tricuspid, pulmonic, mitral and aortic valves	Normal
BCH 1933-241	34	F	4.0	550	13	15	R.h.d.; tricuspid and mitral stenosis; coarctation of aorta	Dilated 5 cm.; atherosclerosis
BCH A-44-391	36	M	3.0	760	15	13	S.b.e. of mitral valve	Dilated
BIH A-33-94	47	F	2.0	420	10	15	Mitral thickening	Atherosclerosis
BIH A-36-89	51	M	2.0	640	8	14	R.h.d. and mitral stenosis	Atherosclerosis of large vessels
PBBH A-33-119	53	M	0.8	340	4	20	None	Normal

Pulmonary vascular lesions												Blood pressure	Signs and symptoms referable to cardiac lesion	Cause of death
Microscopic														
1 mm.			250–500 μ			100–250 μ			25–100 μ					
I*	H†	M‡	I	H	M	I	H	M	I	H	M			
												mm. Hg		
.	.	.	.	.	.	.	.	.	.	.	.	Not given	Effort cyanosis; murmur	Pneumonia
.	.	.	.	.	.	.	.	.	.	.	.	Not given	Cyanosis for 8 mos.	Congestive heart failure
.	.	.	.	.	.	.	.	.	.	.	.	Not given	Intermittent cyanosis	Pneumonia
.	.	.	.	.	.	.	.	.	.	.	.	Not given	None	Septicemia
.	.	.	.	.	.	+	+	.	+	+	.	92/60	Murmurs of mitral disease	Congestive heart failure
+	.	.	.	.	.	+	+	.	.	+++	.	100/70	Transient apical systolic murmur	Congestive heart failure
.	.	.	.	.	.	.	+	.	.	+	.	185/140	Grade I systolic and diastolic murmurs	Glomerulonephritis; uremia
.	.	.	.	.	.	.	.	.	.	+	.	125/75	None	Tuberculous meningitis
.	.	.	+	.	.	++	+	.	++	++	.	120/55	Systolic and diastolic murmurs	Congestive heart failure
+	.	.	.	+	.	++	+++	.	+	+++	.	—	Presystolic and apical systolic murmurs; dyspnea for 6 mos.	Congestive heart failure and pneumonia
+	.	.	.	.	.	+	+	.	+	++	.	—	Presystolic and apical systolic murmurs; r.h.d. for 24 years	Congestive heart failure and bronchopneumonia
+	.	.	.	+	.	++	+++	.	+++	++	.	85/65	Intermittent cyanosis; clubbing; murmur	Congestive heart failure and infection
+	.	.	++	.	.	++	++	.	+	+++	.	170/116	Dyspnea; cyanosis; and ascites	Congestive heart failure and pneumonia
+	.	.	+	.	.	+	+	.	++	+++	.	120/70	Dyspnea and cyanosis for 6 days	Congestive heart failure
+	.	.	.	.	.	+	++	.	++	+	.	110/70	None	Perforated gastric ulcer

TABLE IV (cont'd.)

Autopsy	Age	Sex	Measurement of defect	Heart weight	Thickness of ventricle		Significant associated cardiac defects	Gross
					Right	Left		
	years		*cm.*	*gm.*	*mm.*	*mm.*		
MGH 6580	56	M	2.4 x 1.5	675	8	11	R.h.d.; aortic and mitral stenosis	Dilated; atherosclerosis of smaller branches
PBBH A-47-64	57	M	2.5	600	8	18	None	Dilated (11 cm. in circumference); atherosclerosis of large branches
PBBH A-31-112	58	M	2.0	700	4	16	Hypertensive heart disease	Normal
MGH 9784	59	F	3.0	475	9-11	11-13	R.h.d., and s.b.e. of mitral valve	Normal
BCH A-40-803	60	F	3.0 x 1.5 3.0 x 1.5	495	10	15	None	Normal
PBBH A-36-59	60	M	0.7 x 0.7 0.7 x 0.4	280	4	12	None	Normal
MGH 6776	63	M	0.8	480	4	18	None	Normal
MGH 8298	63	M	0.7	300	3	8	None	Normal
MGH 11,560	70	M	1.0	450	5	15	None	Normal
MGH 6800	76	M	2.0	550	4	21	None	Normal

* Intimal proliferation. † Hyalin. ‡ Medial thickening. § Rheumatic heart disease. || Subacute bacterial endocarditis.

defect exceeded 2 cm. There were 13 cases without significant cardiac lesions, 9 cases with some degree of rheumatic involvement of the mitral valve, 2 cases of hypertensive heart disease, and one case with constrictive pericarditis.

In the 13 uncomplicated cases there was a direct relation between the size of the defect, cardiac enlargement, and right ventricular hypertrophy. The heart was increased in weight in 6, and 5 of these had defects greater than 2 cm. Of the 7 hearts of normal weight, 6 had defects of 1 cm. or less. In this same group of uncomplicated cases the right ventricle was hypertrophied in the 4 cases having the larger defects. In only 2 of the 13 cases was the pulmonary artery dilated.

