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THE EISENMENGER SYNDROME

OR PULMONARY HYPERTENSION WITH REVERSED CENTRAL SHUNT*

BY

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[WITH SPECIAL PLATE]

Nomenclature

Eponymous titles are no longer in fashion, because they frequently lend themselves to controversy over historical precedence, invite criticism on the grounds of descriptive inaccuracy, and can usually be replaced with advantage by a scientific name which simultaneously identifies, defines, and classifies the disease in question. The term "Eisenmenger's syndrome," as used in these lectures, therefore requires some explanation, especially since the Editor of the *British Heart Journal* stated recently that it has "outlived [its] usefulness and should no longer be used in clinical medicine" (Brotmacher and Campbell, 1958).

An eponymous title may be justified, however, when it has been introduced by someone singularly entitled to do so (Abbott and Dawson, 1924), when it has become familiar by customary use on an international scale over a period of 34 years, when the aetiology and precise mechanism of the syndrome are still controversial, and when there is no convenient alternative title likely to stand the test of time. Nothing is gained by changing customary nomenclature prematurely. To dispense with the term altogether, and to regard the Eisenmenger complex simply as a variety of ventricular septal defect, is to deny the very essence of the syndrome, for, as will become clear later, its distinguishing feature lies not in the anatomy of the defect, but in the behaviour of the pulmonary circulation.

It may help at this early stage to state precisely what Eisenmenger described.

Dr. Victor Eisenmenger published his paper on "congenital defects of the ventricular septum" in 1897. He described in detail a typical example of the condition that has since become known as Eisenmenger's complex. His patient was a powerfully built man of 32 who gave a history of cyanosis and moderate breathlessness since infancy. The cyanosis increased considerably on effort. He managed well enough, however, and was able to lead an active life until January, 1894, when dyspnoea increased and oedema set in. Seven months later (August) he was admitted to hospital in a state of heart failure.

Examination revealed marked cyanosis, clubbing of the fingers and toes, thickening of the distal joints, and polycythaemia. The venous pressure was raised, the liver distended, and oedema extensive. The right side of the heart was obviously enlarged, and there was a loud systolic murmur, accompanied by a thrill, maximal in the third and fourth left intercostal spaces near the sternal edge. The murmur was not conducted at all well to either the aortic or the pulmonary areas, and would have been regarded as tricuspid had it not been for the lack of a giant *v* wave in the jugular pulse. The pulmonary second sound was not impressive, but a basal diastolic murmur, presumably from pulmonary incompetence, developed later. He improved with rest and digitalis, but collapsed and died more or less suddenly on November 13 following a large haemoptysis.

The clinical diagnosis of ventricular septal defect was based on the systolic murmur and thrill in the third and fourth left interspaces. The haemoptysis was attributed to pulmonary infarction.

Both were confirmed at necropsy. The defect was round and situated in the membranous septum; it measured 2 to 2.5 cm. in diameter, and was placed in such a way that the lumen of the aortic orifice fell half over the left ventricular outflow tract and half over the right. Both aortic and pulmonary valves appeared to be competent. The left ventricle measured 8 to 10 mm. in thickness, the right 10 mm. The latter was much dilated and obviously the bigger chamber. The tricuspid ring was very widely stretched. There was considerable atherosclerosis of the pulmonary artery and its branches, but none in the aorta. In the left upper and right lower lobes of the lungs there was extensive haemorrhagic infarction secondary to multiple thrombosis.

Eisenmenger interpreted the situation as follows: in ventricular septal defect (he wrote) the difference in pressure between the left and right ventricles ensured a left-to-right shunt; the pulmonary circulation was therefore overfilled, the systemic circulation underfilled; increased stiffness of the lungs hindered ventilation and congestion hampered gaseous exchange; cyanosis depended more, however, on the poor systemic circulation —that is, it was peripheral rather than central. He discussed the "riding aorta" at considerable length and concluded that this was caused neither by a congenital fault of rotation nor by the direction of blood flow through the defect, but that it was a more or less

*The Croonian Lectures delivered before the Royal College of Physicians of London on May 13, 1958.

inevitable consequence of the position of the defect itself in relation to the normal anatomy of the parts concerned, and was more apparent than real. Eisenmenger was unaware that the shunt was reversed in the case he described so carefully, despite his statement that a rise in pulmonary vascular resistance—from multiple thrombosis, for example—would equilibrate the pressures in the two circulations and so prevent both shunt and murmur.

His misinterpretation was based chiefly on two observations: first, since the cyanosis had been present from birth, he could not attribute it to reversed shunt from thrombo-obstructive pulmonary hypertension, for the thromboses were terminal; second, the absence of a giant *v* wave in the jugular pulse forced him to ascribe the systolic murmur and thrill to a left-to-right shunt through the defect rather than to tricuspid incompetence. He had no means of knowing that a high pulmonary vascular resistance might exist from birth independent of thrombo-obstructive lesions, and he was obviously unaware of the character of the venous pulse in cases of tricuspid incompetence with normal rhythm. In his honour, however, may be enumerated the following: (1) The case history that he described was complete, faultless, and wholly typical. (2) He stated that in otherwise uncomplicated ventricular septal defect pulmonary hypertension resulting from obstruction in the pulmonary circulation would abolish both left-to-right shunt and the classical murmur. (3) He took great pains to prove that an overriding aorta played no part in the physiological disturbance of the circulation.

Conflicting Hypotheses

Abbott and Dawson (1924) attributed the cyanosis of Eisenmenger's case to a right-to-left shunt through the defect on account of the overriding aorta, and Abbott described in detail a similar case herself (Baumgartner and Abbott, 1929). In her well-known table, which has recently been reproduced (Abbott, 1952), she analyses seven such cases. She ascribed the systolic murmur to the interventricular shunt.

Taussig (1947) stated that "the essential feature of the Eisenmenger complex is that the aorta is dextroposed and overrides the right ventricle." That she was dissatisfied with this explanation, however, is clear from several other statements that she made: namely, "The dynamics of the circulation may be such that the powerful ejection of blood from the left ventricle into the aorta draws by suction a larger volume of blood from the right ventricle into the aorta than would be shunted through the opening if the force of ejection were the same in the two ventricles" (cf. the common ejectile force from both ventricles invoked by Edwards, 1957); and, "The cause of the cyanosis in these patients is by no means clear. In such individuals there may well be some alteration in the pulmonary epithelium or in the pulmonary vascular bed which prevents complete oxygenation of the blood in its passage through the lungs" (Taussig and Blalock, 1947). At that time she believed that "cyanosis was usually absent in infancy and early childhood," and may have been unable to correlate this with the override hypothesis.

Brown (1950) considered that the essential features of the Eisenmenger complex consisted of "a high defect of the interventricular septum, dextroposition of the aorta, and a normal or dilated pulmonary artery." He stated that the cyanosis was due partly to a right-to-left shunt depending on the degree of override, and partly to "failure of adequate oxygenation in the lungs."

Thus 50 years of cardiology failed to advance Eisenmenger's description, and opinion remained opposed to his belief that the overriding aorta was irrelevant. It was not until 1947 that anyone followed up his suggestion that obstruction in the pulmonary vascular bed would be expected to raise the pulmonary blood pressure and to abolish both the left-to-right shunt and the murmur of uncomplicated ventricular septal defect. This was when Bing *et al.* (1947) demonstrated pulmonary hypertension at systemic level with bidirectional shunt in five cases of Eisenmenger's complex.

Since then innumerable studies have confirmed that pulmonary hypertension at systemic level is invariable in Eisenmenger's complex, typical earlier papers being those of Burchell *et al.* (1950), Wood (1950, 1952), Selzer and Laqueur (1951), and Soulié *et al.* (1953). The part played by pulmonary hypertension may be summed up in Selzer's words "that the most characteristic feature of Eisenmenger's complex is the presence of severe pulmonary hypertension."

As a result of such studies the concept quickly grew up that Eisenmenger's complex is pulmonary hypertension with reversed or bidirectional shunt through a large ventricular septal defect. Anatomical overriding or dextroposition of the root of the aorta may or may not be found at necropsy in clinically indistinguishable cases.

This has not ended the controversy, however, but has merely shifted the grounds of differing opinion. The debate now centres in the nature of the high pulmonary vascular resistance. Does this result from persistence of the foetal type of pulmonary circulation (Civin and Edwards, 1950), independent coincidental congenital disease of the pulmonary circulation (Evans, 1951; Kohout *et al.*, 1955), degenerative or thrombo-obstructive pulmonary vascular disease secondary to high flow or hyperkinetic pulmonary hypertension (Whitaker, 1958; Brotmacher and Campbell, 1958), transmission of a high left ventricular pressure to the pulmonary circulation owing to lack of obstruction at the site of a large defect (Edwards, 1957; Brotmacher and Campbell, 1958), a high right ventricular pressure initially determined by the override so that the right ventricle has to help support the systemic blood pressure (Soulié *et al.*, 1953), or initially from reactive pulmonary vasoconstriction, degenerative and late thrombo-obstructive pulmonary vascular disease being secondary (Wood, 1952, 1956, 1958)? With so many conflicting hypotheses concerning the origin and maintenance of this pulmonary hypertension at the present time, it would be begging the question to introduce new aetiological nomenclature.

