Papers and Originals**OBLITERATIVE PULMONARY HYPERTENSION AND
THROMBO-EMBOLISM***

BY

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Obliterative pulmonary hypertension has been described by Wood (1958a) as pulmonary hypertension due to reduction of pulmonary vascular capacity. It implies obliteration of the pulmonary vascular bed by obstruction to the pulmonary vessels from organic disease. While there are many possible causes of obliterative pulmonary hypertension, it is probable that the commonest is pulmonary thrombo-embolism (Goodwin, 1960), and it is with this type of obliterative hypertension that this paper is principally concerned.

Obliterative pulmonary hypertension is associated with a permanently elevated pulmonary vascular resistance, and in the case of thrombo-embolism the disease is almost invariably confined to the arterial bed and pulmonary arteries, the pulmonary capillary bed, pulmonary veins, and left side of the heart remaining normal. Pulmonary thrombo-embolism may arise in association with congenital heart disease, particularly atrial septal defect, but may occur apparently spontaneously or as a result of large, small, or even minute emboli from peripheral veins. When this occurs the signs in the heart are those of pulmonary arterial hypertension, there being no evidence of underlying disease of the heart or of left-to-right intracardiac shunts.

Unchecked pulmonary thrombo-embolism is a progressive and ultimately fatal disease (Owen *et al.*, 1953; Wood, 1956). The clinical pattern varies with the size and number of thrombo-emboli which occur. Obstruction to the main pulmonary arteries or main pulmonary trunk may produce a picture of progressive right ventricular failure with signs suggestive of pulmonary stenosis (Ball *et al.*, 1956). When obstruction occurs in medium-sized or major branches, repeated episodes of pulmonary infarction may occur with signs of progressive pulmonary hypertension, and ultimately right ventricular failure. When obstruction lies only in the distal arterial bed there may be no clinical evidence of thrombo-embolism whatever, the picture merely being one of progressive and insidious pulmonary hypertension and right ventricular failure. This situation may be clinically indistinguishable from "primary" or "idiopathic" pulmonary hypertension, and even at necropsy microscopical studies may still leave some doubt. It is well known that a variety of stimuli can cause pulmonary arteriolar spasm (Wood, 1958a), and it seems very probable that the impaction of clot could act as a stimulus in this way.

The importance of repeated undetected pulmonary thrombo-embolism which has been allowed to go unchecked can scarcely be exaggerated. The frequency of pulmonary embolism following medical and surgical illnesses has been well recognized in recent years, but the potentially silent nature of the condition, with its

insidious progression, is still not sufficiently well known. Fortunately most patients who suffer one or more attacks of pulmonary embolism during the course of medical or surgical illness apparently cease to form further emboli or to develop thrombosis *in situ*, and recover completely provided that they survive the initial pulmonary embolism. Recognition of progressive pulmonary thrombo-embolism is vital (Thompson and Hamilton, 1962), for prolonged anticoagulant therapy may be the only hope of halting the progress of the disease. When a diagnosis of idiopathic pulmonary hypertension has been made, long-term anticoagulant therapy also may offer the only reasonable prospect of a lasting cure (Wood, 1956; Wilcken *et al.*, 1960).

The object of this paper is to present a series of 19 cases of obliterative pulmonary hypertension due to thrombo-embolism or idiopathic pulmonary hypertension without evidence of pre-existing cardiac disease. The diagnosis, clinical presentation, prognosis, pathology, and treatment will be discussed.

Patients Studied

The 19 cases studied have been divided into two groups according to the presence or absence of clinical evidence of pulmonary embolism or infarction (Tables I, II, III, and IV). All patients had evidence of pulmonary hypertension and all have been repeatedly studied clinically for periods varying from three weeks to five years. Radiological and cardiographic studies were made in all, and 15 patients were examined by cardiac catheterization (one of them on two occasions) and eight by angiocardiology. In group 1 seven of the 11 patients died; but one (Case 1) died elsewhere and there was no necropsy; in the other six cases necropsy studies were made and post-mortem angiograms were performed in five. In group 2 (eight patients) five died (Case 13 had no necropsy), and in four necropsy studies and post-mortem angiocardiology were made. The ages of the patients ranged from 2 to 69 years. Eight patients in group 1 and four in group 2 were treated with long-term anticoagulant therapy.

**Patients with Clinical Evidence of Pulmonary
Embolism or Infarction—Group 1 (Table I)**

In these 11 patients pulmonary embolism or thrombosis was diagnosed clinically by haemoptysis or by recurrent episodes of pleuritic pain. Seven patients had both haemolysis and pleuritic pain. In four patients the haemoptyses were frequent, prolonged, and considerable in amount. A source for pulmonary embolism in the calf veins was evident in six patients, in the pelvis in one patient, and in the right ventricle in another. No source for embolism could be discovered in three patients, and the lesions may have arisen *in situ* within the pulmonary arteries. Only two patients (Cases

*The second half of this paper, containing the Discussion, Summary, and References, will be published next week.

4 and 5) had evidence of underlying general systemic disease.

Vascular obstruction by thrombus in the large and medium-sized branches of the pulmonary arteries was found in four cases (Nos. 1, 2, 3, and 10) by angiocardiology and was confirmed by necropsy in three. Necropsy also showed obstruction to the major pul-

monary arteries in Case 11. Obstruction to vessels of microscopic size only was found in three cases (Nos. 4, 6, and 8) at necropsy. Angiography revealed considerable pulmonary artery enlargement in two (Cases 5 and 8).

Thus in Cases 4, 6, and 8, although the symptoms suggested pulmonary infarction and obstruction to

TABLE I.—*Obliterative Pulmonary Hypertension. Patients with Clinical Evidence of Pulmonary Thrombo-embolism*

Case No.	Age	Sex	Source of Emboli	Anticoagulants		Clinical Progress	Pathology	Other Features
				Duration	Result			
1	69	M	Calf veins	3 years	Died	Recurrent haemoptysis. Steady deterioration	No necropsy	
2	29	M	" "	5 months	"	Death after 6 months of anticoagulants	R.V. large (15 mm.). Thrombus in main P.A. Pulmonary infarction. Leg and pelvic veins normal	Continuous murmur upper zone of right lung
3	50	F	Calf veins and pulmonary arteries	4 years	"	Continued haemoptysis. ³² P for polycythaemia	Bilateral pulmonary artery thrombosis	Polycythaemia—probably secondary
4	61	F	Thrombus in R.V.	(4 weeks)	"	Died of right ventricular failure 2 years after stopping anticoagulants	Thrombosis in R.V. R.V. enlarged. Multiple thrombosis of small pulmonary arteries	Obscure collagen disease
5	44	F	Leg veins	3 months	Alive	One small pulmonary embolism while on anticoagulants		Possible diffuse systemic sclerosis. Clinical episodes of pulmonary embolism. Calf vein thrombosis. No haemoptysis
6	41	M	?	15 "	Died	Acute renal failure due to phenindione	R.V. 7 mm. Multiple pulmonary emboli small vessels	No source for emboli found
7	37	F	Leg veins	2 years	Alive	Sensitive to phenindione, changed to ethyl biscoumatate		Subsequently developed carcinoma cervix
8	38	F		(6 weeks)	Died	Progressive dyspnoea. Pulmonary infarction. Increasing pulmonary hypertension. Sudden death	R.V. hypertrophy. Occluded peripheral pulmonary arteries only. No venous thrombosis found in systemic veins	? Thrombosis <i>in situ</i> of small pulmonary arteries
9	45	M	Calf veins	7 years	No further pulmonary embolism	Remains well on anticoagulants		
10	35	F	Pelvic veins	3 months	Too early to say	Well apart from dyspnoea	Bilateral pulmonary artery thrombosis	Secondary polycythaemia. Epilepsy. Hypercapnoea
11	29	F	Unknown	(1 month)	No benefit. Discontinued because of reaction. Died	Progressive deterioration. Chest infection. Hypercapnoea. Wheezing ++		