In the 13 uncomplicated cases, the pulmonary vascular lesions were not greater than those in the control group of comparable ages. Three

Pulmonary vascular lesions												Blood pressure	Signs and symptoms referable to cardiac lesion	Cause of death
Microscopic														
1 mm.			250–500 μ			100–250 μ			25–100 μ					
I*	H†	M‡	I	H	M	I	H	M	I	H	M			
												mm. Hg		
++	.	.	++	.	.	+++	+	.	++	+++	.	130/70	Dyspnea and ascites	Congestive heart failure
+	.	.	+	.	.	++	++	.	+	+++	.	132/80	Basal systolic murmur	Carcinoma of bladder; congestive heart failure
+	.	.	+	.	.	+	++	.	+++	++	.	240/110	Hypertension	Congestive heart failure and nephrosclerosis
+	.	.	+	.	.	++	++	.	++++	+++	.	110/80	Dyspnea for 4 years	Infection; pneumonia; congestive heart failure
—	—	—	+	.	.	++	+++	.	++	+++	.	160/110	Dyspnea for 2 months	Congestive heart failure and pneumonia
+	.	.	+	.	.	++	++	.	+	+	.	138/68	Apical systolic murmur	Portal cirrhosis; hemorrhage
+	.	.	++	.	.	++	++	.	+	++	.	148/70	None	Pulmonary embolism; carcinoma of colon
—	—	—	+	.	.	+	++	.	+	++	.	130/80	None	Carbuncle; septicemia
++	.	.	+	.	.	+	+++	.	+++	+++	.	140/80	Precordial systolic murmur	Prostatism
+	.	.	.	.	.	+	.	.	.	+	.	170/80	None	Pulmonary embolism

of these patients were in the first decade of life and had no vascular lesions, yet the septal defects were all greater than 2.5 cm. and all had cardiac enlargement with right ventricular hypertrophy. These 3 cases are interesting in regard to the time interval required for the production of pulmonary vascular lesions. Cases with marked pulmonary atherosclerosis have been reported by Wätjen [16] and zur Linden,[17] one in a 6-months-old child and the other in an 11-months-old child. However, both of these had complicating cardiac anomalies. Wätjen's case had an associated interventricular septal defect and transposition of the great vessels, while zur Linden's case had a patent ductus.

One case in this uncomplicated group is of special interest in that accurate measurements of pulmonary arterial pressure and volume flow were made. This was the first opportunity to correlate these measure-

ments with changes in the pulmonary vasculature in a patient having no additional complicating pulmonary or cardiovascular disease. Case PBBH no. A-47-64 was that of a 57-year-old man. There was an interauricular septal defect measuring 2.5 cm. in diameter. The heart weighed 600 gm.; the left ventricle measured 1.8 cm. in thickness, and the right ventricle, 0.8 cm. There was marked dilatation of the right auricle and ventricle. The pressure in the pulmonary artery as measured by means of the venous catheter showed only minimal systolic elevation (35/10 mm. Hg) and the volume flow through the pulmonary artery was 14 liters per minute. The pulmonary artery was dilated to 11 cm. in circumference and there was atherosclerosis of the larger branches. Microscopic examination showed that the pulmonary vascular lesions did not exceed those found in comparable ages in the control group. This patient did not have cyanosis or clubbing. He developed mild congestive failure 1 year before death but this was easily controlled with digitalis. His death was due to carcinoma of the urinary bladder. The remarkable feature in this case was the lack of significant pulmonary vascular lesions even in the presence of a marked increase in the pulmonary blood flow.

In the group of cases complicated by other cardiac lesions, the 9 cases of interauricular septal defect in which there was rheumatic involvement of the mitral valve were of special interest. The aortic valve was stenotic in one case and thickened in another. Ages ranged from 9¾ to 59 years, and each decade was represented except the third and seventh. Every defect was greater than 2 cm., and all of the hearts were significantly enlarged. The right ventricle was hypertrophied in all but one case and preponderantly so in all patients beyond the third decade. Four of these cases had right ventricles measuring more than 10 mm. in thickness, with normal left ventricular measurements. All patients died in terminal congestive failure. Five of the 9 patients in this group had marked dilatation and/or gross atherosclerosis of the pulmonary artery.

Pulmonary vascular lesions were found in excess of the control group and at an earlier age in 8 of the 9 cases, with 2 plus and 3 plus lesions being consistently encountered. The vessels measuring from 25 to 250 μ were most severely involved. No medial lesions were found. Thickening of the capillary basement membranes, described by Parker and Weiss [1] as occurring in mitral stenosis, was not found. VonGlahn and Pappenheimer [18] have described a specific type of arteritis which occurred in the lungs and elsewhere in 10 of 47 cases of rheumatic fever. In the earlier stages there was a subendothelial deposition of fibrin with cellular destruction, while in the later stages

the intima was thickened and vascularized. These lesions were not found in the present group. In short, the pulmonary vascular lesions were those of atherosclerosis and amounted to premature ageing of the vessels.

The most typical case in this group was BCH no. A-44-391, a 36-year-old man with an interauricular septal defect of 3 cm. and rheumatic involvement of the mitral valve. The heart weighed 760 gm.; the right ventricle measured 15 mm., the left ventricle, 13 mm. The pulmonary artery was dilated and pulmonary vascular lesions were pronounced. The patient had intermittent cyanosis and clubbing. This case is similar to Lutembacher's [19] original case, that of a 61-year-old woman with an interauricular septal defect of 4 cm. and mitral stenosis, who had marked dilatation and atherosclerosis of the pulmonary arteries.