Definition

But Eisenmenger's complex may be redefined with great advantage. Almost all writers have defined it as a cyanotic form of congenital heart disease with a large ventricular septal defect and overriding of the aorta, and in recent years pulmonary hypertension has been added. In the light of present knowledge, however, and fitting better with Eisenmenger's description, ideas, and insistence on the artificiality of the override, a better definition would be *pulmonary hypertension at systemic level, due to a high pulmonary vascular resistance* (over 800 dynes sec./cm.^{5}), *with reversed or bidirectional shunt through a large ventricular septal defect (1.5 to 3 cm. across)*. Rarely the systemic and pulmonary vascular resistances may be so delicately balanced as to permit of no material shunt in either direction. To have no definitive name by which to call such cases would be intolerable; nor would ventricular septal defect with pulmonary hypertension suffice, for many such cases are not in the same category at all, the pulmonary hypertension being mainly hyperkinetic (due to a high pulmonary blood flow). The definition of Eisenmenger's complex given above is far too cumbersome to use routinely, and so there is little choice but to continue to employ the eponymous term itself, at least for the time being.

Now this modern definition of Eisenmenger's complex leads on to another very important consideration. The syndrome described is essentially pulmonary hypertension with reversed or bidirectional shunt, and it *matters very little*

where the shunt happens to be. At the bedside it is usually easy enough to diagnose the essential physiological situation, but often extremely difficult, if not impossible, to identify the site of the defect; indeed, to do so with certainty may still prove very difficult after full physiological investigation, including cardiac catheterization, angiocardiography, dye dilution curves, and other special tests. The frequency with which necropsies disclose an anatomical diagnosis different from what was expected is as embarrassing as it is educational. The fact is that a remarkably similar physiological situation occurs when any large communication between the two circulations is complicated by a pulmonary vascular resistance around systemic level. There are no fewer than 12 different anatomical abnormalities which may present in this way (Table I), and, in view of the frequent uncertainty

TABLE I.—*Causes and Frequency of Eisenmenger's Syndrome*

	Total No. of Cases	No. with Eisenmenger Reaction	Frequency of Eisenmenger Reaction (%)
i. Patent ductus arteriosus	180	29	16
ii. Aorto-pulmonary septal defect	10	6	60
iii. Persistent truncus arteriosus	4	4	100
iv. Transposition of the great vessels (with V.S.D.)	12	7	58
v. Corrected transposition (with V.S.D.)	3	3	100
vi. Single ventricle	6	6	100
vii. Ventricular septal defect	136	21	16
viii. Common atrio-ventricular canal or persistent ostium primum	21	9	43
ix. Single atrium	—	—	
x. Atrial septal defect	324	19	6
xi. Hemianomalous pulmonary venous drainage	3	0	0
xii. Total anomalous pulmonary venous drainage	6	1	17
Site uncertain	22	22	
	727	127	17·5

regarding the exact anatomical diagnosis, a term which embraces them all is highly desirable. Since Eisenmenger's case, when seen clinically at that time, was no more likely to have had a ventricular septal defect than any of the other 11 conditions tabulated, with the possible exception of a simple atrial septal defect, I suggested extending the meaning of the expression "Eisenmenger's syndrome" to embrace these 12 conditions when behaving physiologically like "Eisenmenger's complex" proper (Wood, 1956).

In these lectures I propose to elaborate this theme, to discuss in detail the differential diagnosis between the various members of the group both at the bedside and by means of special investigations, to probe the mechanism responsible for the high pulmonary vascular resistance, and finally, in synthesis, to offer a hypothesis which may explain both the common physiological behaviour and the exceptions to it.

Material

The analysis is based on a consecutive series of 127 cases of Eisenmenger's syndrome (as just defined) studied personally over a period of 11 years. Nearly all were catheterized, angiocardiography was carried out when considered necessary, and during the last year dye dilution curves have also been recorded. Eighteen of these 127 patients died, and a necropsy was obtained in 15 of them. The clinical diagnosis of the anatomical defect was correct in nine, half correct but incomplete in four, wrong in two, and unproved because there was no necropsy in the other three. This represents a completely accurate clinical diagnosis in only 60%, or a rate of error far in excess of that experienced with any other form of congenital heart disease, and emphasizes the need for a single term to embrace the whole group clinically. Of the total of 127 cases, 22 have been rejected on the grounds of too much uncertainty with regard to the site of the defect.

In addition, and owing to the kindness of many friends in Britain, I have been able to collect details of a further 38 cases which were well worked out during life and which subsequently came to necropsy. In these the shunt was aorto-pulmonary in 16, interventricular in 11, and interatrial in 11. To avoid duplication—for no doubt many of these cases have been or will be reported elsewhere—I am not including them in the analysis, but merely using them as a means of checking the accuracy of other data, and to facilitate the interpretation of my own findings. Without such necropsy control too many errors of interpretation are likely to be perpetuated. When data from these 38 post-mortem cases is used in this paper the fact is stated.

My own material is presented in Table I and represents 17.5% of a total of 727 cases of congenital heart disease with a communication of some sort between the systemic and pulmonary circulations. The frequency of the Eisenmenger reaction in each type of defect is given in the third column. It simplifies matters considerably if cases are regarded as having a shunt at aorto-pulmonary, ventricular, or atrial level, without stating specifically the nature of the defect. For example, both patent ductus and aorto-pulmonary septal defects have an aorto-pulmonary shunt, although there are specific differences between the two; again, persistent truncus, transposition or corrected transposition with ventricular septal defect, ventricular septal defect itself, single ventricle, and persistent ostium primum all shunt to an important degree at ventricular level, and in this respect may be taken together; similarly, atrial septal defect, single atrium, hemianomalous pulmonary venous drainage, and total anomalous pulmonary venous drainage directly or indirectly into the right atrium form a third group, all having the shunt at atrial level.

Frequency of the Eisenmenger Reaction

Eisenmenger's syndrome, as defined in this paper, accounted for 8% of the first 1,000 cases of congenital heart disease in my series.

Since necropsies prove conclusively that the Eisenmenger reaction is excited only by large communications between the two circulations, the frequency of such reactions in relation to the site of the communication should be assessed only as a percentage of large defects. In the 53 cases of Eisenmenger's syndrome that came to necropsy, the minimal size of aorto-pulmonary, ventricular, and atrial communications was 0.7 cm., 1.5 cm., and 3 cm. respectively. In the absence of the Eisenmenger reaction, defects of this order result in pulmonary blood flows ranging between 15 and 30 litres per minute, or pulmonary/systemic flow ratios of 3.5 to 6, at least in respect of aorto-pulmonary and ventricular communications; atrial septal defects are probably all large enough to excite the Eisenmenger reaction, but only those giving rise to similar pulmonary blood flows have been included in the calculations. The clinical features of these relatively large defects were in harmony with the physiological findings. It is appreciated that these are very artificial criteria for assuming that the defects were as large as those found in the Eisenmenger syndrome, but the object is simply to exclude from the estimates all those cases of mild or moderate severity which are known never to excite the Eisenmenger reaction.

The frequency of the Eisenmenger reaction in relation to large communications between the two circulations is given in Table II. It will be seen that Eisenmenger's syndrome occurs in over half of the cases with aorto-pulmonary or ventricular communications, but in only 9% of those with large atrial septal defects, and it is emphasized that this six-

TABLE II.—*Frequency of the Eisenmenger Reaction in Relation to the Site and Size of the Defect*

Site of Communication	Total No. of Cases	No. with Large Defects	No. with Eisenmenger Reaction	No. with Eisenmenger Reaction Expressed as percentage of Large Defects
Aorto-pulmonary	190	66	35	53
Interventricular	179	97	50	52
Interatrial	333	214	20	9

fold difference must be a conservative estimate, for it is probable that communications at aorto-pulmonary or ventricular level *always* excite the Eisenmenger reaction if they are of sufficient size, and that nearly all atrial septal defects are critical in the sense defined.

No explanation of the physiological mechanism underlying the Eisenmenger reaction is tenable unless it explains this remarkable difference.

Age

The average age of uncomplicated cases of patent ductus, ventricular septal defect, and atrial septal defect when first seen was 18, 13, and 26 respectively; when complicated by the Eisenmenger reaction otherwise similar cases had an average age of 19, 22, and 35 respectively.