R.V. = Right ventricle.

TABLE II.—*Obliterative Pulmonary Hypertension. Patients without Clinical Evidence of Pulmonary Thrombo-embolism*

Case No.	Age	Sex	Anticoagulants		Clinical Progress	Pathology	Diagnosis		Other Features
			Duration	Result			Clinical	Pathological	
12	26	F	—	Died in 15 months	Progressive right ventricular congestive failure, syncope, and epilepsy	Marked right ventricular hypertrophy. Congestive heart failure, occlusion of pulmonary arteries	Idiopathic pulmonary hypertension	Thrombo-embolic pulmonary hypertension	No response of pulmonary hypertension to imidazole, hexamethonium, or phenoxybenzamine
13	16	F	—	Died in car accident	Remained well and symptomatic on phenoxybenzamine	—	Idiopathic pulmonary hypertension	No necropsy	Clinical signs unchanged, but E.C.G. suggested resolution of right ventricular hypertrophy
14	29	F	1 month	Died after thoracotomy	In heart failure. No response to treatment with vasodilators and anticoagulants	Eosinophilia. Abnormal globulins	Idiopathic pulmonary hypertension	Thrombo-embolic pulmonary hypertension	Unfit for investigation. Thoracotomy undertaken to exclude "silent" mitral valve disease or tumour. Lung roots denervated
15	2	M	—	Died after catheterization	Progressive cyanosis and dyspnoea	Right ventricular hypertrophy marked. Patent foramen ovale. Obliteration of pulmonary arterioles	Atrial septal defect. Eisenmenger type	Primary pulmonary hypertension	Dye curve showed right-to-left shunt at atrial level. Squatted after exercise
16	32	F	18 months (off for 6 months Then 6 months on)	Symptom-free. Resolution of pulmonary hypertension	Second catheterization showed fall of P.V.R. to 4 units	—	Thrombo-embolic pulmonary hypertension	—	Withdrawal of phenindione after 18 months was followed by recurrence of pulmonary hypertension. Signs subsided after restarting the drug
17	68	F	1 year	Dyspnoea worse	No change in signs from 1956 to 1961	—	" "	—	Lung disease also. Pco ₂ raised
18	68	F	10 weeks	Died. Anticoagulants given too late	Died; right ventricular failure	Occlusion of small pulmonary arteries with thrombi. Cor pulmonale. Patent foramen ovale. Terminal peritonitis	" "	Thrombo-embolic pulmonary hypertension	Also had systemic hypertension and sclerotic kidneys
19	42	F	1 year	Unknown (patient overseas)	Unknown	—	Obliterative pulmonary hypertension; ? embolic	—	Very unusual physical signs. Angiocardio-gram showed severe pulmonary hypertensive changes

medium-size or large pulmonary vessels, the occlusion was found to involve only small or microscopic-sized vessels. It is thus evident that the clinical and pathological characteristics of the two groups do not always harmonize, and that there is some overlap. However, when profuse haemoptyses and a source for embolism such as the calf veins occurred, the larger pulmonary vessels were always blocked.

Patients Without Clinical Evidence of Thrombo-embolism—Group 2 (Table II)

In group 2 there were no symptoms suggesting pulmonary thrombo-embolism, the condition presenting with progressive dyspnoea, syncope, or occasionally chest pain. All these patients therefore presented clinically in a fashion very similar to the condition described as "idiopathic" or "primary" pulmonary hypertension, in that all had obliterative pulmonary hypertension without obvious cause. However, one patient (Case 16) already reported by Wilcken *et al.* (1960), was thought to have thrombo-embolic pulmonary

hypertension because symptoms started shortly after pregnancy; and another (Case 15), a boy of 2 years, was deeply cyanosed clinically, and was thought to have an atrial septal defect with an early onset of the Eisenmenger reaction. Necropsy in this boy showed that the cyanosis was due to a right-to-left shunt through a patent foramen ovale, and the study of the lung vessels suggested that he had true idiopathic pulmonary hypertension. Necropsy was carried out in four patients, and in three the histological findings indicated thrombo-embolism, although in two of these the clinical picture exactly resembled "idiopathic" or "primary" pulmonary hypertension. In the fourth patient the pathological studies showed medial hypertrophy but no evidence of thrombosis. It was thus not always possible in this group to decide the exact nature of the pulmonary vascular disorder in life.

The important features of all the patients are listed in Tables I, II, and III. Some cases are reported briefly below.

GROUP 1

Case 1

Man aged 69. Repeated calf-vein thromboses and haemoptyses for 10 years. Mild dyspnoea on exertion and oedema of ankles. Examination: Central cyanosis. No clubbing. J.V.P. dominant "a" wave. Right ventricular enlargement. Atrial sound, pulmonary ejection click, accentuated pulmonary closure, and short pulmonary ejection murmur. Bilateral varicose veins. Hb 16.4 g./100 ml.

Cardiography.—Inversion of right precordial T waves (Fig. 1).