It would seem that in patients with interauricular septal defects and superimposed rheumatic mitral valvular disease a mechanical factor is introduced which greatly alters the existing dynamics of blood flow within the heart. Because of the stenosis of the mitral valve, there is an obligatory shunting of blood from the left to the right auricle. This throws a greater burden on the right side of the heart with consequent hypertrophy and dilatation of the right auricle. This in turn results in widening and stretching of the original congenital septal defect. There is an even greater pulmonary blood flow than is found in cases of patent ductus arteriosus, and it is followed by the development of widespread pulmonary vascular sclerosis. Because the vascular lesions vary in severity and distribution from case to case, there is a corresponding variation in the resistance of the pulmonary vascular bed. In an occasional case in which the vascular lesions are severe, there is a true pulmonary vascular block and cor pulmonale will develop. This would account for the case cited above in which there were found a 15 mm. right ventricle, cyanosis, clubbing, and right heart failure. Yet in most cases, because of the extensive pulmonary vascular reserve, the vascular sclerosis is of no clinical significance.

In contrast to the above group with interauricular septal defects and mitral disease, one of the 2 cases complicated by hypertensive heart disease deserves special comment. This was PBBH no. A-46-1, a 16-year-old girl with an interauricular septal defect of 1 cm. and a systemic blood pressure of 185/140 mm. Hg. The heart weighed 460 gm.; the right ventricle measured 6 mm., the left, 20 mm. The pulmonary artery was grossly normal and there were no significant microscopic vascular changes. The pulmonary arterial pressure was determined by

TABLE V

Interventricular Septal Defects

Autopsy	Age	Sex	Measurement of defect	Heart weight	Thickness of ventricle		Significant associated cardiac defects	Gross
					Right	Left		
	years		*cm.*	*gm.*	*mm.*	*mm.*		
BCH 1940–860	6 mo. fetus	M	0.4	4.5	—	—	None	Normal
CH A–45–129	8/12	M	0.4	38	3	9	None	Normal
CH A–34–182	1 7/12	M	0.8	97	7	10	None	Normal
CH A–38–136	3 4/12	F	0.5	120	6	12	Acute bacterial endocarditis	Normal
PBBH A–44–42	5	M	0.5	200	4	12	Acute bacterial endocarditis	Normal
MGH 6531	8	F	0.8 x 0.5	135	3	12	Acute bacterial endocarditis of tricuspid valve	Normal
CH A–40–62	8 9/12	M	0.4 x 0.4 0.8 x 1.0	206	4	14	Acute bacterial endocarditis of mitral, pulmonic, and tricuspid valves	Normal
BCH 1941–325	14	F	0.5	240	3	10	Acute bacterial endocarditis of tricuspid valve	Normal
BCH 1940–860	20	F	2	500	8–10	11–15	None	Normal
BCH 1941–74	34	M	1.6	590	6–8	15–18	Acute bacterial endocarditis of mitral and tricuspid valves	Normal
BCH 1934–657	72	M	0.5	490	9	20	None	Normal

* Intimal proliferation.
† Hyalin.
‡ Medial thickening.

means of the venous catheter and was within normal range. The patient died of glomerulonephritis and uremia.

To date, there is no evidence that significant pulmonary arterial hypertension develops in cases of interauricular septal defects. Dexter and his group [5] found a normal pulmonary arterial pressure in 3 of 8 patients studied by means of the venous catheter. In 4, elevated

Pulmonary vascular lesions													
Microscopic													
1 mm.			250–500 μ			100–250 μ			25–100 μ			Blood pressure	Signs and symptoms referable to cardiac lesion	Cause of death
I*	H†	M‡	I	H	M	I	H	M	I	H	M			
												mm. Hg		
.	.	.	.	.	.	.	.	.	.	.	.	—	—	Maternal death
.	.	.	.	.	.	.	.	.	.	.	.	Not given	Murmur; cyanosis with infection	Pneumonia
.	.	.	.	.	.	.	.	.	+	.	.	Not given	Murmur; cyanosis with infection	Congestive heart failure and pneumonia
.	.	.	.	.	.	.	.	.	.	.	.	95/20	Murmur	Septicemia; *Staphylococcus aureus*
.	.	.	.	.	.	.	.	.	.	.	.	105/25	None	Pneumonia and ulcerative endocarditis
.	.	.	.	.	.	.	.	.	.	+	.	Not given	Murmur	Pneumonia
.	.	.	.	.	.	.	.	.	.	.	.	120/70	Murmur	Septicemia; *Staphylococcus aureus*
.	.	.	.	.	.	+	.	.	+	++	.	100/0	Systolic murmur; dyspnea for 1 year	Septic infarction of lung
.	.	.	.	.	.	+++	.	.	+++	++	.	120/70	Dyspnea; intermittent cyanosis; murmur	Congestive heart failure
.	.	.	.	.	.	.	++	.	+	++	.	138/65	Not given	Pneumonia
.	.	.	+	.	.	+	++	.	++	+++	.	190/55	None	Uremia

pressures were noted but in each instance there were clinical manifestations of congestive heart failure. In one patient without evidence of failure, the pulmonary arterial pressure was moderately elevated (40/14 mm. Hg). In one of Dexter's patients there was a volume flow of 20 liters per minute through the pulmonary artery.[20] This was the greatest volume flow recorded in any patient with a left to right shunt.

In summary, then, the cases having isolated interauricular septal defects without complicating rheumatic valvular disease did not show pulmonary vascular changes greater than those found in the control groups. In contrast, those cases with coexisting interauricular septal defect and mitral stenosis had constant and definite atherosclerotic changes in the pulmonary vessels. Furthermore, these lesions were more severe and appeared at an earlier age than in the control group. From the evidence at hand at the present time, the only additional factor present in this second group of cases appears to be an increase in the left to right shunt and hence an increase in the volume flow through the pulmonary artery.