The great majority of cases of uncomplicated patent ductus and ventricular septal defect (67% and 80% respectively) are referred to specialist clinics in childhood or adolescence. Early recognition of these cases probably depends on their characteristic and impressive murmurs. The bruit de Roger is especially difficult to overlook in view of its central position, and that may be why ventricular septal defect is recognized sooner than patent ductus, for a continuous murmur high up under the left clavicle may not be heard on casual auscultation. That the Eisenmenger group is referred somewhat later may be explained by the absence of these murmurs. Less than 50% of patients with uncomplicated atrial septal defect are referred in childhood or adolescence, no doubt for the same reason; but the much later reference of atrial cases with the Eisenmenger reaction can have no such explanation, and must mean that pulmonary hypertension in atrial septal defects is a late-acquired characteristic. That it is not an inevitable consequence of a high pulmonary blood flow acting on the pulmonary vasculature over a long period of time, however, is shown by the fact that 12% of uncomplicated cases of atrial septal defect and 15% of those with the Eisenmenger reaction were in persons between 50 and 75 years of age. It is clear that 70 years of pulmonary plethora may fail to raise the pulmonary vascular resistance.

Sex

Fig. 1 shows that the sex distribution in patent ductus (M/F=1/2) and ventricular septal defect (M/F=1) is the same in uncomplicated cases and in those with the Eisenmenger reaction. This disposes of the idea that Eisenmenger's complex might be ventricular septal defect associated with coincidental primary pulmonary hypertension, for the M/F sex ratio in the latter is 1/4.

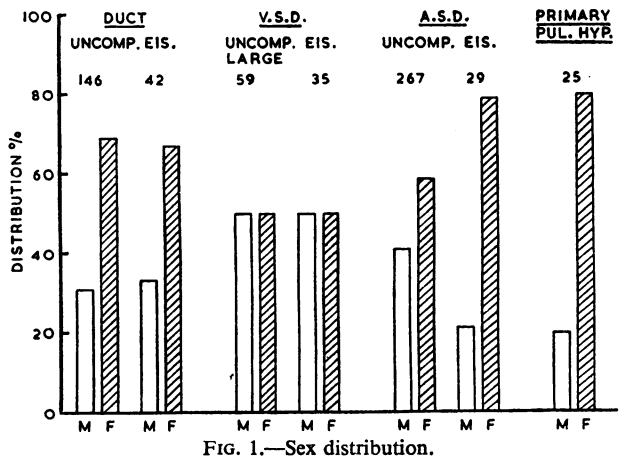

FIG. 1.—Sex distribution.

In atrial septal defect, however, females are more common in the Eisenmenger group, in which they are as frequent as in primary pulmonary hypertension. This confirms that atrial septal defect complicated by a high pulmonary vascular resistance differs fundamentally from Eisenmenger's complex, and from patent ductus with reversed shunt. Its late onset has already been offered as evidence that it is acquired, and now its high female bias suggests that it may have some factor in common with primary pulmonary hypertension.

Associated Anomalies

In a consecutive series of 1,250 cases of congenital heart disease certain relationships between anomalies outside the cardiovascular system and particular kinds of cardiovascular malformation have become firmly established. These may be enumerated as follows.

1. When congenital heart disease occurred in more than one member of a family, which it did in 5% of cases, it was nearly always of the same kind. This rule held good for patent ductus, ventricular septal defect, and atrial septal defect, as well as for coarctation, aortic stenosis, Fallot's tetralogy, simple pulmonary stenosis, and familial cardiomegaly.

2. Arachnodactyly was far more often associated with atrial septal defect than with any other anomaly, as endorsed by Reynolds (1950), and occurred in 15% of uncomplicated cases and in 12% of those with pulmonary stenosis and reversed interatrial shunt.

3. Deformities of the limbs were associated with ventricular septal defect in seven out of eight instances. Each of the three with polydactyly had Fallot's tetralogy.

4. Maternal rubella favoured patent ductus, as stated by Wesselhoeft (1949). When no history of maternal rubella was obtained, cataract and deafness might have similar significance.

5. Mongols are said to be especially prone to have persistent ostium primum or common atrioventricular canal (Brown, 1950). The latter was proved at necropsy in one of our more difficult cases with the Eisenmenger reaction.

6. Hyperteleorism alone, or as part of Turner's syndrome, was recognized in 20% of cases with pulmonary stenosis and reversed interatrial shunt, but in only 1% of cases of Fallot's tetralogy.

In the differential diagnosis of Eisenmenger's syndrome due regard should be paid to these observations.

Clinical Features

Onset.—It was usually possible to establish from the history when the Eisenmenger syndrome was first fully developed. Cases with inadequate data were excluded from the analysis. Table III shows that the Eisenmenger syndrome started in infancy in about 80% of cases of patent ductus and ventricular septal defect, but in only 8% of cases of atrial septal defect; even more remarkable was the fact that it started in adult life in only 2% of cases of ventricular septal defect but in 92% of cases of atrial septal defect. No further proof is needed that a high pulmonary vascular resistance in atrial septal defect is acquired. Conversely, a high pulmonary vascular resistance in the great majority of cases of patent ductus and ventricular septal defect seems to be established at birth, or at the latest in infancy.

TABLE III.—*Onset of Eisenmenger Syndrome*

	Duct. %	V.S.D. %	A.S.D. %
Infancy	79	83	8
Childhood and adolescence	4	15	—
Adult life	17	2	92

Effort Intolerance.—As described elsewhere, four grades of effort intolerance are recognized: slight, moderate, considerable, and gross—or, of course, there may be none. Fig. 2 shows clearly that in the Eisenmenger group patent ductus is by far the best tolerated, nearly half of such cases having only slight breathlessness on effort or none at all. There was little difference between ventricular septal defect and atrial septal defect in respect of effort intolerance; the average grading was 2.5 in both—three-quarters of a grade higher than in patent ductus. The lack of symptoms in patent ductus with reversed shunt is attributed to the relatively normal oxygen tension of blood going to the head

and neck ; in most cases only the blood passing down the descending aorta below the junction of the duct is appreciably desaturated. As a corollary this explanation demands that breathlessness in the Eisenmenger syndrome is due to a low arterial oxygen saturation in blood passing through the chemoreceptors of the head and neck.

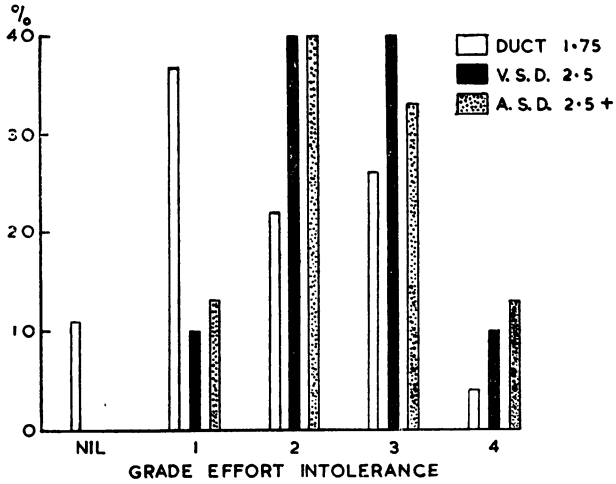

FIG. 2.—Degree of effort intolerance in the three main groups of Eisenmenger's syndrome.

Special Symptoms.—Apart from breathlessness, the chief symptoms of the Eisenmenger syndrome are angina pectoris, syncope, haemoptysis, and congestive heart failure, in that order of onset. The frequency of each in relation to the site of the shunt is given in Table IV.

TABLE IV.—*Symptoms of Eisenmenger Syndrome*

	Duct. %	V.S.D. %	A.S.D. %
Angina	20	14	15
Syncope	15	14	10
Haemoptysis	12	33	25
Congestive failure	12	8	10

Haemoptysis

The frequency of haemoptysis is emphasized. Its occurrence in 33% of cases of Eisenmenger's complex contrasts sharply with its 4% incidence in a parallel series of 27 cases of primary pulmonary hypertension ; and its occurrence in 25% of cases of atrial septal defect with pulmonary hypertension and reversed shunt contrasts equally sharply with its 3% incidence in 300 cases of uncomplicated atrial septal defect. It is clear from these figures that haemoptysis is not a complication of pulmonary hypertension *per se*, nor of pulmonary plethora.

