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PATENT DUCTUS ARTERIOSUS WITH PULMONARY HYPERTENSION

A REVIEW OF NINE CASES, INCLUDING ONE WITH REVERSAL OF BLOOD FLOW THROUGH THE DUCTUS

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It is now well established that the treatment of the typical case of patent ductus arteriosus with classical physical signs is ligation of the vessel with, or without, its division. In recent years, chiefly as a result of investigation of cases of congenital heart disease by means of cardiac catheterization, it has become evident that there are a number of cases of patent ductus arteriosus associated with severe pulmonary hypertension in which the classical signs of the anomaly are not present. Numerous articles have appeared on the subject in the past five years, and in most of these reports the patients were adults or adolescents in whom the disability had been present for a considerable period of time (Johnson, Wermer, Kuschner, and Cournand, 1950; Campbell and Hudson, 1951; Myers, Scannell, Wyman, Dimond, and Hurst, 1951; Adams, 1952; Adams, Diehl, Jorgens, and Veasy, 1952; Bothwell, Van Lingen, Whidborne, Kaye, McGregor, and Elliott, 1952; Lurie, Gray, and Whittemore, 1952; Storstein, Humerfelt, Müller, and Rasmussen, 1952; Dammann and Sell, 1952; Burchell, Swan, and Wood, 1953; Holman, Gerbode, and Purdy, 1953; Hultgren, Selzer, Purdy, Holman, and Gerbode, 1953; Kattus and Muller, 1953; Cosh, 1953; Smith, 1954; Swan, Zapata-Diaz, Burchell, and Wood, 1954; Harris, 1955; Whitaker, Heath, and Brown, 1955).

The present review is of nine children aged from 1 to 6 years who were diagnosed clinically as having patent ductus arteriosus with pulmonary hypertension, this being subsequently demonstrated in all but one case (Brenda G.) by cardiac catheterization or by manometry at thoracotomy. In addition, six of these children have, after varying intervals following ligation of the ductus, been re-catheterized and have been found to have pulmonary arterial pressures and pulmonary arteriolar vascular resistances within normal limits. The survey includes one child who died one month after operation in whom there was fixed reversal of flow through the ductus.

The purpose of the paper is to draw attention to the clinical aspects of the syndrome in early childhood and to stress the beneficial results of occluding the ductus in those cases without fixed reversal of flow as soon as the diagnosis has been confirmed, and the return of the pulmonary arterial pressure to a normal level after operation. This would appear of special importance in view of the probability that with increased duration of a high pulmonary pressure and pulmonary arteriolar resistance irreversible changes may eventually occur which maintain the pulmonary hypertension in spite of ligation.

CLINICAL FEATURES AND INVESTIGATIONS

The outstanding features in the histories of these children are the failure to thrive which all exhibited, together with a marked susceptibility to respiratory illnesses, in some cases of so severe a nature as to precipitate cardiac failure. Four of the children were found at some time to have a classical ductus murmur, though this was inconstant.

All the children were markedly below their expected weight and were of frail or puny physique. All had some chest deformity, in most a considerable asymmetrical bulging of the chest wall in the left parasternal region being a prominent feature. The pulse was collapsing in five (Cases 1, 3, 5, 7, and 9), and was associated with a high pulse pressure. There was clinical evidence of cardiac enlargement in all cases, with displacement of the apex beat laterally, and in all but one also downwards. In four the apex beat was in the anterior axillary line, in the fifth left interspace in three, and in the sixth in one. In the five remaining cases the apex beat was external to the mid-clavicular line, in the fourth left interspace in one, in the fifth in three, and in the sixth

TABLE I

CLINICAL FEATURES BEFORE ADMISSION

Case No., Age (Years), Date of Admission	Pregnancy History	Delivery	Birth Weight (lb. oz.)	Progress until Admission to Westminster Hospital
(1) Elaine S. .. 4 1 12 21.8.1951	Mother had injections because of previous miscarriages	Normal at full term	7 12	Cardiac murmur audible at birth. Failure to thrive particularly during the first year. Repeated respiratory infections. Typical ductus murmur heard at 1 year
(2) Robert R. .. 4 7/12 29.9.1951	Normal	,, ,,	7 8	Failure to thrive with recurrent bronchitis and broncho-pneumonia. Systolic murmur and thrill diagnosed as maladie de Roger at 10 months. More breathless on exertion than average child
(3) Janis C. .. 6 9 12 31.7.1952	,,	,, ,,	6 12	Slow weight gain from early infancy. Congenital heart disease first diagnosed at 4 months. Bronchopneumonia at 18 months. Thought then to have an A.S.D. Had tonsils and adenoids removed at 5 years. Following operation a typical ductus murmur was heard
(4) Brenda G. .. 1 1/12 9.1.1953	,,	,, ,,	6 13	Cardiac murmur first heard shortly after birth. In heart failure at 1 week and was treated in oxygen for subsequent 7 weeks. Very slow weight gain since with easy fatigability and breathlessness on slight exertion. No cyanosis since first week of life
(5) Jean H. .. 1 4.4.1953	,,	,, ,,	5 0	Failure to thrive from birth. Congenital heart disease diagnosed at 3 months. Patent ductus diagnosed at 6 months. Recurrent respiratory infections requiring hospital admissions
(6) June H. .. 2 24.6.1953	,,	,, ,,	7 0	Failure to thrive with frequent attacks of bronchitis and pneumonia since early infancy. Cardiac murmurs first heard at 18 months when in hospital with pneumonia. Breathless on slight exertion with cyanosis on coughing. Toes constantly cyanosed. (A sister 4 years older had been in Westminster Hospital at 18 months with heart failure due to auricular flutter)
(7) Michael D. .. 2 1 12 3.1.1954	,,	Normal Premature	4 15	Very slow weight gain. Congenital heart disease diagnosed at 4 months. Has tended to become breathless on moderate exertion with undue fatigability and fretfulness
(8) Brenda S. .. 4 22.7.1954	,,	Normal at full term	8 0	Slow weight gain with recurrent respiratory illnesses since 6 months of age. Admitted to hospital then with pneumonia and diagnosed as patent ductus with a superimposed endarteritis. Subsequently has had further attacks of pneumonia and is said to have recurrent cyanotic episodes and to tire more easily than she should
(9) Linda C. .. 1 11/12 18.11.1954	German measles in second month	,, ,,	6 12	Apart from a slow weight gain progress said to have been normal. Heart murmur first heard at 3 months