Interventricular Septal Defect

Eleven cases were found with significant unguarded interventricular septal defects. These ranged from 0.4 to 2 cm. in diameter, although only three were greater than 1 cm. in diameter. The patients ranged in age from a 6-months-old fetus to 72 years. Six had complicating bacterial endocarditis. The heart was increased in weight in 9 of the 11 cases. The right ventricle was increased in thickness in 4, while the left ventricle was increased in only 2 cases.

There was no dilatation or gross evidence of atherosclerosis of the pulmonary arteries in any case in this group. Ten did not have microscopic lesions greater than those found in the control group. One case (BCH no. A-40-860), a 20-year-old woman, had a 2 cm. interventricular septal defect, the largest in this series. The heart weighed 500 gm., the right ventricle measured 10 mm. in thickness, while the left ventricle was not thickened. This patient had no complicating endocarditis or valvular disease. There were 2 plus and 3 plus intimal proliferative and hyaline changes in the pulmonary vessels from 25 to 250 μ in diameter. No lesions were present in the larger branches. The media was not involved.

As yet, pulmonary catheterization studies with measurements of pulmonary flow and pulmonary arterial pressures have been carried out in only 3 cases having uncomplicated interventricular septal defects. In 2 the pulmonary arterial pressure was normal, with pulmonary volume flows of 7.1 to 7.9 liters per minute. In the third patient the pulmonary arterial pressure was elevated (100/49 mm. Hg), yet the volume flow through the pulmonary artery was only 8.6 liters per minute. There was no clinical evidence of congestive heart failure in this case. In one of the 2 cases having a normal pulmonary arterial pressure there was a calculated left to right shunt of 4.5 liters per minute.[20]

Experiments in animals in which intracardiac fistulae were produced are of interest. Holman and Beck [21] produced interventricular septal defects up to 3 mm. in dogs. The dogs responded first by an increase in the heart rate and later by an increase in the total mass of circulating blood with return of the heart rate to normal. Protocols of animals that were allowed to live as long as 6 months after operation included studies of the lungs. There was consistent hypertrophy of the right ventricle, yet there was no evidence of pulmonary atherosclerosis in the 10 dogs studied. More recently, Eppinger and Gross [22] have produced similar defects in dogs and limited the defects to 0.4 to 0.6 cm. A left to right shunt was found which ranged from 20 to 50 per cent of the left ventricular output. There was a corresponding increase in pulmonary blood flow. In these animals, the output of each ventricle was markedly increased and there was a uniform cardiac hypertrophy. No study of the pulmonary vasculature was made.

Interventricular septal defects seldom exceed 1 cm. in diameter, in contrast to interauricular septal defects which may measure up to 5 cm. The dynamics of pulmonary blood flow in Roger's disease resemble closely those encountered in patent ductus arteriosus because in both conditions the shunt occurs at systemic arterial pressure. Similarly, the protective factors enumerated above for patent ductus are present in patients having interventricular septal defects.

Combined Lesions Giving a Left to Right Shunt

Six cases were found in which there was a combination of lesions giving a left to right shunt. Three cases were included in which a patent ductus was associated with either an interauricular or an interventricular septal defect. In one of these cases (CH no. A-40-69), a child, 16 months of age, the ductus had an internal diameter of 5 mm., the interauricular defect measured 2 cm., and there was no mitral valvular disease. This patient had no gross or microscopic changes in the pulmonary vessels. By contrast, there were pulmonary changes in excess of the control group in each of the other 2 cases. In one of these there was a small ductus with a large interventricular defect, while in the second there was a large ductus and a large interauricular defect.

The combination of interventricular and interauricular septal defects occurred in 3 cases. In the first, that of a 10-months-old child, both defects were small and only 1 plus lesions in the smallest vessels were present. The second case had a small interauricular defect, an enormous interventricular defect, normal valves, and there were

TABLE VI
Combined Lesions

Autopsy	Age	Sex	Measurement of defect	Heart weight	Thickness of ventricle		Significant associated cardiac defects	Gross
					Right	Left		
	years		*cm.*	*gm.*	*mm.*	*mm.*		Interauricular
CH A-40-27	10/12	F	IASD,§ 0.5; IVSD,‖ 1.0	Not given	6	12	None	Atherosclerosis; pulmonary conus
MGH 11,516	22	M	IASD, 1.5; IVSD, 5.0	300	20	22	None	Normal
BCH 1934-324	39	F	IASD, 4.0; IVSD, 0.3	540	9	12	Mitral stenosis	Dilated 4.2 cm.
								Interauricular
CH A-45-42	1 3/12	F	PDA,¶ 0.3; IVSD 1.3 x 1.1	Not given	7	7	None	Normal
CH A-40-69	1 4/12	F	PDA, 0.5; IASD, 2.0 x 2.0	26	7	10	None	Normal
CH A-42-71	10	—	PDA, 2.0; IASD, 2.0	Not given	15	12	None	Normal

* Intimal proliferation.
† Hyalin.
‡ Medial thickening.
§ Interauricular septal defect.
‖ Interventricular septal defect.
¶ Patent ductus arteriosus.

marked pulmonary vascular changes. In the third case there was a large interauricular septal defect with associated mitral stenosis and an insignificant interventricular defect. The pulmonary artery was dilated, and here again vascular lesions were in excess of those found in the control group.