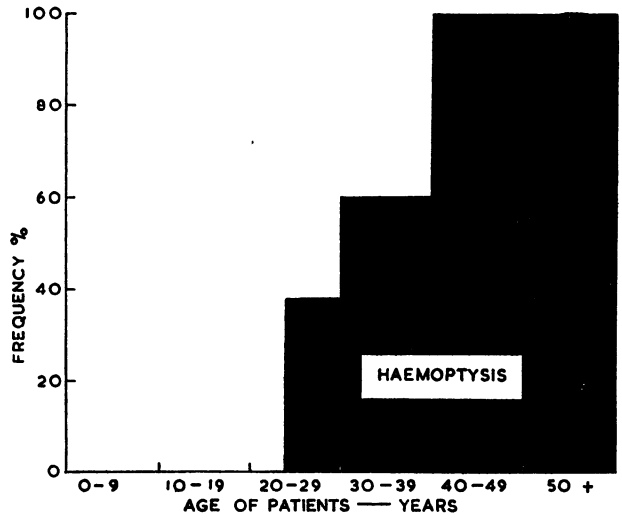

FIG. 3.—Frequency of haemoptysis in relation to age in Eisenmenger's complex.

In patients with Eisenmenger's complex haemoptysis was never seen before the age of 24, but thereafter it occurred with increasing frequency, to reach the 100% mark by the age of 40 (Fig. 3).

At necropsy the common cause of these haemorrhages is pulmonary infarction from pulmonary artery thrombosis (see Pathology), as in Eisenmenger's case. The factor which encourages such thrombosis in Eisenmenger's syndrome rather than in primary pulmonary hypertension may well be polycythaemia ; and the factor which determines its onset relatively late in the course of the disease is probably atherosclerosis.

A large haemoptysis was the immediate cause of death in 29% of 42 fatal cases. As a rule, the patient collapsed and died within a few minutes of the onset of the haemorrhage. The sudden reduction of blood volume and fall in central venous pressure may excite a vasovagal reaction as described by Barcroft *et al.* (1944), and collapse of the peripheral resistance must result in an abrupt and profound fall in arterial oxygen tension as the blood swings away from the lungs.

Cyanosis

Cyanosis, clubbing of the fingers, and polycythaemia were all most florid when the shunt was at ventricular level and least with a patent ductus. Thus no case of Eisenmenger's complex was truly acyanotic even at rest, whereas 60% of cases with patent ductus and reversed shunt were acyanotic in the head and upper extremities. At the other end of the scale 42% of those with ventricular septal defect had considerable or gross cyanosis, compared with only 4% of those with patent ductus.

Clubbing of the fingers was, of course, closely associated with cyanosis: it was absent in 76% of the cases with patent ductus and considerable in only 5%; the respective figures for Eisenmenger's complex were 3% and 36%. With both cyanosis and clubbing cases with interatrial shunt occupied an intermediate position.

Polycythaemia was rather less unevenly distributed, indicating that hypoxia in the lower part of the body provided some stimulus to blood formation.

Differential cyanosis with or without differential clubbing was seen in 50% of cases with reversed shunt through a patent ductus. Not infrequently the left hand was an intermediate colour between the pink right hand and the blue feet.

Squatting was uncommon in all members of the Eisenmenger group, but was relatively more frequent with ventricular septal defect (15%) than with atrial septal defect (5%) or patent ductus (3%).

These five facets of arterial desaturation show that shunt reversal in the Eisenmenger complex is usually greater than in cases with atrial septal defect, and that shunt reversal in patent ductus is usually deflected down the descending aorta.

Pulse and Blood Pressure

The *pulse* was usually small or normal. It was small about twice as often with atrial septal defect (88%) as with ventricular septal defect (37%) or patent ductus (50%). When full or water-hammer in quality, atrial septal defect was never present except in one case with severe anaemia. Bidirectional aorto-pulmonary shunts otherwise provided the only examples of water-hammer pulses (12%).

The blood pressure was much the same in the three main groups comprising Eisenmenger's syndrome, averaging 117/74 with patent ductus, 116/78 with ventricular septal defect, and 110/72 with atrial septal defect.

Jugular Venous Pressure and Pulse.—Both venous pressure and pulse were commonly normal, but a small dominant *a* wave measuring about 3 mm. Hg was seen in 20 to 25% of cases of each type. A giant *a* wave measuring

at least 6 mm. Hg was seen in 18% of cases with atrial septal defect, but very rarely when the shunt was elsewhere. Large *v* waves from tricuspid incompetence occurred in 5% of all cases.

Palpation and Auscultation

As might be expected from previous evidence indicating that pulmonary hypertension in atrial septal defect is commonly acquired, the most pulsatile right ventricles were three times as common in this group, in which a considerable right ventricular lift was recorded in 57%. In the majority of other cases a left parasternal impulse was either slight or moderate in degree. The left ventricle was nearly always impalpable or could not be recognized. An impulse over the pulmonary artery was felt in approximately 66% of cases in each group.

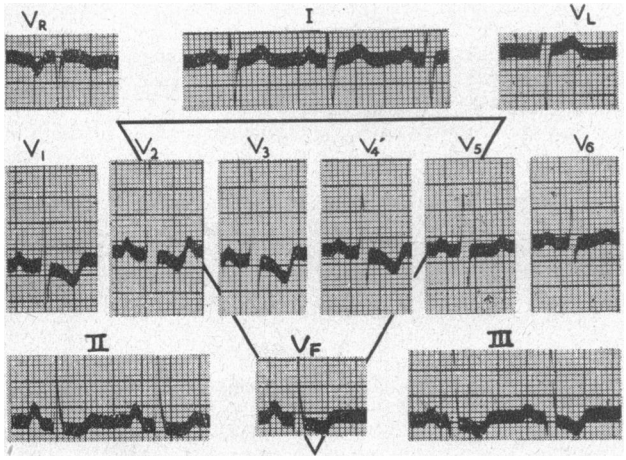

FIG. 4.—Electrocardiogram in a case of pulmonary hypertension with reversed interatrial shunt showing absent Q waves in V_5 and V_6.

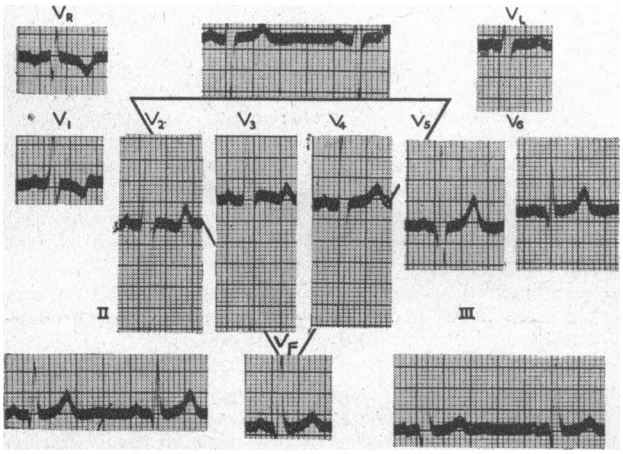

FIG. 5.—Electrocardiogram in a case of pulmonary hypertension with bidirectional shunt through a patent ductus showing prominent Q waves in leads V_5 and V_6.

Right atrial gallop was heard in 38% of cases with interatrial shunt, but in only 2 to 3% of the others, a relationship similar to that of the giant *a* wave. A sharp *pulmonary ejection click* was heard in about two-thirds of all cases. *Diastolic gallop* was rare (3%).

A functional *pulmonary ejection murmur*, usually of moderate intensity and relatively short duration, occurred in 80% of all cases, and was loud in one-quarter of them. A thrill accompanied one-half of the loud murmurs, and was therefore present in 10% of all cases.

A *pulmonary diastolic murmur* was heard in 50 to 66% of all groups, and was accompanied by a thrill in 10%.

The *second heart sound* was single in 55% of cases of Eisenmenger's complex, but in only 6% of cases with patent ductus and in none with atrial septal defect. Close splitting of the second sound did not distinguish Eisenmenger's complex from patent ductus with reversed shunt. Obvious or wide splitting of the second sound, however, was rare (12%) in Eisenmenger's complex, but common (50%) with patent ductus, and very much the rule (86%) with atrial septal defect. The split widened with inspiration in the normal manner in cases with patent ductus, but remained fixed in cases with atrial septal defect.

The pulmonary component of the second sound was palpable and sharply accentuated in 90% of cases with patent ductus or ventricular septal defect, and in 57% of cases with atrial septal defect. The lower incidence in the atrial group was attributed to the frequency with which such cases had a pulmonary artery pressure below systemic level (see below).

Electrocardiogram

The *P wave* was normal in 55% of all cases, 2 to 2.5 mm. high in 25%, and 3 mm. high or more (rarely) in 20%. Measurements were similar in all groups. Two patients with patent ductus had a P mitrale.

Paroxysmal atrial tachycardia or flutter (rarely fibrillation) occurred in nearly 20% of those with atrial septal defect, but in none with unquestionable ventricular septal defect, and in only 5% (fibrillation) of those with patent ductus.

Q waves were absent in lead V_6 (Fig. 4) in 87% of the atrial cases, but in only 18% of those with patent ductus. Good Q waves were seen in both leads V_5 and V_6 in only one of the atrial cases, but in half of those with patent ductus (Fig. 5). Patients with Eisenmenger's complex occupied an intermediate position in respect of Q, which was absent in lead V_6 in two-thirds, and present in both leads V_5 and V_6 in one-quarter.