Radiography of Chest.—Suggested pulmonary hypertension with thrombosis of right main pulmonary artery. Both

TABLE III.—Symptoms in Obliterative Pulmonary Hypertension and Thrombo-embolism

Case No.	Duration of Symptoms	Dyspnoea	Syncope	Chest Pain	Haemoptysis	Cough	Infected Sputum	Wheeze
1	10 years	+	0	++	++	++	0	0
2	6 months	++	0	++	++	++	0	0
3	10 years	++	0	++	++	++	0	0
4	"	++	0	++	++	++	0	0
5	3 weeks	++	0	++	0	0	0	0
6	18 months	++	++	++	++	++	0	0
7	7 years	++	++	++	++	++	0	0
8	6 months	++	0	++	++	++	0	0
9	8 "	++	0	++	0	0	0	0
10	9 years	+	0	++	0	0	0	0
11	Since childhood	+	Epilepsy	+	+	+	+	+
12	12 months	+	+	0	0	+	+	0
13	15 "	++	+	+	0	++	0	0
14	2 years	++	0	0	0	++	0	0
15	6 months	++	0	0	0	++	0	0
16	1 year	++	0	0	0	++	0	0
17	5 years	++	+	+	0	+	+	0
18	2 "	++	Convulsions	0	0	0	0	0
19	? All life	+						

TABLE IV.—Physical Signs in Obliterative Pulmonary Hypertension and Thrombo-embolism

Case No.	Grade of Jugular Venous Pressure "a" Wave	Grade of Right Ventricular Hypertrophy	Grade of Accentuation of Pulmonary Closure	Grade of Early Diastolic Murmur	Grade of Ejection Systolic Murmur	Grade of Ejection Click	Grade of Pan-systolic Murmur	Grade of Congestive Cardiac Failure	Grade of Third Heart Sound	Grade of Fourth Heart Sound	Cyanosis
1	1	1	2	0	2	2	0	0	0	2	+
2	2	3	Wide (W.P.W.)	0	1	0	0	+	3	2	+
3	1	2	2	0	0	1	1	+	0	2	+
4	4	2	2	0	0	0	0	+	0	0	0
5	1	1	2	0	0	0	0	0	0	0	0
6	3	3	2	0	0	0	0	0	0	0	0
7	1	3	2	0	0	2	2	0	2	0	0
8	1	1	2	0	0	0	2	0	0	0	0
9	2	1	2	0	0	1	0	0	0	0	0
10	1	0	2	0	1	1	0	0	0	0	0
11	3	2	1	0	0	0	0	+	0	3	+
12	4	2	3	1	0	2	0	+	0	2	0
13	3	3	2	0	2	0	0	0	0	2	0
14	3	3	3	0	0	0	2	+	3	3	0
15	3	3	3	0	0	1	1	0	3	3	0
16	2	1	2	0	1	1	0	0	0	0	0
17	2	2	3	0	3	2	0	0	0	0	0
18	1	2	1	0	0	0	2	0	2	2	+
19	2	(LV+)	3	0	1	4	0	+	0	0	0

Grades of intensity: 1, Slight. 2, Moderate. 3, Marked. 4, Extreme. WPW= Wolff-Parkinson-White (accelerated conduction) syndrome. LV+= Left ventricular hypertrophy.

FIG. 1.—Selected leads from cardiograms in cases of group 1.

pulmonary arteries considerably enlarged; right main branch terminating suddenly in lower zone without normal segmental branches issuing from it. Peripheral lung fields unduly clear; vascular markings diminished. Tomography of the hilar region: calcification in right main pulmonary artery. Angiography: Right lower lobe of main branch did not fill with contrast medium (Table V).

Cardiac Catheterization.—Right ventricular pressure 84/4 mm. Hg; arterial oxygen saturation 80%. Total pulmonary vascular resistance probably around 14 units. No left-to-right shunt (Table VI).

The arterial oxygen saturation rose to 90% on breathing oxygen for five minutes, showing that the desaturation was due to imbalance between ventilation and perfusion and not to a right-to-left shunt through a patent foramen ovale (Table VII).

Progress.—The patient was stabilized on phenindione, the prothrombin time being maintained at $2\frac{1}{2}$ to 3 times normal. But haemoptyses continued, dyspnoea increased, and he died suddenly in 1961 in another hospital. Necropsy was not permitted.

Comment.—This patient was able to survive many episodes of pulmonary thrombo-embolism and remain relatively well without right ventricular failure in the face of gross disorganization of the pulmonary vascular bed. The efficacy of anticoagulants in this case seems

questionable in view of the persistence of haemoptyses and the fatal outcome. However, phenindione may have prolonged life. There was no further evidence of calf-vein thrombosis or that progressive thrombosis in the pulmonary vessels rather than repeated embolism was presumably the cause of death.

Case 2

Man aged 29. For six months thrombophlebitis of calf, dyspnoea, haemoptysis, and pleural pain. Examination: J.V.P. large "a" wave, right ventricular enlargement, pulmonary ejection click, narrowly split second heart sound with accentuated pulmonary closure. Atrial sound. Faint continuous murmur over right upper chest and in axilla (Fig. 2).

Radiography of Chest.—Right ventricle, right atrium, and main pulmonary arteries enlarged. Irregular pulmonary vascular shadows in periphery of lung fields, with areas of increased translucency and diminution of vascular markings in right mid-zone and left upper zones. Haemoglobin 14.5 g./100 ml.

Cardiography.—Pre-excitation (Wolff-Parkinson-White syndrome): deep T-wave inversion in precordial leads from V1 to V4 (Fig. 1).

Cardiac Catheterization.—Pulmonary artery pressure 114/51 mm. Hg (mean 69); total pulmonary vascular resistance 8.5 units. No left-to-right shunt; arterial oxygen saturation 88% (Table VI).

Pulmonary Arteriography.—Great enlargement of the main pulmonary artery right and left main branches: no filling of left lower zone and very sparse filling of upper zone on same side. Right lung peripheral vessels narrowed and irregular with little filling at apex and few vessels of normal calibre supplying lower lobe (Fig. 3, Table V). These findings were consistent with extensive pulmonary thrombo-embolism, and partial obstruction of artery to right upper lobe was thought to explain the continuous murmur.

Measurements of ventilation and regional blood flow, using radioactive oxygen combined with carbon dioxide ($^{15}\text{CO}_2$), by Dr. C. T. Dollery showed that although ventilation was comparable in the two lungs the blood flow was diminished through the upper and lower zones of the left lung, giving rise to imbalance between ventilation and perfusion which would account for the reduced arterial oxygen saturation (Table VIII).

TABLE V.—*In vivo* Angiographic Studies of Pulmonary Arteries

Case No.	Main Pulmonary Arteries Enlarged	Peripheral Arteries			Major Arterial Obstruction
		Normal	Tortuous	Deficient in Number (Pruning)	
1	+	0	+	+	+
2	+	0	+	+	+
3	+	0	+	+	+
5	+	+	0	0	0
8	+	+	0	0	0
10	+	0	+	+	+
17	+	0	+	+	Segmental obstruction 0
19	+	0	+	+	

TABLE VI.—*Haemodynamic Data*

Case No.	Pulmonary Artery Pressure (mm. Hg)	Total Pulmonary Vascular Resistance (Units)	Pulmonary Wedge Pressure (mm. Hg)	Cardiac Output (l. min.)	Arterial Oxygen Saturation
1	84/4 (RV)	c. 14	—	3.3	80
2	114/51	8.5	—	8.0	88
3	53/40	13	—	3.0	85
4	70/35	13	—	3.0	92
5	75/10	c. 13	—	3.6	99
8	95 (RV)	9	—	2.5	94
10	60/35	9	—	4.6	88
11	92/55	18	—	4.0	75
12	100/40	20	—	2.5	98
13	80/50	10	—	6.0	98
14	75/40 (RV at operation)	—	—	—	—
15	120/90	—	13	—	76
16	65/28	7.5	5	4.7	98
17	124/20	6.5	8	9.2	85-93
19	106/42	20	8 (at bronchoscopy)	2.7	82