in one. The apical impulse was definitely of left ventricular type in four instances. In the others it was tapping or diffuse.

With regard to the heart sounds, in most the second sound in the pulmonary area was accentuated and normally split. An apical presystolic triple rhythm was observed in two of the children and marked accentuation of the first sound at the apex in one other. Murmurs were present in all. A loud holosystolic bruit audible over the whole praecordium but maximal in the pulmonary area, usually with an accompanying thrill in this region, was the commonest finding. In four there was also a diastolic murmur in or near the pulmonary area, but this was inconstant in three. In two children this was, with the systolic bruit, of a characteristic machinery nature. Systolic and diastolic murmurs also occurred in the mitral area in two cases, and a soft, early diastolic murmur in a third.

With electrocardiography signs of right ventricular hypertrophy were found in three children and of left ventricular hypertrophy in two. The remainder had electrocardiographs within normal limits.

Chest radiographs and screening showed in all instances well-marked pulmonary plethora with increased pulsation of the smaller vessels on screening. The main pulmonary arteries were dilated and in most cases the right ventricle was enlarged. In six the left ventricle was also considerably enlarged. In four cases left auricular enlargement was remarked.

Gas analysis was performed on a Van Slyke apparatus in six of the patients and on a Brinkmann haemoreflector in the remaining three (in one case samples were analysed by both methods). Pressures were recorded on a saline manometer in the first two and on a Sanborn manometer in the

others. Mean pressures were recorded directly and all were corrected with reference to the sternal angle.

With the exception of Case 4, in which the pulmonary artery was not entered, and Case 6, in which there was a reversal of blood flow, all showed a significant rise in oxygen saturation on passing from the right ventricle to the pulmonary artery. The aorta was entered in four instances. In Case 3 there was evidence of the coexistence of a ventricular septal defect, and this was confirmed at subsequent re-catheterization about two and a half years after ductus ligation.

In Case 4 the catheter findings, although incomplete, were interpreted as excluding the presence of a septal defect or anomalous pulmonary venous drainage. The high pressure in the right ventricle, associated with the radiographic evidence of pulmonary plethora, enlargement of the pulmonary artery and pulsation of pulmonary vessels, was considered to be strongly in favour of the presence of a patent ductus arteriosus with pulmonary hypertension.

In Case 6 at thoracotomy, and in the other seven, the mean pressure in the pulmonary artery was considerably elevated. Peripheral pulmonary

TABLE II

CLINICAL FINDINGS ON ADMISSION TO WESTMINSTER HOSPITAL

Case	Age (Years)	Weight (lb.), Height (in.)	Expected Weight (lb.) and Height (in.)	Physique	Cardiovascular and Respiratory Signs
(1) Elaine S.	4 1 12	26¾ 35½	35 40	Small build. Prominent sternum with bilateral Harrison's sulci. Left parasternal bulge	A.B. 5th L.I.S. in A.A.L. Forceful impulse. Systolic thrill just internal to apex. Presystolic triple rhythm. Rough S.M. with rumbling mid-D.M. at apex. To-and-fro murmur under L. clavicle, the diastolic element inconstant and short. Pulse collapsing. Capillary pulsation in nail beds. B.P. 110 50 mm. Hg. No clubbing or cyanosis
(2) Robert R.	4 7 12	32½ 40	40 42	Frail build. Marked precordial bulge with Harrison's sulci, right more than left	A.B. 6th L.I.S. in A.A.L. Forceful L.V. type of impulse. Systolic thrill in L. parasternal region. Heart sounds I and II heard normally in all areas. Long harsh S.M. over whole praecordium, max. in 2nd and 3rd L. parasternal spaces. Low-pitched D.M. below L. clavicle and in 2nd and 3rd interspaces. Pulse of good volume. B.P. 130/80 mm. Hg. No cyanosis or clubbing
(3) Janis C.	6 9 12	34 44	46½ 47	Very thin. Precordial bulge with prominent sternum	A.B. 5th L.I.S. just outside M.C.L. Thrusting apical impulse. Diastolic thrill at apex. First heart sound accentuated at apex. Second sound split in pulmonary area. Soft systolic and low-pitched mid-diastolic murmurs at apex; soft D.M. midway between pulmonary area and mid-clavicle. Pulse collapsing. B.P. 110/45 mm. Hg. No cyanosis or clubbing
(4) Brenda G.	1 1 12	14¼ 28	20 28	Small child. High arched palate. Barrel chest with Harrison's sulci	A.B. 6th L.I.S. ½ in. outside mid-clavicular line. Systolic thrill palpable at pulmonary area. Apical presystolic rhythm. P. II normally split. Systolic and diastolic murmurs at pulmonary area. Pulse of good volume. B.P. 100/80 mm. Hg. No cyanosis or clubbing
(5) Jean H.	1	13 26	20 28	Puny infant. High arched palate. Precordial bulge	A.B. 5th L.I.S. 2½ in. from midline. Tapping apical impulse. Lifting outflow tract and pulsation in 2nd L. interspace with systolic thrill in same area. P. II split and accentuated. S.M. with late accentuation in the 2nd L.I.S. with an inconstant, short diastolic murmur—these together of machinery type. Pulse collapsing. B.P. 105/50 mm. Hg. No cyanosis or clubbing
(6) June H.	2	16 29½	26½ 33	Small, puny child. Precordial bulge	Marked clubbing with slight cyanosis of toes. Slight clubbing of fingers. A.B. 4th L.I.S. just external to M.C.L. Apical impulse tapping. Systolic thrill at apex. Palpable pulmonary arterial pulsation. Loud P. II. Harsh S.M. throughout praecordium, max. in pulmonary area. B.P. 100/70 mm. Hg. Rhonchi throughout lung fields
(7) Michael D.	2 1 12	17¾ 30	29 34	Small child. Prominent sternum with precordial bulge. Lower intercostal recession	A.B. 5th L.I.S. just external M.C.L. Diffuse apical impulse. Systolic thrill at base with very loud S.M. conducted towards apex. P. II markedly accentuated. Pulse collapsing. B.P. 100/50 mm. Hg. No cyanosis or clubbing
(8) Brenda S.	4	29½ 39	35 40	Small child. Prominent sternum with indrawing of lower intercostal spaces. High arched palate. Long fingers and toes	Suggestion of cyanosis of finger-tips. A.B. in 5th L.I.S. in A.A.L. Forceful apical impulse. Marked R.V. heave under xiphisternum. Systolic thrill in L. parasternal region. P. II loud and widely split. Loud S.M. throughout praecordium, max. in pulmonary area. Soft early D.M. in mitral area. Pulse of good volume. B.P. 120/70 mm. Hg. No clubbing
(9) Linda C.	1 11 12	21¾ 33	26 33	Small child	A.B. in 5th L.I.S. in A.A.L. Apical impulse tapping. P. II loud. Loud S.M. over whole praecordium, max. in pulmonary area. Pulse very full volume. B.P. 105/50 mm. Hg. No cyanosis or clubbing