The QRS-T complex showed considerable (or gross) right ventricular preponderance in about half of all cases (Fig. 6),

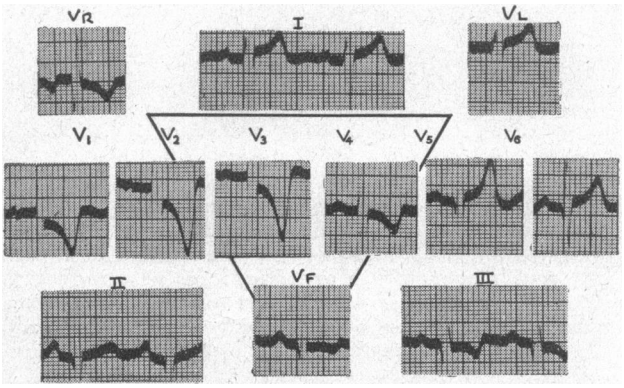

FIG. 6.—Gross right ventricular preponderance in a case of Eisenmenger's syndrome.

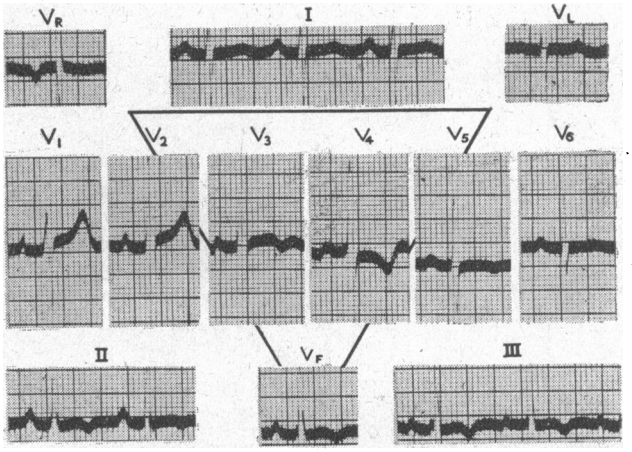

FIG. 7.—Electrocardiogram showing relatively minor changes in a case of Eisenmenger's complex proper.

but significantly more so (80%) in cases with atrial septal defect than when the shunt was elsewhere (44%). Absent or only slight right ventricular preponderance was never seen in atrial cases, but occurred in 37% of the others (Fig. 7). In about two-thirds of the 22% without simple right ventricular preponderance there was some evidence of left ventricular enlargement in addition to right (chiefly with patent ductus) or the QRS complexes were large and biphasic right across the chest (chiefly with ventricular shunts).

X-ray Appearances

A right-sided aortic arch was demonstrated in 16% of cases of Eisenmenger's complex, but was never associated with patent ductus or atrial septal defect. Since a right-sided arch was not seen with uncomplicated ventricular septal defect, whereas it occurred in 17% of a parallel series of 150 cases of Fallot's tetralogy, its association with Eisenmenger's complex cannot be ignored embryologically.

A rounded shadow overlying the aortic knuckle, which therefore looked double-edged, was seen in two cases of patent ductus (Special Plate, Fig. A), and was believed to represent the duct itself.

Calcification of the duct, or in one or other of the great vessels at the junction of the duct, was seen in only one case.

As a rule, however, the characteristic feature at the base in all varieties of the Eisenmenger syndrome is *conspicuous dilatation of the pulmonary arc.* This was so in 90% of the whole series (Fig. B).

Dilatation of the right branch of the pulmonary artery was remarkable in only 6% of cases with ventricular septal defect, and 10% of cases with patent ductus; with atrial septal defect, on the other hand, it was the rule, and occurred in no less than 60% (Fig. C). Since conspicuous dilatation of the right branch of the pulmonary artery is common in cases of uncomplicated atrial septal defect, but was not a feature of a parallel series of 27 cases of primary pulmonary hypertension, nor of 60 cases of mitral stenosis with extreme reactive pulmonary hypertension, it must be concluded that a large right pulmonary artery depends upon increased flow rather than upon high pressure, and therefore provides further evidence that pulmonary hypertension in atrial septal defect is usually acquired.

Diminished pulmonary vascular markings beyond the main hilar branches, due to oligaemia, were observed in 54 to 62% of all groups (Fig. D). Increased markings, radiologically interpreted as indicating increased flow, were seen in 10 to 23% of all groups (Fig. E). In the remainder (about 23%), the peripheral vascular markings could not be distinguished from normal (Fig. F).

Cardiac enlargement, attributed mainly to the right ventricle, was greatest with atrial septal defect. Thus little or no radiological enlargement was recorded in 54% of those with patent ductus, 60% of those with ventricular septal defect, and 15% of those with atrial septal defect. In contrast, considerable enlargement was observed in 15%, 17%, and 50% of these groups respectively. Dilatation, due to considerably increased flow in the past, is the probable explanation for the larger hearts of the majority of the atrial cases.

Summary of Clinical Features

Common to all cases of the Eisenmenger syndrome are central cyanosis, clubbing, polycythaemia, and breathlessness on effort, usually dating from infancy or early childhood; recurrent haemoptysis begins in adult life, and may prove fatal; if patients survive other risks, such as cerebral abscess, bacterial endocarditis, and ill-advised surgical intervention, they succumb finally to heart failure, usually in the fourth or fifth decade.

Physical signs common to all groups include a small or normal pulse, normal venous pressure with or without slight dominance of the *a* wave, an impalpable left ventricle, a slight or moderate lift over the right ventricle and pulmonary artery, a loud pulmonary ejection click followed by a short pulmonary systolic murmur, a palpable and sharply accentuated pulmonary component of the second heart sound, and often a loud pulmonary diastolic murmur. The characteristic venous pulse and auscultatory signs of tricuspid incompetence may complicate the picture.

The electrocardiogram shows a normal or rather prominent P wave, and usually moderate or considerable right ventricular preponderance.

Skiagrams reveal conspicuous dilatation of the pulmonary artery, slight to moderate cardiac enlargement (chiefly of the right ventricle), and peripheral vascular markings that are usually oligaemic, but which may be normal or even slightly plethoric.

Distinguishing Features of Individual Members of the Eisenmenger Group

Patent ductus with the Eisenmenger reaction has the following special characteristics which help to distinguish it from other members of the group. Effort intolerance is relatively slight, squatting is very rare, and most cases are acyanotic when first seen. Differential cyanosis is pathognomonic. The only helpful physical sign is clear splitting of the second heart sound, which widens normally during inspiration. An electrocardiogram with good Q waves in leads V_5 and V_6 favours a shunt at aorto-pulmonary or ventricular level. Skiagrams may reveal a rounded shadow overlying the aortic knuckle, or characteristic calcification, both of which are highly suggestive, but rare.

Aorto-pulmonary septal defect with a high pulmonary vascular resistance resembles Eisenmenger's complex closely; indeed, there is no bedside method of distinguishing the two, and neither electrocardiogram nor skiagrams are helpful.

Eisenmenger's complex itself is the most probable diagnosis if the patient is male. Breathlessness, cyanosis, and clubbing date from infancy or early childhood in the great majority of cases, and squatting is very suggestive. A single second heart sound strongly favours ventricular septal defect. A pansystolic murmur and thrill in the Roger area are rarely caused by a ventricular septal defect with reversed or bidirectional shunt, just as they are never found in Fallot's tetralogy. When present such a murmur may well be mitral, when it suggests persistent ostium primum or common atrioventricular canal, or tricuspid.

Single ventricle is clinically indistinguishable from Eisenmenger's complex.

Persistent truncus with a high pulmonary vascular resistance is physiologically similar to a large aorto-pulmonary septal defect and cannot be distinguished from it at the bedside—or therefore from Eisenmenger's complex. It is excluded, however, by an obviously split second sound and favoured by gross pulmonary and aortic incompetence. Skiagrams do not show the characteristic dilated pulmonary arc of other members of the Eisenmenger group, and dilated right and left pulmonary arteries may be displaced cranially (Fig. G).

Transposition or corrected transposition with ventricular septal defect and a high pulmonary vascular resistance is clinically identical with Eisenmenger's complex. Skiagrams, however, may show the narrow vascular pedicle described by Taussig (1938), when the aorta lies immediately anterior to the pulmonary artery (Fig. H); or a left-sided ascending aorta forming a long slightly convex shadow below the aortic knuckle and overlying the left branch of the pulmonary artery, for which it may well be mistaken—indeed, its true identity may not be revealed until its continuity with the great vessels is demonstrated during cardiac catheterization or by means of angiocardiography (Fig. I). Good examples were described by Goodwin *et al.* (1949) and by Astley and Parsons (1952). Corrected transposition may be suggested by partial or complete atrio-ventricular block (Walker *et al.*, 1958).