TABLE VII.—*Blood Gases*

Case No.	Arterial Oxygen Saturation (%)			Mixed Venous Pco_2 mm. Hg
	Rest	Exercise	After Inhalation of 100% Oxygen	
1	80	—	98	—
2	88	—	—	—
3	92	65	—	—
10	94	80	100	38
11	75	66	92	55-70
13	98	98	—	—
16	97	88	105	—
17	83-93	78	100	50-60
18	80	66	92	36

FIG. 2.—Case 2. Phonocardiogram showing continuous murmur over upper zone of right lung. The murmur, although continuous, shows the maximum systolic accentuation in late systole rather than at the second heart sound. (P.A.=pulmonary area. R.M.Z.=mid-zone of right lung. H.F.=high frequency. A₂=aortic valve closure. P₂=pulmonary valve closure. S.M.=systolic murmur. D.M.=diastolic murmur.)

Subsequent Progress.—The patient was maintained continuously on phenindione, but deteriorated progressively and developed irreversible right ventricular congestive failure. Occasional further episodes of pleural pain with small

FIG. 3.—Case 2. Pulmonary arteriogram, postero-anterior projection. There is no filling of arteries of left lower zone and very sparse filling of left upper zone vessels. Peripheral arteries to right lung are narrowed and irregular, especially in upper and lower zones.

TABLE VIII.—Respiratory Function in Obliterative Pulmonary Hypertension and Thrombo-embolism

Case No.	Airways Obstruction			Hyper-ventilation	Ventilation/Perfusion Imbalance	Mixed Venous PCO_2 , mm. Hg	Regional Pulmonary Blood Flow $^{14}\text{CO}_2$
	F.E.V.	F.V.C.	F.E.V./%V.C.				
1	3.06	4.16	73	+	+		No regional difference in flows. Reduced flow all areas. Patterns of severe pulmonary hypertension. But in Case 2 perfusion, and O_2 uptake less in left than right lung
2	—	—	—	—	—		
3	2.15	2.8	78	—	—		
10	2.36	3.08	77	+	+	38	
11	0.6	1.9	30	+	+	55-70 (terminally 48)	
16	3.0	3.3	90	+	0		50-60 36
17	1.05	1.1	87	—	—		
18	1.6	—	—	—	—		

F.E.V. = 1 second forced expiratory volume. F.V.C. = forced vital capacity.

haemoptyses indicated that the anticoagulant therapy was not entirely effective in preventing further episodes of thrombo-embolism. He died suddenly after a large haemoptysis.

Necropsy Findings.—The right ventricle was enlarged to about three times the normal thickness. The most striking finding was the presence of a large mass of thrombus occupying most of the lumen of the main pulmonary artery. Thrombus appeared to have developed initially in the right and left pulmonary arteries on their anterior walls. There it was almost completely discoloured, being pale grey and firmly adherent to the vessel wall with successive lamination upon it. The thrombus extended into the lungs for a distance of 1 cm. Patency was maintained by a small slit posteriorly. The thrombus in the main pulmonary artery was recent. There were numerous old infarcts in the lungs, and microscopy of the vessels showed evidence of repeated thrombo-embolism. The leg and pelvic veins were dissected but no abnormality was found.

Comment.—This patient had suffered repeated pulmonary emboli from the thromboses in the veins of the lower limb, and it is probable that secondary thrombosis occurred in the pulmonary arterial tree as a result of the preliminary emboli. Extensive obstruction and

obliteration of the arteriolar bed must have occurred to produce the gross pulmonary hypertension and elevation of pulmonary vascular resistance which was demonstrated. In addition to the obstruction to the arteriolar bed there was extensive and irregular blockage of arteries of segmental and even larger size, and on the right side the partial obstruction of an arterial branch gave rise to a continuous murmur. This murmur was presumably produced by a gradient across the partial stenosis throughout the cardiac cycle because of the high systolic and diastolic pressures in the main pulmonary artery proximal to the peripheral obstruction (Gunning, 1957). The disease was too far advanced before medical aid was sought for a favourable outcome to be expected. The severity was reflected by the very high pulmonary artery pressure. Progressive right ventricular failure was due to obliteration of the arteriolar bed and to obstruction of the larger vessels.

Case 3

Woman aged 50. Ten-year history of multiple thromboses involving brain, spleen, calf veins, and possibly pulmonary arteries. R.B.C. 6.6 mm./c.mm.; W.B.C. 9,700/c.mm.; platelets 420,000/c.mm. By 1957 effort dyspnoea was severe and angina had developed. Examination: plethoric cyanosed woman. Varicose veins. J.V.P.: accentuated "a" wave; right ventricle enlarged, pulmonary closure accentuated, atrial gallop, systolic click. B.P. 130/80 mm.Hg.

Radiography of Chest.—Considerable enlargement of right ventricle and main pulmonary arteries, which pulsated poorly; the lung fields showed patchy loss of vascular shadows, mainly in the upper zones (Fig. 4).

FIG. 4.—Case 3. Postero-anterior chest radiograph showing massive enlargement of both main pulmonary arteries and patchy loss of vascular markings in upper zones. Segmental branches to right lower lobe are obviously deficient and the rounded lower margin of right main artery is suggestive of thrombosis.

Cardiography.—Right ventricular hypertrophy and inversion of T waves in all chest leads (Fig. 1). Hb 18 g./100 ml.; P.C.V. 60%; W.B.C. 8,000/c.mm.; platelets 124,000/c.mm.

Cardiac Catheterization.—Pulmonary artery pressure 53/40 mm. Hg (mean 45); pulmonary arteriolar resistance 13 units; cardiac output 3 litres/min. (Table VI). Arterial O_2 85%. No cardiac shunts.

Respiratory Function.—Normal airway resistance (Table VIII).

Radioactive Oxygen Test.—Slight reduction in ventilation in the right lung with reduced oxygen uptake. Arterial O_2 saturation 92% at rest and 65% (Table VII) on exercise, suggesting impairment of ventilation-perfusion balance or

a right-to-left shunt through a patent foramen ovale or the lung.

Pulmonary Arteriography.—Enlargement of both main pulmonary arteries; poor filling of lower arteries suggesting obstruction (Table V).

Anticoagulants and several courses of radioactive phosphorus were given. She gradually deteriorated, developing increasing dyspnoea and congestive heart failure, and died in December, 1961, from a cerebral thrombosis.