TABLE III

ELECTROCARDIOGRAPHIC AND RADIOLOGICAL FEATURES

Case	E.C.G.	Radiograph
(1) Elaine S.	R.V. preponderance (Phonocardiography: long S.M. and short D.M. in 2nd L.I.S.)	Heart appears displaced to the left. Well-marked pulmonary vascular shadows which pulsate on screening. Pulmonary conus enlarged and enlargement of both left and right ventricles Tomography, a rounded lesion in the right middle lobe anteriorly, probably tuberculous Angiocardiography, inconclusive
(2) Robert R.	Very tall V7R	Both ventricles appear to be enlarged. The main branches of the pulmonary vessels are large
(3) Janis C.	No axis deviation	Enlargement of right and left ventricles; pulmonary plethora; pulmonary vessels pulsate peripherally
(4) Brenda G.	Normal	Enlargement of the heart, especially right ventricle, left auricle, and pulmonary artery. Pulmonary plethora with pulsation of the middle thirds of the pulmonary vessels
(5) Jean H.	R.V. preponderance	Enlargement of heart mainly of left ventricle but also of left auricle. There is dilatation of the main pulmonary artery and pulmonary plethora with good pulsation of the vessels
(6) June H.	,, ,,	Large pulmonary artery with generalized enlargement of heart. Lung fields congested
(7) Michael D.	Normal	Cardiac enlargement mainly left ventricular. There is enlargement of the left auricle. Pulmonary plethora with increased pulsation in the pulmonary vessels
(8) Brenda S.	,,	Considerable enlargement of the right ventricle and some enlargement of the left auricle. Small aortic knuckle. Well-marked pulmonary plethora
(9) Linda C.	L.V. hypertrophy in a vertical heart	Enlargement of heart involving both ventricles. Pulmonary plethora. The appearances are those of a left to right shunt. There is an abnormal vein visible on the right side

vascular resistances (in dynes/sec./cm.$^{-5}$) were raised and were as follows: (1) 1,430, (2) 1,304, (3) 411, (5) 1,163, (6) 1,462, (7) 768, (8) 490, and (9) 2,647.

TREATMENT

All the children were subjected to thoracotomy soon after the confirmation of the diagnosis by catheterization. Ligation of the patent ductus was performed in all of them, and in Cases 7 and 8 the vessel was also divided. The findings at operation and the post-operative courses are shown in Table V.

With the exception of Case 6 all the children made rapid post-operative recoveries and gave little or no cause for concern during this period. It was