Acquired Lesions Producing a Left to Right Shunt

There was no opportunity to study patients who had an acquired left to right shunt. To date, several hundred patients have had a systemic vessel anastomosed to the pulmonary artery to overcome the disordered pulmonary hemodynamics occurring in pulmonary stenosis with or without a coexisting septal defect.[23-27] These patients comprise the most important group with acquired left to right shunt. It

Microscopic													Blood pressure	Signs and symptoms referable to cardiac lesion or ductus	Cause of death
1 mm.			250–500 μ			100–250 μ			25–100 μ						
I*	H†	M‡	I	H	M	I	H	M	I	H	M				
septal defect with interventricular septal defect													*mm. Hg*		
.	.	.	.	.	.	.	.	.	+	.	.		Not given	Systolic and diastolic murmur	Congestive heart failure and pneumonia
+	.	.	+++	+	.	++	+	.	+	+++	.		110/96	Clubbing; cyanosis for 1 year	Congestive heart failure and pneumonia
.	.	.	.	.	.	++	++	.	+++	++	.		—	Systolic and diastolic murmurs; dyspnea for 2 years	Congestive heart failure and pneumonia
septal defect or interventricular septal defect with patent ductus arteriosus															
.	.	.	.	.	.	++	+	.	+++	+	.		Not given	Systolic murmur; cyanosis with infection	Pneumonia
.	.	.	.	.	.	.	.	.	.	.	.		Not given	None	Pneumonia
.	.	.	+	.	.	++	+	.	+++	+	.		—	Basal systolic and diastolic murmur; effort cyanosis	Generalized peritonitis

was with this group in mind that this study was undertaken in an attempt to predict the long-standing effects of such a procedure on the pulmonary vascular tree.

While the life expectancy following successful operation undoubtedly may be improved, because of the remarkable cardiac reserve of these young patients, the question arises as to whether such an operation will accelerate the development of pulmonary atherosclerosis. This might result in gradual obliteration of the finer radicles of the pulmonary arterial tree and diminution in the volume of blood delivered to the pulmonary capillaries. The present series of cases would seem to be of value in answering this question since the altered dynamics of flow produced by these operations are comparable to those found with patent ductus arteriosus. Judging from the cases in this series, the

pulmonary vascular bed is able to handle a large increase in volume flow for considerable periods of time without the development of significant vascular changes. The fact that this increased volume of blood is delivered at systemic pressure into the pulmonary tree is of little importance since the numerous protective mechanisms indicated above are at work to avoid the development of significant peripheral resistance. Consequently, the systemic pressure is rapidly dissipated and significant elevation of the pulmonary arterial pressure does not occur. There appears to be individual variation in the vulnerability of pulmonary arteries to atherosclerosis. It may be that in the rare case particularly vulnerable to atherosclerosis, changes of such severity may develop that there will be a true vascular block proximal to the capillary bed. Such an occurrence would nullify the effects of the anastomosis.

Summary

The lungs from 67 patients having congenital cardiac anomalies in which there was a left to right shunt were studied to determine the effect of the altered hemodynamics on the pulmonary vascular bed. The lesions were graded according to the degree of intimal proliferative, intimal hyalin, and medial changes found.

Control groups of 10 cases for each of the first 7 decades of life were examined to determine the effects of ageing alone on the pulmonary vessels. The incidence of pulmonary atherosclerosis was found to be remarkably high in this group.

Twenty-five cases of patent ductus arteriosus with significant defects were studied. With one exception the changes in the pulmonary vascular system were no greater than changes in the control group in comparable ages. In all cases the changes present were atherosclerotic in type, and no medial lesions were found.

Twenty-five cases with interauricular septal defects of 0.8 cm. or more were selected. In uncomplicated cases the pulmonary vascular lesions were not greater than in the control group. In 9 cases complicated by rheumatic mitral disease, marked and constant atherosclerosis was found in excess of the control group.

Eleven cases having isolated interventricular septal defects were studied. Most of these had defects of less than 1 cm., and the pulmonary vascular lesions were not greater than those of comparable ages in the control group. In one patient with a 2 cm. defect marked atherosclerosis of the pulmonary artery was observed.

Six cases having a combination of lesions giving a left to right shunt were studied. The degree of pulmonary atherosclerotic change in each case was proportionate to the age and to the magnitude of the shunt.

The common factor in the production of pulmonary vascular lesions in the occasional cases in each of the above groups appeared to be a marked increase in the pulmonary blood flow.