Necropsy.—The immediate cause of death was thrombosis of the left posterior cerebral artery with infarction of the left half of the crus cerebri. Hyperplasia of the bone-marrow and splenomegaly due to polycythaemia were found. Thrombosis in the innominate vein and old infarct scars in spleen and kidneys were present. The heart weighed 490 g. The right ventricle was hypertrophied, measuring 9 mm. in the conus. The left ventricle was of normal thickness (15 mm.). There was a valvular foramen ovale 10 mm. in maximal diameter. The main pulmonary trunk and most of the left pulmonary artery were free from thrombus from its origin onwards. There was a narrow remaining channel along the upper border. This thrombus extended into all the segmental arteries. On the left there was thrombus in the terminal part of the main artery and in all the segmental arteries.

Post-mortem Pulmonary Angiography.—All parts of both lungs were injected. This was due to recanalization of the occluding thrombus in the segmental arteries, the recanalization coming mainly via greatly enlarged bronchial arteries. The occlusions extended into the first divisions of the segmental arteries, but did not often extend below this level. Distal to the occlusions, the pulmonary arteries, both elastic and muscular, were without signs of hypertrophy. A small proportion of the muscular pulmonary arteries showed irregular or concentric fibrous intimal lesions that almost certainly represent healed thrombi. The lung itself was healthy and there were neither infarcts nor scars of old infarcts.

Comment.—This patient had multiple occlusions of the pulmonary arteries, presumably arising from emboli from the leg veins. The polycythaemia was probably

secondary. Anticoagulant therapy failed to save her because it was started too late.

Case 10

Woman aged 35. Abortion at age 25, followed by irregular vaginal bleeding; Hogben test positive; curettage; no evidence of chronic epithelioma. At age 27, dyspnoea on exertion, multiple pulmonary cavitations, jaundice (? repeated pulmonary infarction). Subsequently increasing dyspnoea on effort, especially in pregnancy at age 33. Examination: Hyperventilation at rest. Sole signs of pulmonary hypertension were slight accentuation of pulmonary closure, systolic click, and short soft ejection murmur. B.P. 120/40 mm. Hg.

Radiography of Chest.—Prominence of main pulmonary arteries, linear strictions in right middle and lower lobes, and thickening of right horizontal fissure; no obvious loss of vascular markings (Fig. 5).

Right ventricular angiography: Right ventricle and pulmonary arteries enlarged; both right and left lower lobe arteries small and partly occluded (Fig. 6).

Cardiography.—T-wave inversion in right precordial leads (Fig. 1).

Cardiac Catheterization.—Pulmonary artery pressure 60/35 mm. Hg (mean 47); cardiac output 4.6 l./min.; pulmonary arteriolar resistance 9 units. Arterial O₂ saturation 88%; no shunts (Table VI). The pulmonary artery pressure failed to fall after acetylcholine or inhalation of 100% oxygen (Table IX, Fig. 7).

Respiratory-function Tests.—Normal lung volumes, and ventilatory capacity with high alveolar ventilation and dead space, suggesting that large parts of the lungs were being

FIG. 5.—Case 10. Six-foot postero-anterior radiograph of chest. There is prominence of main pulmonary arteries; linear striations in right, middle, and lower lobes; and thickening of horizontal fissure of right lung. There is no obvious loss of vascular markings. The appearances suggest chronic inflammatory changes.

FIG. 6.—Case 10. Postero-anterior projection of right ventricular angiogram. There is enlargement of right ventricle and main pulmonary arteries. Both right and left lower lobe arteries fail to fill, and left upper lobe arteries are small and partly occluded. The angiogram thus shows gross pulmonary vascular obstruction involving major arteries, which was not apparent from the plain chest film.

TABLE IX.—Responses of Pulmonary Circulation to Drugs and 100% Oxygen

Case No.	Drug	Result
4	Hexamethonium	Pulmonary and systemic vascular resistances fell
10	Acetylcholine	No change in pulmonary pressure. Fall in systemic pressure
	100% oxygen	No change
11	Acetylcholine	"Mean" pulmonary artery pressure fell
12	100% oxygen	No change
13	Imidazoline	Pulmonary and systemic pressures fell
16	Hexamethonium	" " vascular resistances fell
	100% oxygen	" " "
	Aminophylline	" " "
	Imidazoline	No change

ventilated but not perfused. Tests of airways resistance were normal (Table VIII). Arterial O_2 saturation 94% at rest, falling to 80% on exercise, and rising to 100% on breathing 100% oxygen (Table VII).

Anticoagulant therapy with phenindione was given but the period has so far been too short to assess the results.

FIG. 7.—Case 10. Pulmonary artery and systemic arterial pressures before and after injection of acetylcholine into pulmonary artery. Neither this drug nor the inhalation of 100% oxygen produces any selective fall in pulmonary artery pressure.

Comment.—The history was strongly suggestive of multiple thrombo-embolism to the lungs, but the physical and radiological signs were unimpressive for this diagnosis, only the angiogram providing conclusive proof. The abnormalities of respiratory function—hyperventilation, low PCO_2 , impaired ventilation/perfusion relationships, normal lung volumes, and large dead space—may be characteristic of pulmonary thrombo-embolism. The cardiogram suggested the diagnosis by the inversion of the T waves in the right precordial leads (Caird and Stanfield, 1962).

Case 11

Woman aged 29. Repeated respiratory infections in childhood and dyspnoea on exertion. Examination: Cyanosis; no clubbing. Wheezing. Jugular venous pressure normal with right ventricle enlarged; pulmonary closure accentuated; atrial gallop. B.P. 125/80 mm. Hg. Spleen not enlarged.

Radiography of Chest.—Enlargement of right ventricle and main pulmonary arteries; scanty peripheral vessels suggesting severe pulmonary hypertension; no patchy loss of vascular markings and no evidence of pulmonary infarction or pleural effusion (Fig. 8); inflammatory changes at right base.

Cardiography.—Grade 3 right ventricular hypertrophy, marked right atrial enlargement, and T-wave inversion in leads V4R to V7 (Fig. 1).

Cardiac Catheterization.—Pulmonary artery pressure 92/55 mm. Hg (mean 70), cardiac output 4 l./min., total pulmonary vascular resistance 18 units; arterial O_2 saturation 75%. Dye dilution curves: No right-to-left shunt (Table VI). Pulmonary vascular resistance on 100% oxygen (Table IX).

Respiratory-function Tests.—Greatly reduced forced expiratory volume and maximum breathing capacity.

Marked inequality of ventilation and perfusion, and increased lung volumes. The mixed venous PCO_2 varied from 55 to 70 mm. Hg (Table VIII). Arterial O_2 saturation was 75% at rest, decreased to 66% on effort and increased to 92% on breathing 100% oxygen (Table VII). These findings suggested emphysema and airways obstruction with possibly secondary pulmonary-artery thrombosis.

Anticoagulant therapy was given, but owing to sensitivity to phenindione was discontinued. Steroid and antibiotic therapy was ineffective and respiratory infections and progressive pulmonary and congestive heart failure continued. Hyperventilation developed and PCO_2 fell to 49 mm. Hg. Death occurred in April, 1962.