Atrial septal defect with reversed shunt secondary to a high pulmonary vascular resistance is unusual in men. Symptoms, especially cyanosis, are rare in infancy and childhood, and commonly do not appear before adult life. A late onset is always strongly in favour of atrial septal defect. It is probable that most of those that do begin in infancy are persistent ostium primums or common atrio-ventricular canals. Of the physical signs, a giant *a* wave and right atrial gallop are very suggestive, and a well-split second sound which does not widen on inspiration is virtually diagnostic. The right ventricle and atrium are usually larger in atrial septal defect than in other members of the Eisenmenger group, particularly in those in which cyanosis began in adult life; this is reflected in both the electrocardiogram and the skiagram. A dense dilated right pulmonary artery is also very suggestive.

Single atrium with pulmonary hypertension is indistinguishable from atrial septal defect as just described; *hemianomalous pulmonary venous drainage* closely resembles atrial septal defect clinically, but splitting of the second heart sound may vary with respiration. No cases with the Eisenmenger reaction were recognized in the present series. *Total anomalous pulmonary venous drainage* into the superior vena cava or inferior vena cava also resembles atrial septal defect clinically, but is easily recognized by the characteristic skiagram; no such distinguishing feature marks total anomalous pulmonary venous drainage into the coronary sinus. Severe pulmonary hypertension is also rare in these cases.

Physiological Findings

As defined in the introduction, the Eisenmenger syndrome is pulmonary hypertension at or around systemic level due to a high pulmonary vascular resistance (over 10 units) associated with reversed or bidirectional shunt through a large communication between the systemic and pulmonary circulations at aorto-pulmonary, ventricular, or atrial level; occasionally the physiology of the two circulations is so precisely balanced that there is no shunt in either direction. Each member of the group, however, tends to have its own distinctive characteristics.

TABLE V.—*Eisenmenger Syndrome. Physiological Data*

	Duct.	V.S.D.	A.S.D.
Defect catheterized	90%	28%	66%
L.A. samples: O_2 sat. %	—	90–96	
Pul. venous samples: O_2 sat. %	—	95–99	95–99
Pul. cap. ven. pres. mm. Hg.	−1 to 6	0–8	0–6
B.P. minus P.A.P. ,,	Zero	Zero	27/34 in 70%
Bidirectional shunt	42%	90%	84%
Av. increase in O_2 sat. % in chamber receiving direct shunt	8·6	14·5	13
Pul./Sys. flow ratio		0·9	1·0
Pul. blood flow, l./min.	2–7	2·1–7·4	2·1–5·5
Pul. vasc. resistance (units)	22	20	17
Arterial O_2 sat. %	77 (Fem.)	79	82

General Characteristics of the Eisenmenger Syndrome (Table V)

1. *The catheter passed through the defect* in 90% of the ducts, one-third of the aorto-pulmonary windows, 28% of ventricular septal defects, and two-thirds of atrial septal defects.

2. *A patent foramen ovale was penetrated* in four cases of Eisenmenger's complex, but in no case of patent ductus. Left and right atrial pressures were similar and left atrial samples were 90 to 96% saturated with oxygen. In these cases, and also in atrial septal defect with reversed shunt, *pulmonary venous samples* were fully saturated (95 to 99%). This proves that there is ordinarily no pulmonary factor contributing to the cyanosis of the Eisenmenger syndrome.

3. *The pulmonary capillary venous pressure* was uniformly normal or low, averaging 2 mm. Hg. and ranging between −1 and 6 mm. Hg with reference to the sternal angle in all groups. Only in one case with heart failure was it elevated. It is presumably raised, however, in those cases of total anomalous pulmonary venous drainage in which the common vein carrying all the blood from the lungs is stenosed at its junction with the superior or inferior vena cava.

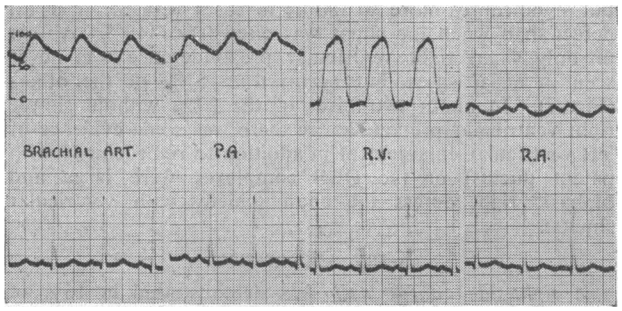

FIG. 8.—Identical systolic pressures in the brachial artery, pulmonary artery, and right ventricle in a case of Eisenmenger's complex. Note the normal right atrial pressure pulse.

4. *Pulmonary and systemic blood pressures* were practically identical in all varieties of Eisenmenger's syndrome in which the shunt was at aorto-pulmonary or ventricular level (Fig. 8). Their unity was preserved in the presence of any agent which normally influences one or other circulations more or less selectively—for example, exercise, pulsus alternans, ectopic beats, systemic vasodilators such as amyl nitrite, and systemic vasoconstrictors such as noradrenaline. This is well illustrated by the effect of the Valsalva manœuvre (Fig. 9).

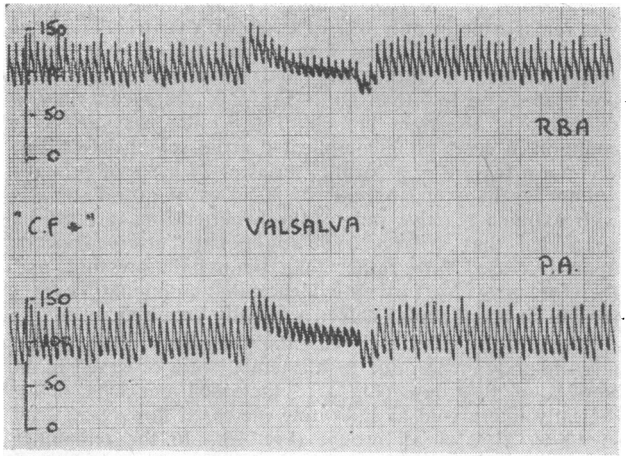

FIG. 9.—Identical pressures in the right brachial artery and pulmonary artery during the Valsalva manœuvre in a case of Eisenmenger's complex.

5. *Shunts were bidirectional* rather than wholly reversed in 42% of cases with patent ductus, 90% of those with ventricular septal defect, and 85% of those with atrial septal defect. The left-to-right component of a bidirectional shunt commonly increased the oxygen saturation of samples from the relevant chamber and beyond by about 10%; the average increase was 8.6% in patent ductus, 14.5% in ventricular septal defect, 16% in single ventricle, and 13% in atrial septal defect, omitting from the calculations cases in which the shunt was wholly reversed or absent altogether. In two cases of patent ductus there was no shunt either way.

6. *Pulmonary incompetence* increased the oxygen saturation or right ventricular samples in cases with aorto-pulmonary bidirectional shunt, and *tricuspid incompetence* influenced right atrial samples similarly in cases with bidirectional ventricular shunt.

7. *The pulmonary blood flow* ranged between 2 and 7 litres per minute in all groups, and averaged 4 litres per minute. The pulmonary/systemic flow ratio averaged close to unity, and never exceeded 1.75. The oxygen saturation of samples from the pulmonary artery rarely exceeded 75 to 80%.

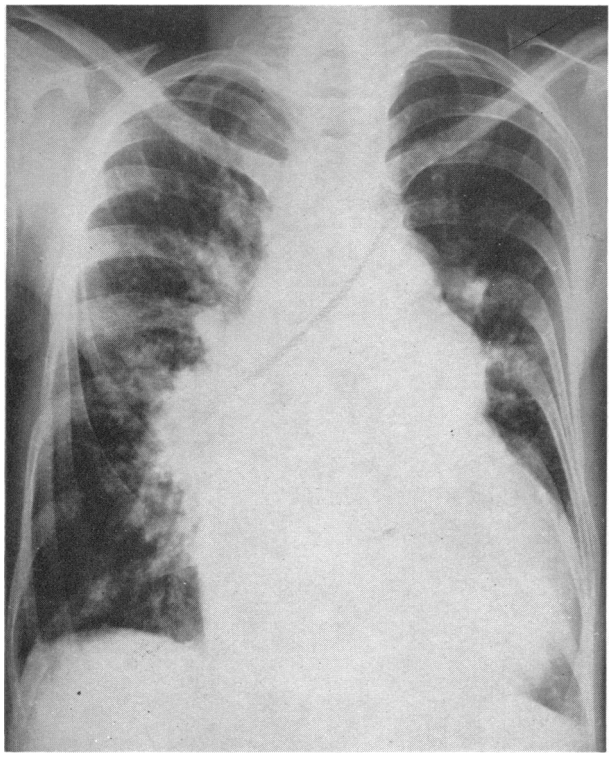

FIG. A.—Skiagram showing a "double aortic knuckle" above a dilated pulmonary artery in a case of patent ductus.