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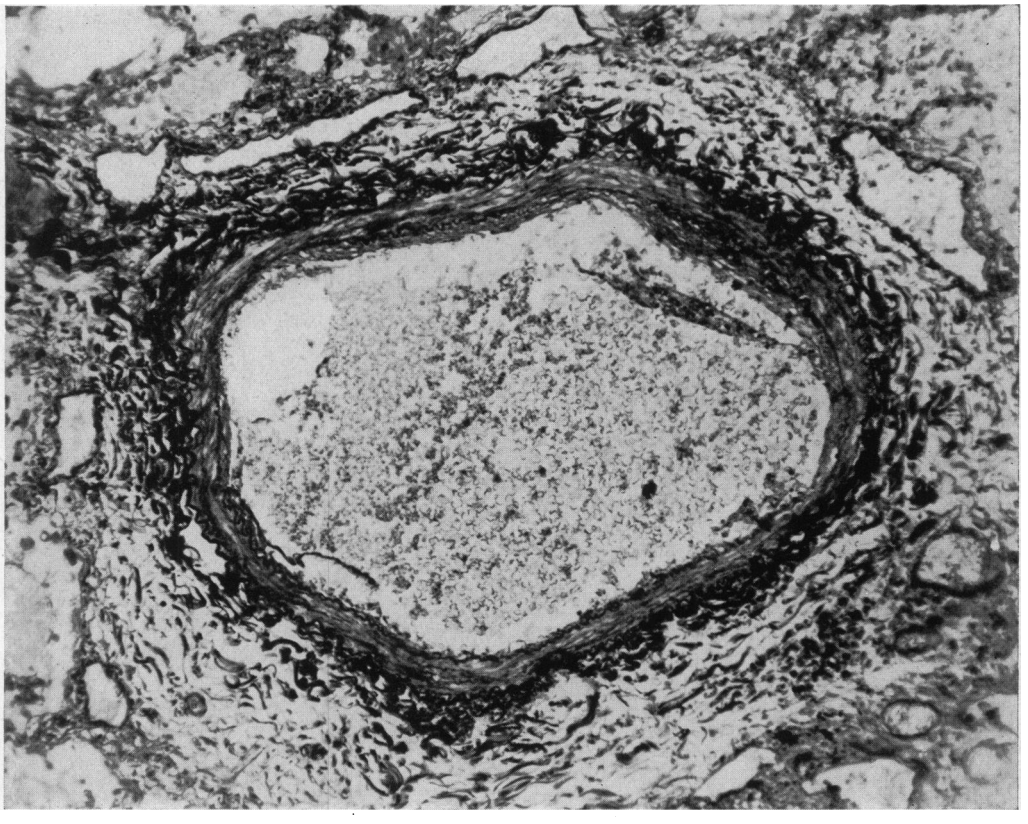
DESCRIPTION OF PLATES

PLATE 120

FIG. 1. Pulmonary vessel from the group measuring 100 to 250 μ in external diameter, showing 1 plus intimal proliferation. Van Gieson-Weigert's elastic tissue stain. × 135.

FIG. 2. Pulmonary vessel from the group measuring 100 to 250 μ in external diameter, showing 3 plus intimal proliferation. Van Gieson-Weigert's elastic tissue stain. × 180.

1



2

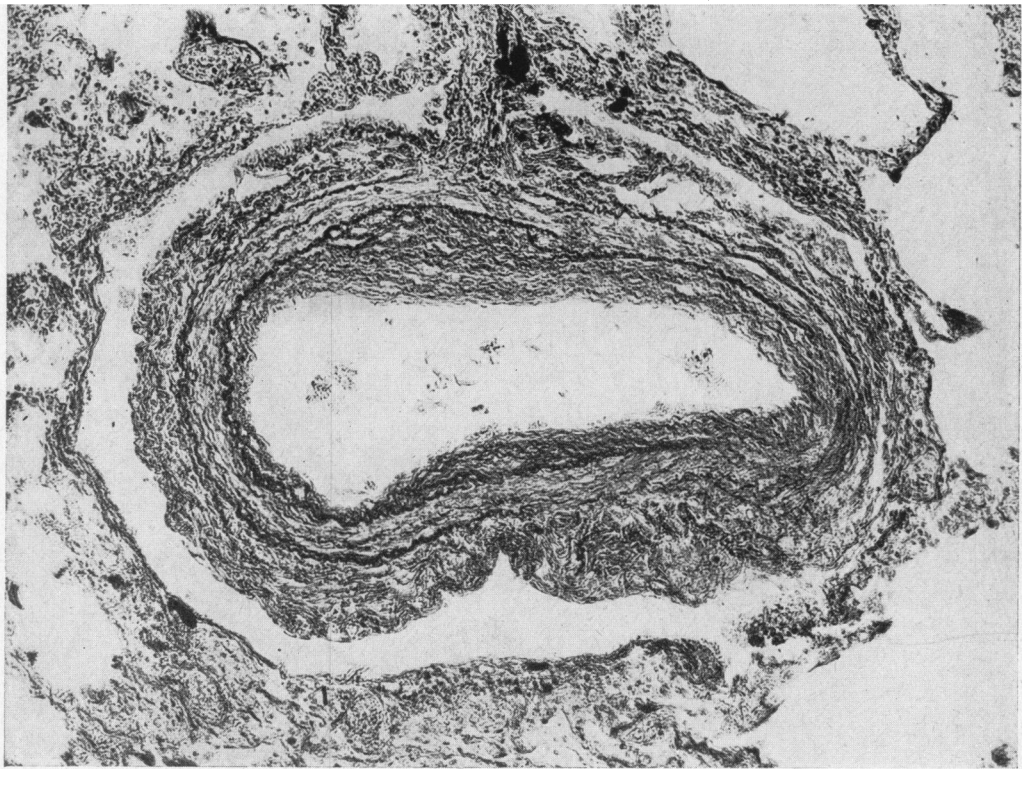
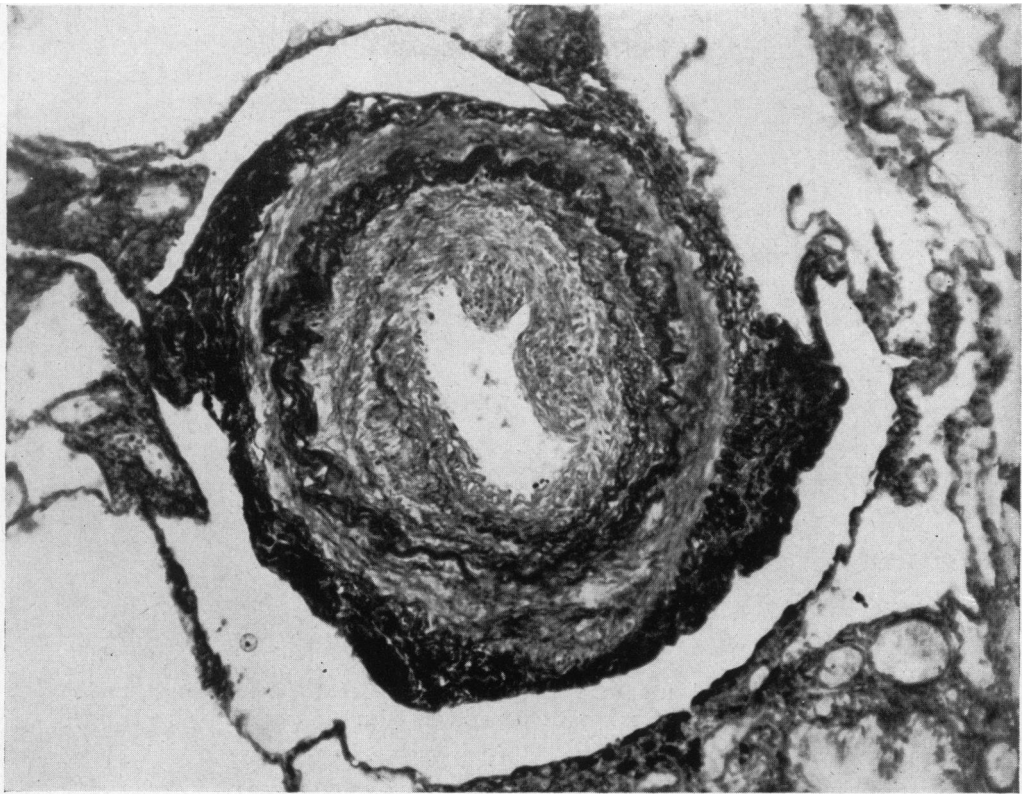