Necropsy.—The heart weighed 476 g. and showed an enormous degree of right ventricular hypertrophy, the conus being 13 mm. thick. The left ventricle was small. There was a thrombus in the right pulmonary artery, but it did not obstruct any of the branches though there was a 3-cm. infarct in the posterior base of the lower lobe. Another thrombus was found in the left pulmonary artery and nearly the whole of the upper lobe was recently infarcted. The pulmonary arteries were dilated. The left lung was inflated, and was studied for the presence of bronchitis and emphysema; the right lung was injected for study of the vasculature. In the left lung emphysema was mild, affecting some 15 to 20% of the lung substance, and was mainly in the anterior part. There was evidence of severe chronic bronchitis. Radiographs of the injected right lung showed a dilated pulmonary artery 40 mm. in diameter. The lobar and segmental arteries were moderately dilated and the smaller elastic arteries were normal. There was no appreciable loss of background filling apart from localized translucent areas of emphysema. The appearances were not like those of other cases of embolic pulmonary hypertension.

Microscopically there was evidence of pulmonary thrombosis or embolism at all levels from small elastic pulmonary arteries down to arterioles. All stages from fresh occlusion to complete organization would be found. The proportion of arteries obstructed, about one in five, was much smaller than in other cases, and it seems improbable that the

FIG. 8.—Case 11. Six-foot postero-anterior radiograph of chest. There is enlargement of the right ventricle and main pulmonary arteries with scanty peripheral vascular markings suggesting severe pulmonary hypertension. Inflammatory changes are evident at right base.

pulmonary hypertension was due only to vascular obstruction. There was, however, good evidence of chronic bronchitis, and this may well account for the greater part of the pulmonary hypertension. The right pulmonary artery showed fibrous replacement of the media underlying much of the thrombus. The history suggested that this was an aneurysmal dilatation with secondary thrombosis overlying it. The emboli in the lungs could well have come from the thrombi lying in the right and left pulmonary arteries. The probable sequence of events in this patient was chronic bronchitis with pulmonary hypertension, dilatation of the hypertensive pulmonary arteries with local thrombosis, and, finally, embolization of both lungs by fragments from the thrombi.

Comment.—This patient had extensive thrombo-embolic pulmonary disease, presumably secondary to chest infection in childhood. Her hypercapnoea was quite atypical of thrombo-embolic disease, and was presumably due to obstruction of the airways. It is possible that this was secondary to thrombo-embolic disease, but the reverse seems more probable. Anti-coagulant therapy was ineffective owing to its short duration and the presence of severe pulmonary failure. The polycythaemia was thought to be secondary to the thrombo-embolic disease. The terminal hyperventilation was unexplained, but presumably was the cause of the fall in PCO_2 .

No other case reports are given of patients in this group, but attention is drawn to Cases 6, 7, and 11, in which sensitivity to phenindione developed. In Case 6 acute renal failure developed, presumably as a result of phenindione sensitivity (*Brit. med. J.*, 1960b), which has been reported in others (Barritt and Jordan, 1960; Brooks and Calleja, 1960). In Cases 7 and 11 a pyrexia and a rash developed while on phenindione, which led to its withdrawal.

In this group there was no definite clinical evidence to indicate thrombo-embolism, but of the four patients who came to necropsy there was clear microscopical evidence of thrombo-embolism in three, while the fourth appeared to have "primary" pulmonary hypertension.

GROUP 2

Case 12

Woman aged 26. Syncope after exertion and dyspnoea on exertion and at rest. No pregnancies. Examination: Signs of severe pulmonary hypertension (including pulmonary diastolic murmurs) without underlying cardiac or pulmonary disease. B.P. 130/95.

Radiography of Chest.—Enlargement of the right atrium, right ventricle, and pulmonary arteries with small peripheral arterial branches and abnormal clarity of the lung fields.

Cardiography (Fig. 9).—Grade 4 right ventricular hypertrophy and right atrial hypertrophy with slight increase in the P-R interval and inversion of the T waves from V4R to V5. There being no evidence of disease of the left side of the heart, intrinsic lung disease, or congenital heart disease, a diagnosis of idiopathic pulmonary hypertension was made. No evidence was found historically or clinically to suggest a source of emboli to the lungs.

Cardiac Catheterization.—No left-to-right shunt; pulmonary artery pressure 100/40 mm. Hg; right atrial pressure: presystolic "a" wave of 10 to 12 mm. Hg. Arterial O_2 saturation: 98% (Table VI). Imidazoline 10 mm. injected into the pulmonary artery failed to reduce the pulmonary-artery pressure, despite subjective symptoms (Table IX).

The patient was treated with the usual methods for congestive heart failure, and with imidazoline, hexamethonium, and finally phenoxybenzamine. None of these

drugs appeared to influence the pulmonary hypertension, and she died suddenly after a convulsion in August, 1955.

Necropsy.—The heart weighed 417 g. There was striking hypertrophy of the right side of the heart with moderate dilatation. All the valves were normal, but the main pulmonary arteries were enlarged. The lungs were of normal weight and appeared healthy externally. The pulmonary arteries were injected with contrast medium after death. Radiography showed a greatly enlarged main pulmonary artery with segmental branches of normal size. But the immediate branches were somewhat narrowed and all further elastic arteries narrowed. The background filling of muscular arteries was remarkably sparse.

Microscopically the main and segmental pulmonary arteries showed atheroma and hypertrophy. The elastic pulmonary arteries showed medial hypertrophy equal to four times the thickness of corresponding controls. Large muscular arteries (over 200 μ external diameter) showed apparent hypertrophy, but only a very few had any intimal fibrosis. Of the small muscular arteries a half were either narrowed or totally obliterated owing to intimal fibrosis, and about four-fifths of the arterioles were narrowed or obliterated. The veins and lung parenchyma were normal.

The degree of organic obstruction in the small pulmonary arteries and arterioles was clearly sufficient to produce obstructive pulmonary hypertension. We originally regarded this patient as an example of the latter, but comparison with other cases in this series and the finding of an occasional artery with a double lumen and one artery containing thrombus, together with the absence of any significant degree of medial damage, led us to suspect that this patient too may have had embolic hypertension.

Comment.—This case illustrates the very close similarity between idiopathic and thrombo-embolic hypertension when the latter involves the microscopic arteries only. It is impossible to deny that an underlying arteritis may have preceded the occlusions, but the lack of signs of inflammatory change in the vessels speaks against this. An attractive hypothesis would envisage an initial intense pulmonary artery vasoconstriction

Fig. 9.—Selected leads from cardiograms of patients in Group 2.

followed by medial hypertrophy, succeeded by thrombosis. The possibility of thrombo-embolism from the pelvic veins cannot be entirely neglected. Although the condition was far advanced when the patient was first seen, anticoagulant therapy might have prolonged her life.

Case 14

An Indian woman aged 29. Progressive dyspnoea, fainting, and lassitude on effort, followed by congestive heart failure over the next 12 months. Examination: Small anxious woman. Cold extremities. Signs of severe pulmonary hypertension, pulmonary venous pressure 6 cm. above sternal angle; augmented "a" wave and poor "x" descent due to tricuspid incompetence. Small regular arterial pulse. B.P. 100/70. Liver 4 cm. below costal margin, tender and pulsatile.