TABLE IV

FINDINGS AT CARDIAC CATHETERIZATION

Case, Date	Position of Catheter	Mean Pressure (mm. Hg)	Oxygen Saturation (%)	Oxygen (Vol. %)
(1) Elaine S. 25.9.1951	I.V.C.		64	9·9
	S.V.C.		65	10·0
	R.A.	7·5	71	11·0
	R.V.	42·0	70	10·9
	M.P.A.	71·0	86	13·3
	R.P.A.	66·0	83	12·7
	Fem. art.		95	14·6
	Capacity		100	15·4
	Oxygen consumption 61·5 ml./minute			
	Systemic blood flow 1·5 litres/minute			
	P.D.A. shunt 2·33 litres/minute			
	Peripheral pulmonary vascular resistance 1,430 dynes/sec./cm.$^{-5}$			
(2) Robert R. 1.10.1951	I.V.C.		69	11·1
	S.V.C.		66	10·6
	R.A.	1·0	70	11·3
	R.V.	51·0	75	12·1
	M.P.A.	70 0	89	14·4
	R.P.A.	71·0	72	11·6
	Aorta	78·7	96	15·5
	Capacity		100	16·1
	Oxygen consumption 126 ml./minute			
	Systemic blood flow 2·85 litres/minute			
	P.D.A. shunt 1·5 litres/minute			
	Peripheral pulmonary vascular resistance 1,304 dynes/sec./cm.$^{-5}$			
(3) Janis C. 5.8.1952	S.V.C.		57	9·8
	R.A.	0	49	8·4
	R.V.	30·0	64	11·0
	L.P.A.	67·0	69	11·9
	R.P.A.		71	12·2
	Aorta	81·0	77	13·3
	Capacity		100	17·2
	Oxygen consumption 182 ml./minute			
	Systemic blood flow 6·5 litres/minute			
	P.D.A. shunt 6·5 litres/minute			
	Peripheral pulmonary vascular resistance 411 dynes/sec./cm.$^{-5}$			
(4) Brenda G. 27.1.1953	S.V.C.		65	9·0
	R.A.		62	8·5
	R.V. (low)		64	8·8
	R.V. (high)	40·0	64	8·8
	Capacity		100	13·8
	Oxygen consumption 82 ml./minute			
	Systemic blood flow 1·8 litres/minute (assuming arterial blood 95% saturated)			
(5) Jean H. 7.4.1953	I.V.C.		56	8·8
	R.V.	44		
	P.A.	60	71	11·1
	Aorta	79	81	12·6
	Capacity		100	15·6
	Oxygen consumption 66 ml./minute			
	Systemic blood flow 1·74 litres/minute			
	P.D.A. shunt 2·38 litres/minute			
	Peripheral pulmonary vascular resistance 1,163 dynes/sec./cm.$^{-5}$			
(6) June H. 20.8.1953	I.V.C.		45	10·4
	R.A.		51	11·7
	Low R.V.		52	12·0
	High R.V.	39	57	13·1
	P.A.	36	57	13·1
	Aorta	24	65	15·0
	Capacity		100	23·0
	Oxygen consumption 82 ml./minute			
	Systemic blood flow 2·5 litres/minute			
	P.D.A. shunt (from P.A. to aorta) 1·8 litres/minute			
	Peripheral pulmonary vascular resistance 1,462 dynes/sec./cm.$^{-5}$			
	(The pressure tracings showed excessive damping. Simultaneous brachial and femoral arterial samples taken one week before catheterization were 63% and 38% saturated respectively. In estimating the peripheral pulmonary vascular resistance the mean pulmonary arterial pressure measured at thoracotomy before ligation of the ductus has been used)			

TABLE IV—*continued*

Case, Date	Position of Catheter	Mean Pressure (mm. Hg)	Oxygen Saturation (%)	Oxygen (Vol. %)
(7) Michael D. 7.1.1954	I.V.C.		72	9 4
	R.A.	5	62	8·1
	R.V.	43	60	7·8
	P.A.	68	90	11·8
	P.C.V.		99	13 0
	Capacity		100	13·1
	Oxygen consumption 85 ml./minute			
	Systemic blood flow 1·7 litres/minute			
	P.D.A. shunt 5·4 litres/minute			
	Peripheral pulmonary vascular resistance 768 dynes/sec./cm.$^{-5}$			
(8) Brenda S. 27.7.1954	I.V.C.		75	11·5
	S.V.C.		69	10 6
	R.A.	4	67	10 4
	Low R.V.	45	66	10·2
	High R.V.		69	10·6
	P.A.	78	87	13·5
	Capacity		100	15·4
	Oxygen consumption 140 ml./minute			
	Assuming peripheral arterial blood 95% saturated			
	Systemic blood flow 3·28 litres/minute			
	P.D.A. shunt 8·69 litres/minute			
	Peripheral pulmonary vascular resistance 490 dynes/sec./cm.$^{-5}$			
(9) Linda C. 30.11.1954	I.V.C.		64	11·8
	R.A.	0	55	10·1
	R.V.	40	56	10·3
	P.A.	63	79	14·5
	Femoral artery		87	16·0
	Capacity		100	18·4
	Oxygen consumption 55 ml./minute			
	Systemic blood flow 0·94 litres/minute			
	P.D.A. shunt 0·96 litres/minute			
	Peripheral pulmonary vascular resistance 2,647 dynes/sec./cm.$^{-5}$			

early noticeable in many of them that they had more inclination to play and exert themselves than they had had previously. Fretfulness and irritability, features observed in most of these children but particularly marked in Cases 2 and 7, were replaced by a more contented and happy disposition.

The operations on Cases 1, 2, 3, and 5 were performed by Sir Clement Price Thomas and the remainder by Mr. C. E. Drew.

Follow-up of Six Cases

Cases 1, 3, 5, 7, 8, and 9 were readmitted to the hospital at varying intervals following operation for detailed assessment of their clinical progress and re-catheterization.

Without exception the parents of these six children were impressed with the improvement which they had witnessed in the general health, capacity for exercise, and demeanour of the children after operation. They had all increased in height and weight and had been free from respiratory illnesses which had previously been a marked feature in most of their histories. With the exception of Case 3, who has a ventricular septal defect, and Case 9, who was reviewed only five months after thoracotomy, there was no clinical evidence of cardiac enlargement. Murmurs were inconspicuous or absent in all except Case 3, and radiographic and electrocardiographic findings were normal or very much improved.