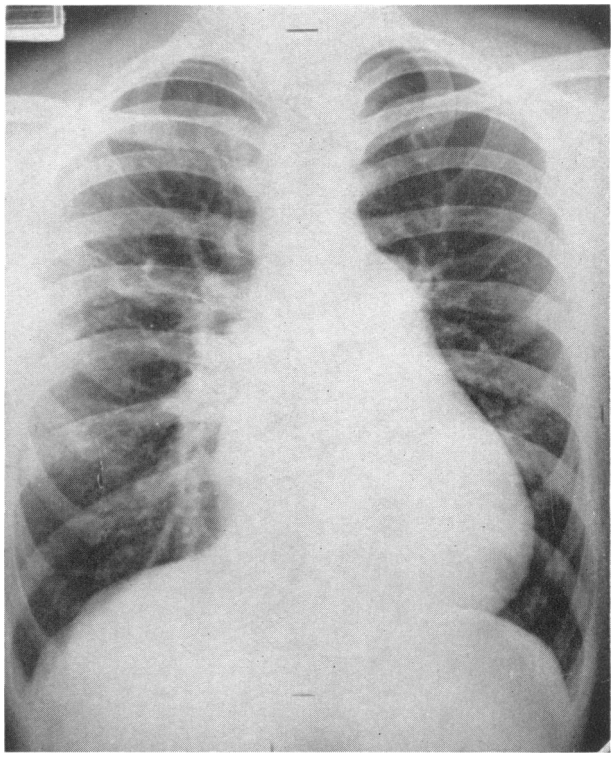

FIG. B.—Typical radiological appearances in Eisenmenger's syndrome; the pulmonary arc is conspicuous, and the pulmonary vascular markings are fairly normal. A case of aorto-pulmonary septal defect.

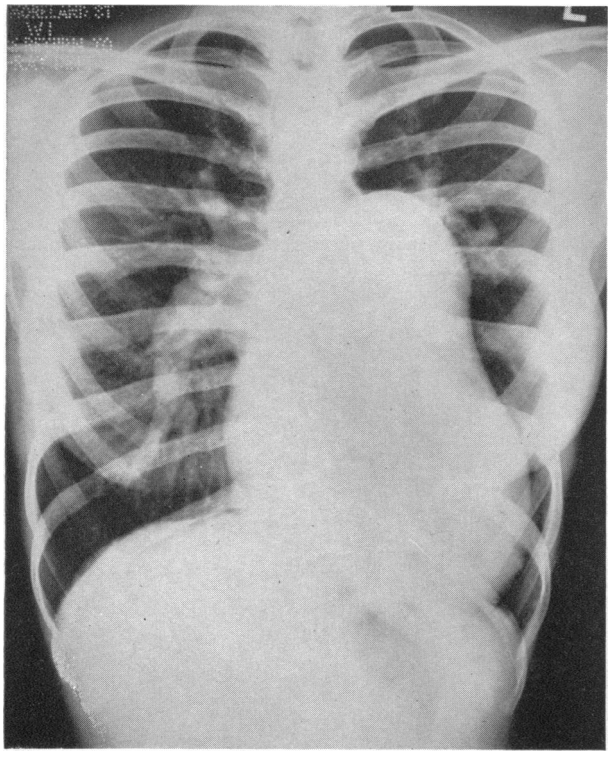

FIG. C.—Skiagram showing gross dilatation of the pulmonary artery and the right branch in a case of pulmonary hypertension with reversed interatrial shunt.

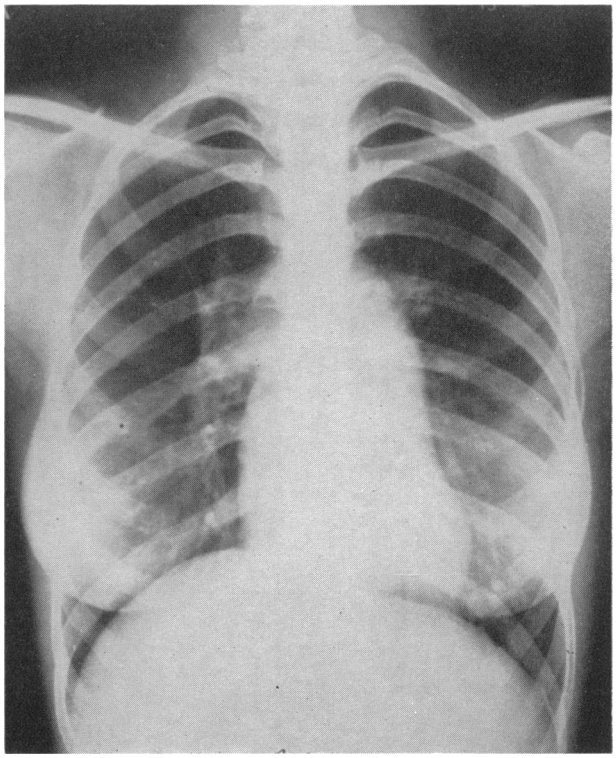

FIG. D.—Diminished pulmonary vascular markings in a case of Eisenmenger's complex with corrected transposition.

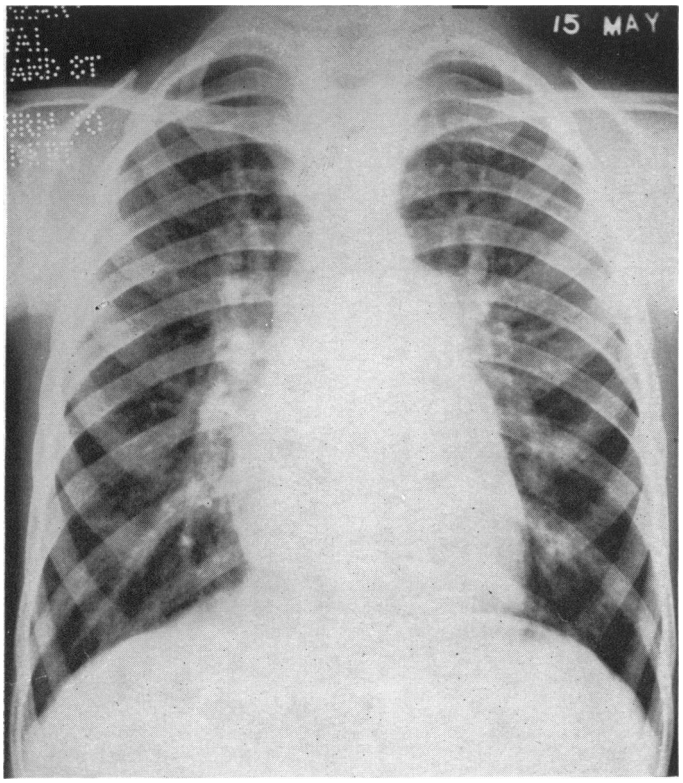

FIG. E.—Moderate pulmonary plethora and slight dilatation of the left atrium in a case of Eisenmenger's complex with increased pulmonary blood flow, probably associated with a single ventricle.

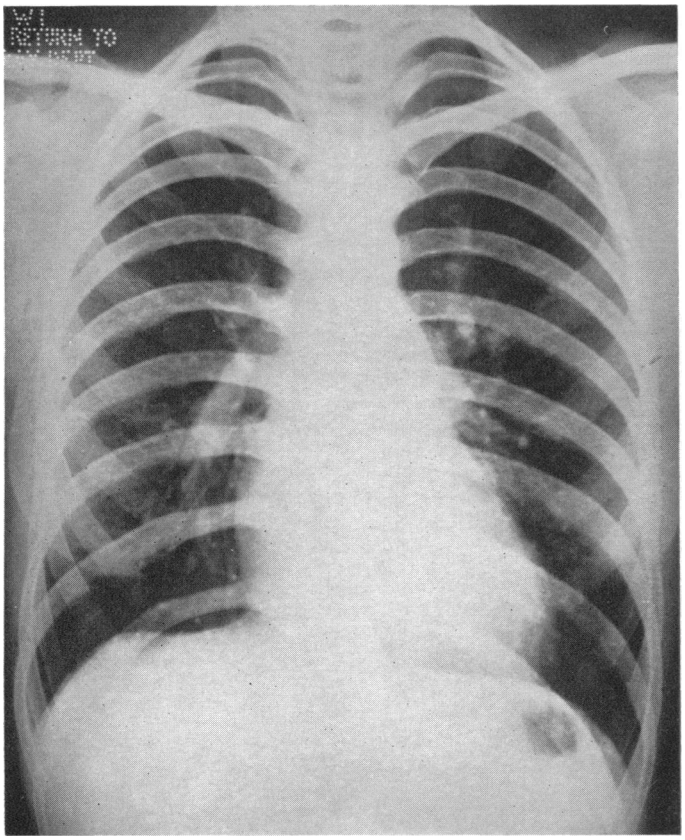

FIG. F.—Relatively normal pulmonary vascular markings in a case of Eisenmenger's complex.