Radiography of Chest.—Pulmonary artery and right ventricular enlargement (Fig. 10); translucent peripheral lung fields due to deficiency of vascular markings.

FIG. 10.—Case 14. Six-foot postero-anterior radiograph of chest, showing enlargement of right atrium, right ventricle, and main pulmonary arteries, with diminished peripheral vascular markings and remarkable translucency of lung fields.

Cardiography.—Grade 3 right ventricular hypertrophy with extensive T-wave inversion in the precordial leads, partly due to digitalis: right atrial hypertrophy (Fig. 9).

Hb 80%; eosinophils 9%; W.B.C. 9,000/c.mm.; serum proteins 7.5 g./100 ml. (albumin 3.1 g., globulin 4.4 g.); A/G ratio 4.7; large beta and gamma peaks. No L.E. cells. Urine: trace of albumin; urinary 5-hydroxyindole acetic acid normal.

Digitalis, diuretics, low-salt diet, and anticoagulants were given. Despite these measures she began to deteriorate. No cause for her severe obliterative pulmonary hypertension was discovered, and examination of the stools revealed no ova to account for a parasitic infestation. Examination of the pelvis was normal, and there was no evidence of chorion-epithelioma or metastasizing tumour.

The diagnosis of polyarteritis nodosa affecting the pulmonary vessels was considered, but was felt to be unlikely in view of the absence of any confirmatory signs. It was thought possible that the patient might have tight mitral stenosis with an extremely high pulmonary vascular resistance and low cardiac output so that the classical murmurs were not audible. Repeated auscultation was undertaken, and on more than one occasion a faint diastolic rumble was audible at the apex. Phonocardiography confirmed the

signs of pulmonary hypertension and showed a soft apical diastolic murmur.

The patient was unfit for angiocardiology or cardiac catheterization, and as she was deteriorating on full medical treatment an attempt was made to exclude obstructive mitral-valve disease by thoracotomy. If no mitral-valve disease was discovered denervation of the lung root was planned.

Thoracotomy by Mr. W. P. Cleland revealed a small left atrium with normal pressure, and elevated right ventricular pressure (75/40 mm. Hg). The mitral valve was found to be quite normal and there was no tumour in the left atrium. The left vagus nerve was divided and all its visible branches to the pulmonary artery were stripped. Despite this procedure the patient failed to regain consciousness after the anaesthetic and died two hours after the operation.

Necropsy.—The heart weighed 274 g. and showed pure right ventricular hypertrophy without valvular disease. The right ventricle was 8 mm. thick in the conus. The lungs appeared normal externally. Post-mortem angiography showed main pulmonary arteries and elastic pulmonary arteries of normal size, but the muscular arteries were grossly narrowed. Microscopically the elastic pulmonary arteries between 4,500 μ and 1,500 μ external diameter were hypertrophied to twice the thickness of corresponding controls and a few showed atheroma. The larger muscular pulmonary arteries (over 200 μ) appeared hypertrophied, but were mostly patent; less than one in seven showed narrowing. Of the small muscular arteries, on the other hand, the vast majority were narrowed or obliterative and many had multiple lumina. A similar degree of narrowing or obliteration was seen in the arterioles. Veins and lung parenchyma were normal. It was concluded that there was sufficient vascular occlusion to account for the pulmonary hypertension, and that, in view of the numerous arteries with multiple lumina, the obliterative was probably embolic although impacted emboli were not seen.

Comment.—The cause of the pulmonary thrombo-embolism was quite unknown. As in Case 12, an underlying arteritis with secondary thrombosis cannot be excluded but seems improbable. Treatment with anticoagulants was valueless because it was not begun until congestive heart failure had manifested itself, by which time most of the pulmonary vascular bed had clearly been obliterated.

Case 15

Boy aged 2½. At 2 years became tired and dyspnoeic. Cyanosed at 2½ years. Examination: Considerable central cyanosis and clubbing. Jugular venous pressure +6 cm. Right ventricular enlargement. Atrial sound. Narrow split of second heart sound with accentuation of pulmonary closure.

Radiotherapy of Chest.—Considerable enlargement of right atrium, right ventricle, and pulmonary artery (Fig. 11).

Cardiography.—Initially grade 4 right ventricular hypertrophy with right atrial enlargement and T-wave inversion in leads V1 and V2. Subsequently the T waves had become positive (Fig. 9). Hb 16.3 g./100 ml.; W.B.C. 5,000/c.mm. Provisional diagnosis: Obliterative pulmonary hypertension with reversed shunt due to atrial or ventricular septal defect (Eisenmenger syndrome).

Cardiac Catheterization.—Pulmonary artery pressure 130/90 mm. Hg, and pulmonary "wedge" pressure 13 mm. Hg; large right-to-left shunt at atrial level, no left-to-right shunt. Arterial O₂ saturation 76% (Table VI).

The child died unexpectedly a few hours after the investigation.

Necropsy.—The heart weighed 160 g. (normal for the age is 58 g.). There was a valvular foramen ovale 5 mm. in diameter but no other congenital deformity. The right ventricle was bigger than the left and was 8 mm. thick in the conus; the left ventricle was 8 mm. thick. The lungs were apparently healthy. Post-mortem angiography was

carried out on both lungs, the arteries being injected on the left and the veins on the right. The pulmonary venous system was normal both in the angiogram and in histological sections. The arterial angiogram was compared with a control of the same age and sex. The only change detected was a moderate dilatation of the segmental arteries and their first and second divisions. The background filling of muscular pulmonary arteries was similar to that of the control.

FIG. 11.—Case 15. Six-foot postero-anterior radiograph of chest, showing considerable enlargement of the right atrium and ventricle. The main pulmonary artery is prominent. Lungs show increased translucency at periphery.

Microscopically no qualitative changes were detected in the pulmonary arterial system; in particular, there was no intimal thickening at any level. There appeared to be hypertrophy of the arterial walls. This was confirmed by measuring the wall thickness as a percentage of the external diameter in the elastic arteries and comparing the figures with those of corresponding arteries in a control. In the latter the mean wall-thickness was 2.2% of the external diameter, while in the patient the mean thickness was 3.3%. Since the arteries measured in the patient were dilated as compared with the control, there was no possibility of the increased wall-thickness being due to contraction, and it appears fair to regard it as true hypertrophy. The elastic pattern in the large arteries was also studied, and it was of aortic pattern. This finding is consistent with the assumption that the hypertension was congenital. Since, however, the elastic pattern at 2 years 9 months was not fully changed to pulmonary types in normal controls this finding is of uncertain significance.

Since parenchymatous lung disease and congenital heart disease could be excluded, and since the only demonstrable change in the pulmonary vasculature was a pure medial hypertrophy, we believe that this child suffered from true idiopathic pulmonary hypertension.