These re-catheterization studies are of great interest, as they demonstrate a return to normal of pulmonary arterial pressures and peripheral pulmonary vascular resistances in all six cases. The intervals ensuing between ductus ligation and re-catheterization varied between three years five months and five months. From the histories of rapid improvement in health and exercise tolerance after operation, together with the return to normal pressures in nine and five months in the last two cases, it is fair to assume that vascular readjustment is quickly attained. (In these cases gas analysis was performed on a Brinkmann haemoreflector and pressures were recorded on a Sanborn or Minirack manometer.)

Discussion

The genesis of pulmonary hypertension in some cases of patent ductus arteriosus is not yet known. It is also still obscure what factors at birth initiate closure of the ductus arteriosus, but it is generally believed that an alteration in the pressure relationship between the pulmonary artery and aorta and a desaturation of blood entering the ductus from the pulmonary artery are necessary excitants. Some have put forward the view that the pulmonary hypertension is due to a persistence of the foetal type of small pulmonary artery with a muscular media and the maintenance of a high resistance (Civin and Edwards, 1950; Campbell and Hudson, 1951). This theory would explain the patency of the ductus in these patients and would be in keeping with the very early onset of symptoms. But it cannot be so invoked in the ordinary case of patent ductus in which pulmonary vascular changes are not observed (Welch and Kinney, 1948). That the pulmonary hypertension is in some way related to patency of the ductus would appear to be proved by our results, and these suggest that the hypertension is secondary to a failure of ductus closure with a consequently increased pulmonary blood flow. The mechanism whereby this may be produced has recently been discussed by Harris (1955). It has been thought that prolonged anoxia at birth may be a factor in certain cases in perpetuating a patent ductus arteriosus, but in the children under review there is no history of difficulty in initiating respiration or of gross respiratory embarrassment or cyanosis in the first few hours of life.

TABLE V

FINDINGS AT OPERATION AND POST-OPERATIVE COURSE

Case, Date	Findings at Operation	Post-operative Course
(1) Elaine S. 3.10.1951	A mass of enlarged glands overlying the left hilum dissected away, displaying a large patent ductus which was ligated. The glands were tuberculous	Apart from laryngeal stridor immediately after operation her recovery was uninterrupted. Post-operative B.P. 105/80 mm. Hg. No thrills palpable. Soft S.M. internal to apex
(2) Robert R. 10.10.1951	Ligation of patent ductus	Rapid recovery. B.P. 100/80 mm. Hg. High-pitched S.M. internal to apex
(3) Janis C. 22.10.1952	Ligation of patent ductus. Biopsy specimen taken from lingula showed: "The appearances are those of chronic pulmonary hypertension. Both the muscular arteries and the arterioles show prominent thickening, the latter forming club-shaped projections into irregular air-spaces created as a result of emphysema, apparently secondary (in some way) to the hypertension. The capillaries generally are congested and foci of macrophages containing altered blood-pigments are observed. "The elastic tissue in the muscular arteries is increased and the club-shaped projections have a substantial elastic content, though it is not always clear whether this is hypertrophy due to arteriolosclerosis, or retraction of ruptured alveolar walls due not merely to congestion of capillaries but to increased reticulin and elastic tissue." (Dr. A. D. Morgan) See Figs. 1 and 2	Uneventful recovery. Rough S.M. over whole praecordium maximal in 3rd and 4th left parasternal spaces
(4) Brenda G. 3.2.1953	A patent ductus 0·95 cm. in diameter was ligated. The diameter of the P.A. was 2·2 cm., and of the aorta 1·1 cm. above and 1·6 cm. below the insertion of the ductus	Satisfactory until 18th day when she developed consolidation of the lingula. This responded rapidly to treatment. Loud S.M. without thrill in pulmonary area
(5) Jean H. 13.5.1953	Ductus ligated. The vessel was 7 mm. in diameter and ½ in. in length	Uneventful recovery. No murmurs audible on discharge
(6) June H. 25.9.1953	The lungs were congested and scattered over pleurae were numerous petechiae. A large mass of soft hilar glands surrounded the left pulmonary artery. These were dissected away and the heart beat became more forceful. The blood pressure, before unrecordable by sphygmomanometer, rose to 100/80 mm. Hg. A large ductus measuring 0·75 cm. in diameter was defined. The aorta at the level of the ductus was 0·94 cm. in diameter Electromanometry before and after ligation of the ductus showed: Before (mm. Hg) / After (mm. Hg) Aorta .. .. .. 95/70 Mean 82 / 82/70 Mean 76 Main P.A. .. .. 95/67 ,, 79 / 86/64 ,, 73 R.P.A. .. .. .. 98/68 ,, 83 (All pressures corrected to level of R.A.)	Her condition was good for five days when she became restless, cyanosed, and developed marked respiratory distress. There were numerous crepitations at both bases and liver enlargement. A diagnosis of congestive cardiac failure was made and she improved for some days with "digoxin." Subsequently she deteriorated, with increasing cyanosis, left pulmonary collapse, pulmonary oedema, hepatic enlargement, and died on the 29th post-operative day Post-mortem examination showed: (1) Collapse of left lung with chronic pulmonary congestion. Histology of the lungs showed a severe degree of pulmonary arteriosclerosis affecting the smaller vessels (Fig. 3) and evidence of prolonged passive congestion. This had resulted in intra-alveolar haemorrhages and larger numbers of alveoli and bronchioles were filled with macrophages containing ingested red cells and haemosiderin. The mediastinal lymph-nodes were severely congested. (2) Generalized cardiac enlargement with gross right ventricular hypertrophy and dilatation of the right auricle. The tricuspid and pulmonary valves were normal. The trunk of the pulmonary artery was grossly hypertrophied and dilated and its wall was twice as thick as that of the rather attenuated aorta. The previously patent ductus was ligated and the operation site was healthy. The left auricle was within normal limits. The mitral valve was a small slit and clearly hypoplastic, being no more than 1 cm. in diameter. The left ventricle had a small cavity, but was extremely hypertrophied with a wall nearly an inch thick. The endocardial lining of the left chambers was thick and strikingly pale and histologically showed fibro-elastosis. The aortic valve was stenosed. (3) The liver and kidneys showed changes of passive congestion consistent with congestive cardiac failure (Dr. A. D. Morgan)
(7) Michael D. 13.2.1954	Division of ductus under hypothermic anaesthesia. Pressures (in mm. Hg) before and after clamping and division were: aorta, 100/50 and 100/60, and P.A. 90/60 and 45/20. The ductus had a diameter of 1·6 cm. The pulmonary artery proximal to the duct was 1·9 cm. in diameter, and distal 1·3 cm.	Rapid post-operative recovery with marked change in temperament from almost constant misery to cheerfulness and playfulness. Blowing S.M. maximal in 3rd left interspace
(8) Brenda S. 11.8.1954	Division of a very large, tense ductus with longitudinal suturing of aorta and pulmonary artery	Satisfactory recovery from operation. No bruits on discharge
(9) Linda C. 3.12.1954	Ductus ligated. The measurements of the vessels were: Ductus, 1 cm. Aorta, 1·2 cm. P.A., 1·7 cm.	Uneventful recovery. No cardiac murmur on discharge