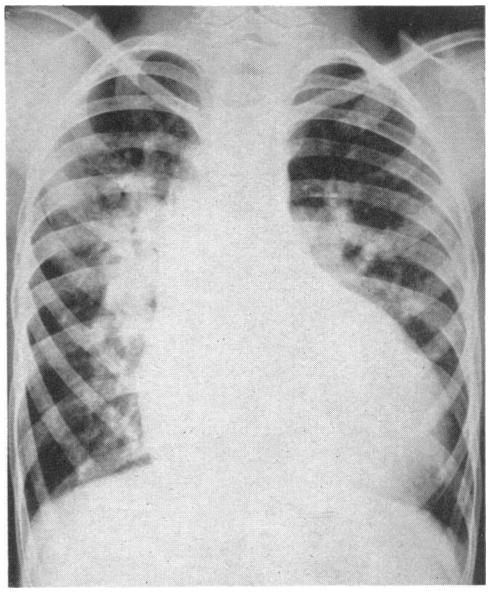

FIG. G.—Persistent truncus arteriosus showing a bay in the region of the pulmonary arc and considerable dilatation of the proximal pulmonary artery branches which are coming off the trunk.

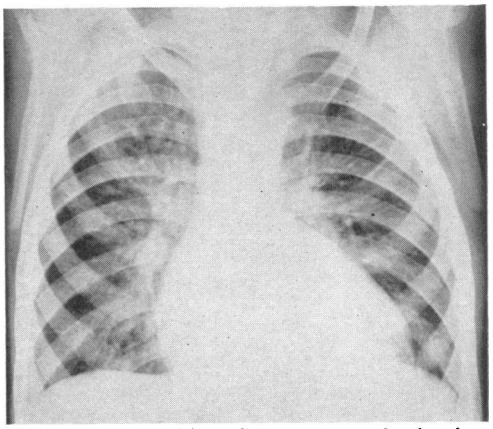

FIG. H.—Transposition of the great vessels, showing the slender waist and slight pulmonary plethora despite the high pulmonary vascular resistance.

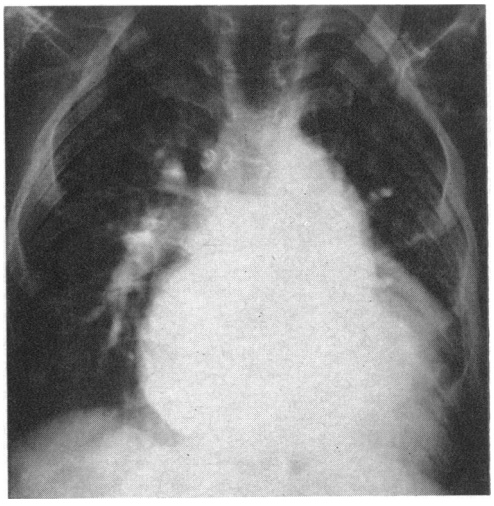

FIG. I.—Angiocardiogram showing a left-sided ascending aorta in a case of Eisenmenger's syndrome associated with transposition or corrected transposition.

8. *The pulmonary vascular resistance* ranged between 10 and 45 units (800 to 3,600 dynes sec./cm.^{5}), and averaged 22 units in patent ductus, 20 units in Eisenmenger's complex, and 17 units in atrial septal defect. When considering the resistance, due allowance should be made for the smaller blood flows of infants and small children.

9. *The arterial oxygen saturation* (femoral in cases of patent ductus) averaged between 77 and 82% in all groups, and was remarkably close to the mean in three-quarters of all cases.

[*The second part, together with a list of references, will appear in our next issue.*]

ARTERIAL OCCLUSION COMPLICATING THORACIC OUTLET COMPRESSION SYNDROME

BY

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It is well known that a cervical rib, a fibrous band in the anterior border of the scalenus medius, or an enlargement on the first rib may cause symptoms of vascular disease in the upper limb, but it is less well appreciated that the result may be a major amputation, ischaemic contracture of the fingers, or ischaemic muscle pain in the forearm and hand. Three cases have been recorded in the literature in which proximal spread of arterial thrombosis had reached the bifurcation of the innominate artery and caused hemiplegia. We believe that this complacency may be attributed to the excellent collateral circulation in the upper limb, which in the more minor lesions leads to minimal symptoms and spontaneous recovery; to the still widely held theory of a nervous origin for these symptoms, leading possibly to inadequate examination of the patients' vessels; and to the paucity of cases of major arterial occlusion due to cervical rib recorded in the literature. The admission of six such patients to this unit within the past 12 months, however, suggests that the incidence of these major occlusions may be higher than is generally realized.

In 1911 Todd, having noticed that the lowest trunk of the brachial plexus is intimately related to a cervical rib more often than is the subclavian artery, suggested that vascular symptoms associated with such a rib might be due to paralysis of the sympathetic fibres running in this trunk. With increasing knowledge of the function of the autonomic system, Telford and Stopford (1931) rightly pointed out that the colour changes induced are those of overactivity, not of paralysis, of the sympathetic fibres. By administration of ergot they induced endarteritis and thrombosis of the vessels in the combs of cocks and concluded that if arterial "spasm" be continued for a long period occlusion of the affected vessels can occur, and that irritation of the sympathetic fibres crossing the cervical rib in the lowest trunk of the brachial plexus would thus explain all the vascular features seen in these patients, including disappearance of the brachial pulse. Moreover, they showed by a series of dissections that in some subjects the sympathetic fibres are aggregated into a bundle in the lower part of this trunk, and argued that only in such a patient could these fibres be irritated, thus explaining the much greater incidence of neurological than of vascular symptoms associated with cervical rib.

Lewis and Pickering (1934) exposed the shortcomings of this theory by pointing out, firstly, that chronic irritation of a nerve trunk results in paralysis, not stimulation, of the fibres, and that there appears to be no reason why autonomic fibres should behave differently; and, secondly, that in cases of cervical rib the patients with vascular symptoms rarely have neurological features, whereas on the basis of this theory mixed cases should be regularly seen. Their own patient showed periarterial fibrosis, and it was demonstrated at operation that the subclavian artery was nipped between the abnormal rib and the clavicle when the arm was abducted. They suggested, therefore, that in these cases damage to the subclavian artery is followed by local mural thrombosis and that all the vascular features can be explained by embolism or by spreading thrombosis. Eden (1939) strongly supported this theory with the evidence of two further cases, and we submit that our experiences can be explained on no other basis. Support for this theory is also to be found in the not infrequent occurrence of a systolic murmur over the subclavian artery in these patients, indicating turbulence in the blood flow at this point.

Brachial Artery Occlusion

In patients with occlusion of the brachial artery a careful history revealed that a sudden onset of ischaemic symptoms in the hand and forearm was followed by a gradual recovery which may have been marred by one or more further acute episodes. On examination a powerful brachial pulse ceased abruptly in the vicinity of the lower border of the pectoralis major or the middle of the arm, points corresponding approximately to the origins from the brachial artery of major collateral vessels. After treatment, or even spontaneously, pulsation may return in the radial artery, though not in the lower brachial artery. These are the typical history and findings of a brachial embolus, which affords a much more convincing explanation of such a clear-cut picture than does a series of events consequent on sympathetic irritation. Injury may play a part in liberating an embolus, as illustrated by Cases 1 and 2, and may be a single blow or the repeated minor traumata associated with a particular occupation.

Case 1

A man aged 46 gave the history that following a fall on to his outstretched left hand at the end of February, 1957, the hand had suddenly become "numb," painful, cold, and white. On March 3 at another hospital a left upper thoracic ganglionectomy was performed, following which he noticed a pulsating swelling in his neck but no improvement of his hand. On March 17 he again had sudden severe pain in his hand, with marked pallor and coldness, and a brachial embolectomy was attempted but with only transient success.

He was admitted to our wards on June 28 with gangrene of the tips of the thumb and index and middle fingers and ischaemic atrophy of the hand. All the interphalangeal joints were almost fixed and movements at the metacarpophalangeal joints were greatly restricted by ischaemic contractures. The hand was white when elevated, cyanosed when dependent. The pulsation in the neck was the subclavian artery, which showed no aneurysm but was more prominent following division of the scalenus anterior at the sympathectomy. The brachial pulse ceased abruptly at the middle of the arm. *X*-ray examination showed no cervical rib, but a large boss on the first rib in the region of the subclavian groove.

At operation on July 10 the left first rib was removed, following which the colour and temperature of the hand