Comment.—The histological findings leave little doubt that the condition was not due to thrombo-embolism. The sudden onset of symptoms at the age of 2 in a previously healthy child suggests that the condition may have been acquired and been due to some unknown process causing excessive pulmonary arteriolar tone and progressive pulmonary hypertension. The central cyanosis was explained by a shunt from right

to left atrium through the patent foramen ovale. Failure of the neonatal high pulmonary vascular resistance to fall during the first two years of life, and persistence of the thick-walled foetal type of pulmonary arterioles such as occurs in the Eisenmenger syndrome, might be considered as a cause, but it is unusual for the pulmonary vascular resistance to remain elevated at birth unless there is a defect capable of producing a large left-to-right shunt (Wood, 1958b). But personal experience has shown that the Eisenmenger reaction can, very occasionally, occur in patients with only a small septal defect. However, the diagnosis in this boy must presumably be regarded as true "idiopathic" pulmonary hypertension, which has previously been reported in children (Goodale and Thomas, 1954; Berthrong and Cochran, 1955; Schafer *et al.*, 1956; Evans *et al.*, 1957; Chapman *et al.*, 1957) and may have a familial incidence (Fleming, 1960). This case contrasts with the others in group 2 in having idiopathic rather than thrombo-embolic hypertension at an early age.

Case 19

An Egyptian woman aged 42. Effort intolerance all her life. Heart murmur at age 34, congenital heart failure at 35. Several syncopal attacks with convulsions. Examination: Obese. Jugular venous pressure +5 cm. Long systolic thrill at left sternal edge. Grade 4 long ejection murmur at pulmonary area; pansystolic murmur at lower left sternal border. Pulmonary closure soft and delayed. Soft pulmonary diastolic and apical diastolic murmur. B.P. 110/80 mm. Hg.

Cardiography.—Grade 4 right ventricular hypertrophy, right atrial enlargement, and T-wave inversion from V1 to V7 (Fig. 9).

Radiography of Chest.—Marked cardiomegaly with massive right atrium, right ventricle, and pulmonary artery and main branches; peripheral pulmonary artery exiguous. E.E.G. normal. Hb 14.7 g./100 ml. It was thought initially that the patient had pulmonary stenosis and a ventricular septal defect of unusual type.

Cardiac Catheterization.—Pulmonary artery pressure 106/42 mm. Hg (mean 55); cardiac output 2.7 l./min.; arterial O₂ saturation 82%; pulmonary "wedge" pressure 8 mm. Hg. No left-to-right shunt (Table VI).

Pulmonary Arteriography.—Large main pulmonary arteries with pruning of small branches; no area of localized obliteration: segmental branches tortuous (Fig. 12, Table V).

FIG. 12.—Case 19. Postero-anterior projection of pulmonary arteriogram, showing enormous main pulmonary arteries with pruning of segmental branches, which are tortuous. Outline is that of obliterative hypertension without obstruction to large arteries.

A diagnosis of obliterative pulmonary hypertension of unknown cause, presumed thrombo-embolic, possibly secondary to vasoconstriction, was made, and she was started on phenindione. She returned to Egypt and has not been seen since.

Comment.—The physical signs were most unusual in this patient, the loud ejection murmur and soft pulmonary closure being unexplained. A long, loud systolic murmur arising from the pulmonary artery is exceptional in severe pulmonary hypertension with low cardiac output. However, the delay in pulmonary closure may have been due to a partial defect of conduc-

tion in the right bundle branch resulting from right ventricular enlargement, and the pansystolic murmur to tricuspid insufficiency. The history of symptoms from an early age suggests that the condition may have started as "idiopathic" pulmonary hypertension but was succeeded by thrombosis or embolic occlusion. In either event, anticoagulant treatment seemed to offer the only hope of relief.

[The second half of this paper, together with a list of references, will appear in our next issue.]

RUBELLA EMBRYOPATHY

AN INTERIM REPORT ON A NEW ZEALAND EPIDEMIC

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It is firmly established that maternal rubella is a cause of embryopathy and that the risk varies inversely with the duration of pregnancy. However, the likelihood of foetal malformation in a particular pregnancy complicated by rubella remains a matter of speculation, since the incidence has differed widely in reported prospective surveys. The occurrence of an unusually extensive rubella epidemic in 1959 presented an opportunity to determine statistics in New Zealand.

Material and Methods

The time-course of the epidemic is indicated in the Chart which is constructed from the returns of a group of 10 general practitioners who voluntarily notify certain infectious diseases not usually notifiable. General practitioners and obstetricians in the Auckland city area were asked to notify all cases of maternal

Average weekly notification of 10 general practitioners.

rubella irrespective of the period of gestation. Those cases fulfilling the following criteria were included in the survey: (1) the rash was seen and diagnosed as rubella by a doctor, (2) pregnancy was progressing normally at the time of notification, and (3) the date of the last menstrual period and the appearance of the rash were known accurately.

There were 89 acceptable cases. Therapeutic abortion was performed in 15 and spontaneous abortion ended a further seven pregnancies, leaving 67 viable pregnancies for study.

D

Babies were examined soon after delivery by a paediatrician wherever possible. Subsequently each child was examined after the age of 6 months by a paediatrician, an ophthalmologist, an audiometrist, and in some cases by a paediatric cardiologist. Further follow-up visits were arranged at intervals until the presence of a major malformation could be excluded. The ages of the children at the last examination ranged from 10 to 24 months.

Results

Three infants died. The youngest of these was aged 28 hours, and post-mortem examination revealed atelectasis and a patent ductus arteriosus. This is not included as a rubella malformation. The second death occurred at 5 weeks from cardiac failure in a baby with patent ductus arteriosus, atrial septal defect, and bilateral cataracts. The third death occurred at 15 months from pneumonia in an infant with bilateral cataracts, gross mental retardation, brachycephaly, and probable deafness.

Table I gives details of the 12 cases with abnormalities attributed to rubella. This includes the two deaths previously mentioned. Although only one was born prematurely by gestation the average birth weight of these babies was only 5½ lb. (2,610 g.). In all cases with rubella embryopathy, rubella had occurred in the first 15 weeks of pregnancy. Eight of the 12 cases had multiple abnormalities. In all of these babies maternal rubella had occurred within the first eight weeks of pregnancy. Two additional babies had functional murmurs—one was identified as a venous hum (rubella at 16 weeks) and the other murmur disappeared within 12 months (rubella at 22 weeks). The only abnormality found after 15 weeks was the absence of one pinna in a baby whose mother had rubella at 39 weeks' gestation.

Table II lists the frequency of the various types of rubella abnormality. There were nine infants with eye defects, including four with bilateral cataracts, two with unilateral cataracts (one of these with glaucoma in the opposite eye), and three with pigmentation of the retina; one of the latter also had a unilateral cataract. All the babies with cataracts had needling operations at various times during the first year of life. Eight infants had