TABLE VI
CLINICAL FINDINGS

Case, Age (Years), Date of Readmission	Time since Thoracotomy	Health since Discharge	Clinical Examination
(1) Elaine S. .. 7 7/12 10.3.1955	3 5/12 years	Exceptionally well without any disablement	Weight, 44 lb. Height, 47 in. Excellent nutrition. No cardiac enlargement. Soft blowing S.M. in pulmonary area. B.P. 115/80 mm. Hg. Chest radiograph, N.A.D. E.C.G., normal
(3) Janis C. .. 9 4/12 3.3.1955	2 5/12 ,,	Most satisfactory progress. Full physical activity without undue fatigue	Weight, 50 lb. Height, 52½ in. Thin, spare build. A.B. in 5th L.I.C.S. in M.C.L. No thrills. Harsh S.M. over whole praecordium, maximal lower end of sternum. Short D.M. to left of sternum and at apex. B.P. 110/65 mm. Hg. Chest radiograph, marked improvement in the pulmonary plethora since 1952. There is enlargement of the right ventricle. Fibrosis is present in the right mid-zone and left lower lobe. E.C.G., normal
(5) Jean H. .. 3 28.3.1955	1 10/12 ,,	Perfectly well	Weight, 25½ lb. Height, 32 in. Cheerful child. No cardiac enlargement. Soft basal S.M. B.P. 105/70 mm. Hg. Chest radiograph, the pulmonary arteries now appear normal. There is a little enlargement of the right ventricle. Thickened mediastinal pleura on the left, probably the result of operation. E.C.G., normal
(7) Michael D. .. 3 5/12 2.5.1955	1 3/12 ,,	Has grown well since operation with marked improvement in temperament. Effort tolerance normal	Weight, 25½ lb. Height, 35 in. Fairly well built. Happy disposition. No cardiac enlargement. Soft basal S.M. B.P. 115/85 mm. Hg. Chest radiograph, the size of the pulmonary arteries is now almost normal. There is still enlargement of the left auricle. E.C.G., normal
(8) Brenda S. .. 4 10/12 16.5.1955	9 months	Happy and "full of life." Apart from winter colds no illnesses	Weight, 34½ lb. Height, 41 in. Well nourished. No cardiac enlargement. Soft S.M. in pulmonary area. B.P. 120/90 mm. Hg. Chest radiograph, considerable improvement in the pulmonary plethora. E.C.G., normal
(9) Linda C. .. 2 4/12 23.4.1955	5 ,,	Perfectly well. Active and cheerful	Weight, 26½ lb. Height, 34 in. Plump child. A.B. 4th L.I.C.S. just outside M.C.L. No murmurs. B.P. 95/60 mm. Hg. Chest radiograph, the main pulmonary arteries and second and third divisions are still dilated. Both ventricles are enlarged. Thickened mediastinal pleura on the left. E.C.G., moderate R.V. preponderance

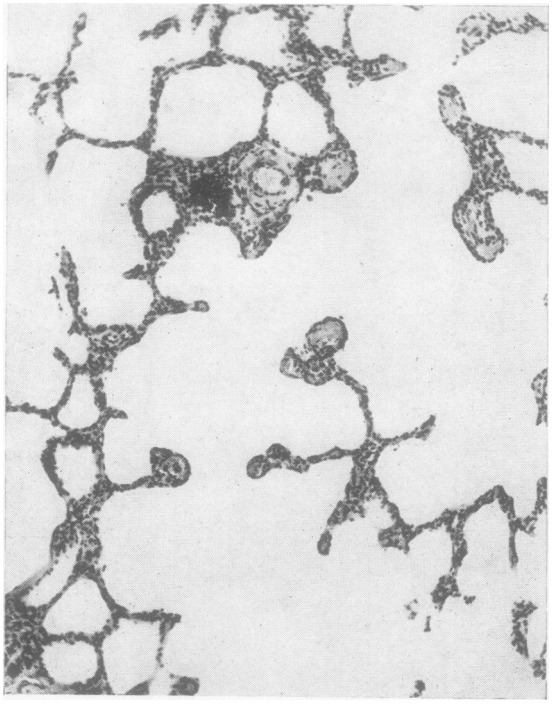

FIG. 1.—Lingula showing thickened arterioles and clubbed processes in emphysematous lung. Haematoxylin-eosin, × 50.