PLATE 121

FIG. 3. Pulmonary vessel from the group measuring 100 to 250 μ in external diameter, showing 4 plus intimal proliferation. Van Gieson-Weigert's elastic tissue stain. $\times$ 225.

FIG. 4. Pulmonary vessel from the group measuring 100 to 250 μ in external diameter, showing 1 plus hyaline deposition. Van Gieson-Weigert's elastic tissue stain. $\times$ 715.

3



4

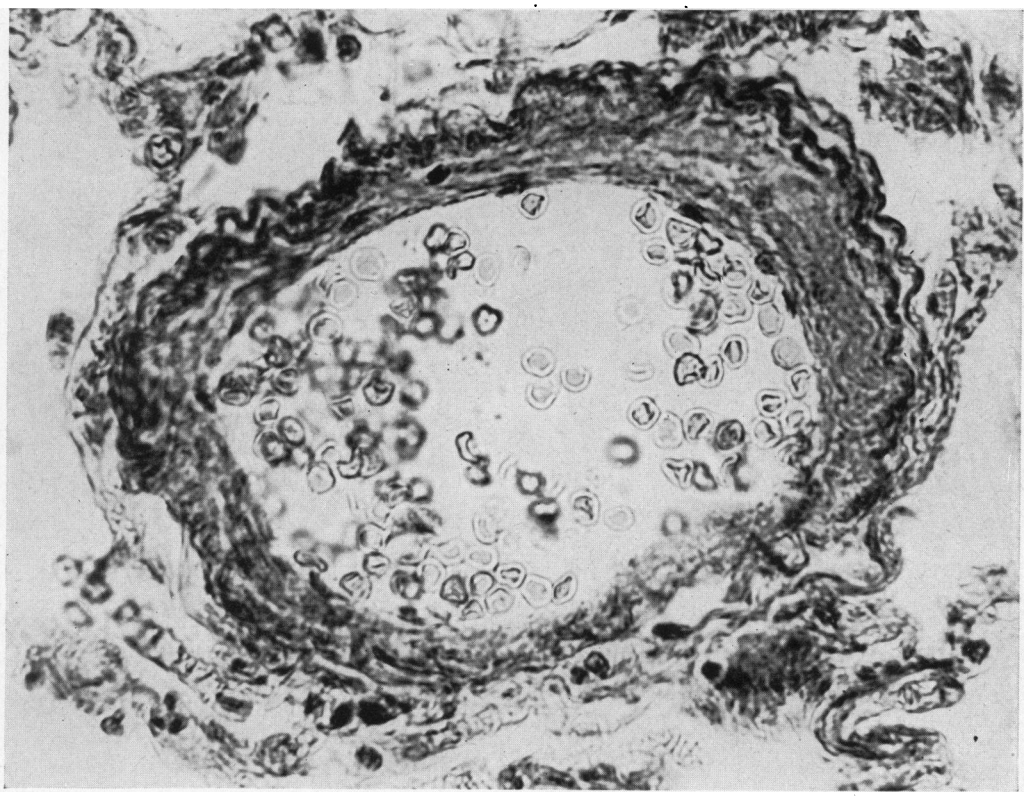
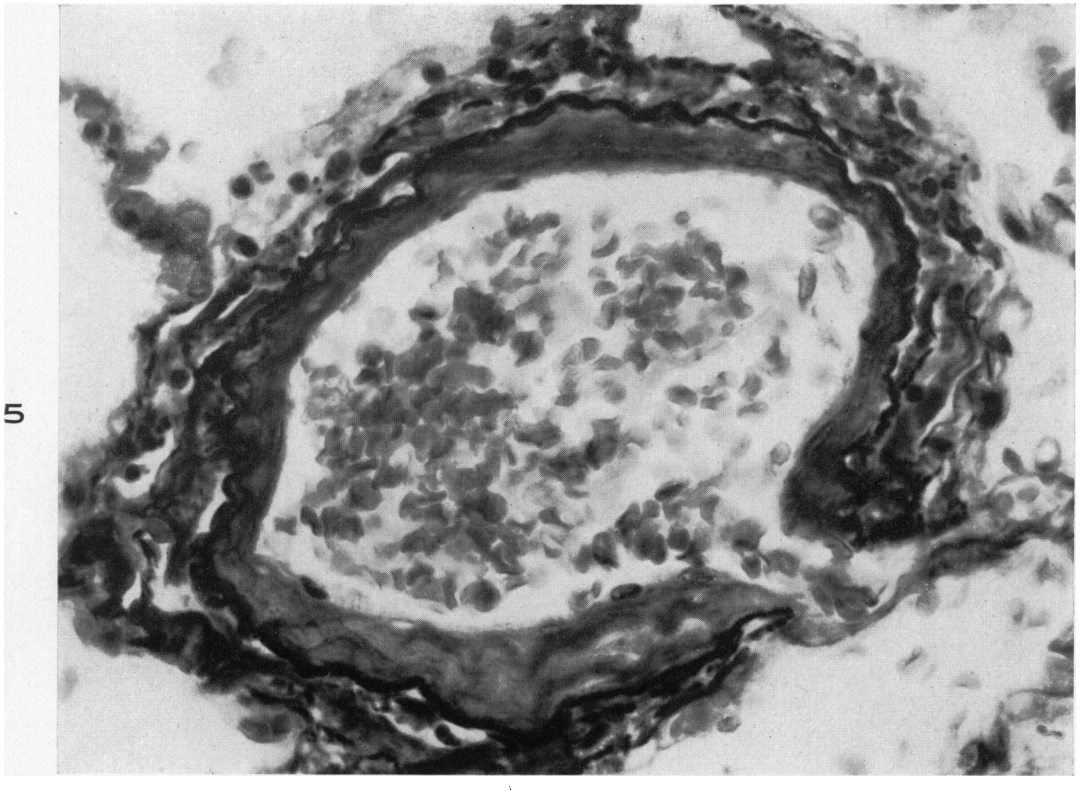