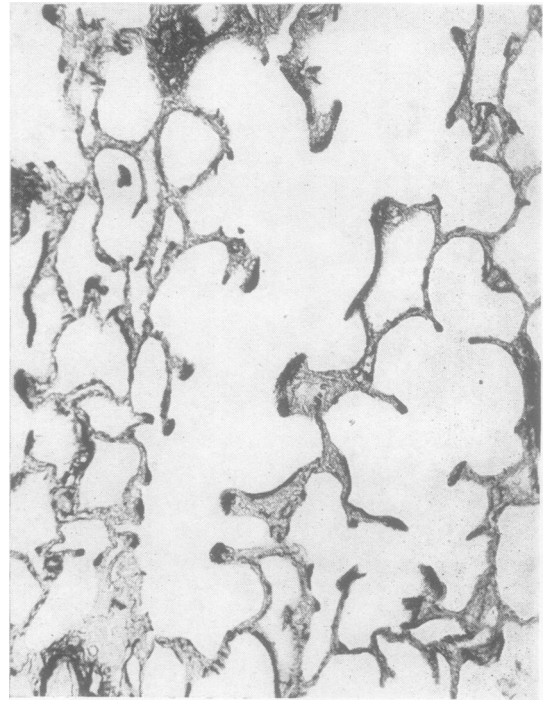

FIG. 2.—The same as Fig. 1, stained with elastic-Van Gieson, to show coils of elastic tissue in clubbed processes, × 50.

TABLE VII

RE-CATHETERIZATION STUDIES

Case, Date	Position of Catheter	Mean Pressure (mm. Hg)	Oxygen Saturation (%)	Oxygen (Vol. %)
(1) Elaine S. 17.3.1955	I.V.C.		69	11·6
	R.A.	−5	66	11·1
	R.V.	10	66	11·1
	M.P.A.	10	71	11·9
	R.P.A.	8	67	11·3
	P.C.V.	6	96	16·1
	Fem. art.		96	16·0
	Capacity		100	16·8
	Oxygen consumption 128 ml./minute			
	Systemic blood flow 2·6 litres/minute			
	Peripheral pulmonary vascular resistance 245 dynes/sec./cm.$^{-5}$			
(3) Janis C. 10.3.1955	I.V.C.		72	12·5
	R.A.	0	63	10·9
	Low R.V.		72	12·5
	High R.V.	16	79	13·7
	P.A.	16	79	13·7
	Fem. art.		90	15·7
	Capacity		100	17·4
	Oxygen consumption 208 ml./minute			
	Systemic blood flow 4·3 litres/minute			
	Peripheral pulmonary vascular resistance 123 dynes/sec./cm.$^{-5}$			
(5) Jean H. 29.3.1955	I.V.C.		74	12 7
	R.A.	1	67	11·5
	R.V.	11	72	12·4
	P.A.	10	67	11·5
	Fem. art.		94	16·2
	Capacity		100	17·2
	Oxygen consumption 160 ml./minute			
	Systemic blood flow 3·4 litres/minute			
	Peripheral pulmonary vascular resistance 235 dynes/sec./cm.$^{-5}$			
(7) Michael D. 3.5.1955	I.V.C.		84	15 0
	R.A.	−3	74	13 2
	R.V.	16	73	13 0
	P.A.	14	75	13 4
	L.P.A.	14	72	12·8
	P.C.V.	4	94	16·7
	Fem. art.		95	16·9
	Capacity		100	17·8
	Oxygen consumption 152 ml./minute			
	Systemic blood flow 4·1 litres/minute			
	Peripheral pulmonary vascular resistance 273 dynes/sec./cm.$^{-5}$			
(8) Brenda S. 17.5.1955	I.V.C.		78	12·5
	R.A.	0	63	10 1
	R.V.	14	64	10·2
	P.A.	13	63	10·1
	L.P.A.	10	66	10·6
	Fem. art.		92	14·7
	Capacity		100	16·0
	Oxygen consumption 175 ml./minute			
	Systemic blood flow 3·8 litres/minute			
	Peripheral pulmonary vascular resistance 275 dynes/sec./cm.$^{-5}$			
(9) Linda C. 28.4.1955	I.V.C.		70	11·9
	R.A.	−2·5	62	10·5
	R.V.	9	62	10·5
	P.A.	9	62	10·5
	Femoral artery		90	15·3
	Capacity		100	17·0
	Oxygen consumption 120 ml./minute			
	Systemic blood flow 2·5 litres/minute			
	Peripheral pulmonary vascular resistance 285 dynes/sec./cm.$^{-5}$			

It would appear from our experience that, although the presence of pulmonary hypertension in association with a patent ductus is generally accompanied by clinical signs unlike those of an uncomplicated ductus, it is possible to encounter cases in which many of the classical physical findings of the latter are present. Thus in four children a typical ductus murmur had been heard before admission. In two of these a machinery murmur, though inconstant, was audible up to the time of operation. In one instance this was demonstrated by phonocardiography. A consideration of the haemodynamics existing in those cases in which the aortic pressure is greater than the pulmonary artery pressure would seem to confirm that a continuous murmur could still arise from the flow of blood from the aorta to the pulmonary artery along the ductus. The less the difference in pressures becomes the smaller will be the shunt through the ductus. With severe pulmonary hypertension, therefore, one would expect a ductus murmur either to disappear or to become inconstant. Again, the fact that in four children a typical ductus murmur was heard before their admission and that on admission this was audible in only two, and then inconstantly, suggests that, whatever is the pathological process causing the pulmonary hypertension, it is a progressive condition.

The progressive nature of the pulmonary lesion is also suggested by the increasing disability suffered by patients and by the apparent reversal of the process by early ductus ligation. In all our cases the ductus was of large calibre and the pulmonary shunt (with the exception of Case 6, in which the flow was reversed) was considerable in relation to the systemic blood flow. Wood (1950) was unable to demonstrate any constant relationship between the size of the shunt and the pulmonary artery pressure on catheterization. On *a priori* grounds one would expect the volume of blood shunted to be inversely proportional to the pulmonary artery pressure and the peripheral pulmonary resistance. That large shunts occur in spite of these factors being elevated suggests that they are the results and not the causes of the abnormal flow of blood.

In our one re-catheterized child in whom lung biopsy was performed by thoracotomy, severe pathological lesions were found on histological examination (Case 3). The muscular arteries and the arterioles showed a marked thickening with elastic tissue and club-shaped masses of elastic tissue projected into irregular air-spaces resulting from emphysema (Figs. 1 and 2). It was not clear whether these projections were due to proliferation of arteriolar elastic tissue in the course of development of arteriolo-sclerosis, or whether they were derived from ruptured alveolar walls secondary to emphysema due to ischaemia of the lung

parenchyma. In spite of these degenerative changes, after ligation of the ductus the child's health and physique improved, and two years five months later her pulmonary arterial pressure and peripheral pulmonary vascular resistance were within normal limits. It would seem, therefore, that in spite of presumably permanent lung changes being present, closure of the ductus is still a curative procedure in such cases. This emphasizes the importance of early diagnosis and treatment, since there must be a point reached in the pathological process in the lungs beyond which improvement cannot take place. In addition, if it is accepted that the pulmonary hypertension is progressive, the longer the conditions producing it are present the more likely is the blood flow through the ductus to become reversed and then fixed. When this has occurred it is now generally accepted that ligation of the ductus should not be performed. We have only experience of one such case (Case 6) reported in this paper, and the child died in congestive cardiac failure about one month after operation. At necropsy she was found to have fibro-elastosis (Fig. 3) with mitral and aortic stenosis.

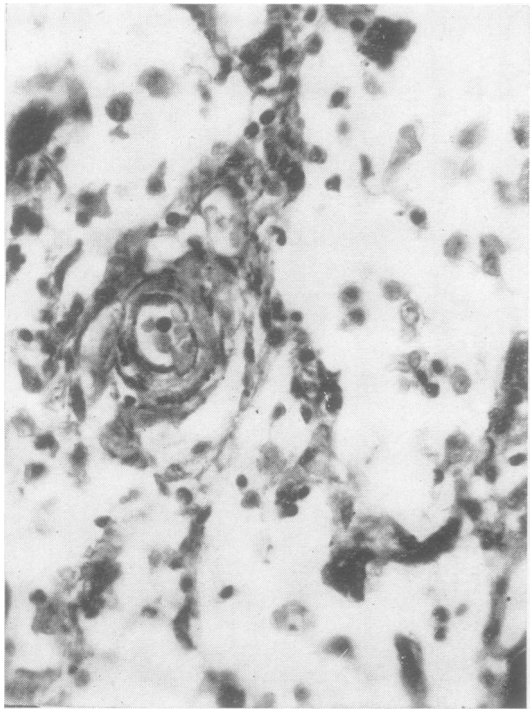

FIG. 3.—Pre-capillary vessel showing muscular hypertrophy. Sheridan's elastic stain, × 340.

The striking features in these children were the early onset of symptoms, the failure to thrive with repeated respiratory illnesses, the early diagnosis of congenital heart disease, and chest deformity, usually a marked left parasternal bulge. In four of them a typical ductus murmur was heard at some time, four of them had collapsing pulses in association with a high pulse pressure, and in three a diastolic murmur was present in the mitral area. In all cases chest radiography and screening showed well-marked pulmonary plethora with increased pulsation of the smaller vessels. The main pulmonary arteries were dilated, in most both ventricles were enlarged, and in four there was also considerable left auricular enlargement. Infants and children presenting with such manifestations should be subjected to cardiac catheterization, a procedure they stand well, so that precise diagnosis can be made and operative treatment instituted. Thoracotomy is well tolerated and post-operative recovery is usually rapid and satisfactory. Generally there is a marked improvement in the child's emotional, as well as physical, behaviour within a few days of the procedure.

Cases 2 and 4 were not re-catheterized for different reasons. The parents of Case 2 were unwilling to have the child readmitted, but when seen recently he was clinically well and had gained weight satisfactorily. Case 4 was subjected to catheterization, but the procedure was abandoned after repeated attempts to pass the catheter past the pelvic brim via the left internal saphenous vein, and downwards into the superior vena cava via the right median basilic vein. Thoracotomy had been performed two years before readmission and in the interval she had remained well, was active and cheerful, and had gained 12 lb. in weight.

SUMMARY

A survey of nine children with patent ductus arteriosus with pulmonary hypertension is presented. All were subjected to thoracotomy and ductus ligation, having previously been investigated by cardiac catheterization. All the children were greatly improved following operation, except for one with reversal of blood flow through the ductus who died one month post-operatively. Post-mortem examination showed the coexistence of endothelial fibro-elastosis with mitral and aortic stenosis.

Six children were re-catheterized at varying intervals after thoracotomy and were found to have normal pulmonary arterial pressures and peripheral pulmonary vascular resistances. The

significance of these findings is discussed and the inference drawn that the pulmonary hypertension is secondary to patency of the ductus and the increased pulmonary blood flow. The importance of early diagnosis and treatment of the syndrome is stressed.

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