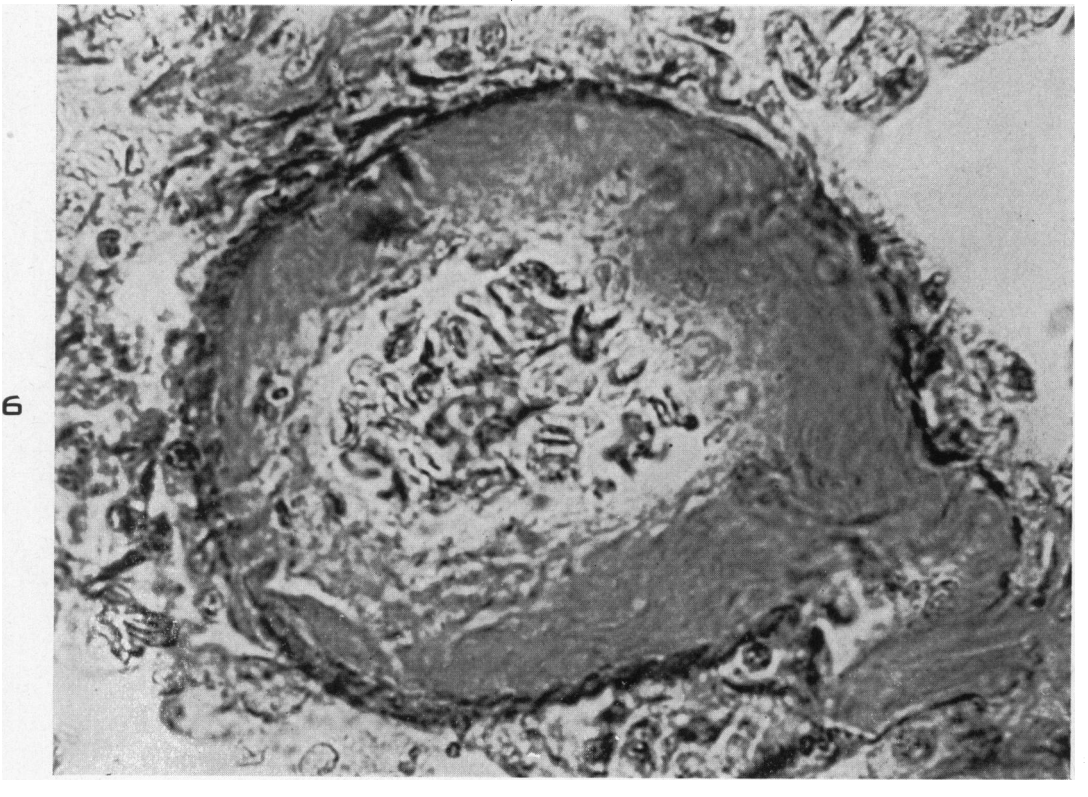
PLATE 122

FIG. 5. Pulmonary vessel from the group measuring 100 to 250 μ in external diameter, showing 3 plus hyaline deposition. Van Gieson-Weigert's elastic tissue stain. $\times$ 580.

FIG. 6. Pulmonary vessel from the group measuring 100 to 250 μ in external diameter, showing 4 plus hyaline deposition. Van Gieson-Weigert's elastic tissue stain. $\times$ 1075.



5



6