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THE EISENMENGER SYNDROME

OR PULMONARY HYPERTENSION WITH REVERSED CENTRAL SHUNT*

BY

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Distinctive Characteristics of Individual Members of the Eisenmenger Group

Patent Ductus.—(1) The catheter passed through the duct more easily than through any other central communication between the two circulations. It did so in 90% of cases, and usually took an anticlockwise course to enter the descending aorta. (2) The shunt was wholly reversed far more frequently (50%) than with other defects. (3) Patent ductus was the only lesion which was occasionally associated with no shunt in either direction. (4) Differential oxygen desaturation between right brachial and femoral samples was pathognomonic of patent ductus, and occurred in all but two cases in which there was no shunt in either direction. The oxygen saturation of samples from the right brachial artery averaged 89.6% (range 81 to 96%), and from the descending aorta or femoral artery 77.1% (range 65 to 88%).

Aorto-pulmonary Septal Defect.—(1) When the catheter passed through the defect it entered the ascending aorta from the pulmonary artery. (2) In other respects the findings were similar to those of patent ductus with bidirectional shunt but no differential desaturation.

Eisenmenger's Complex.—(1) Passage of the catheter via the defect (28%) into the ascending aorta followed a characteristic medial course as in Fallot's tetralogy. (2) An appreciable left-to-right shunt at ventricular level, as described by Bing *et al.* (1947), could be detected in all but two cases, in both of which the diagnosis was subsequently proved at necropsy. (3) Pulmonary artery samples were always between 5 and 20% less saturated than aortic or arterial samples.

Single Ventricle.—In all respects but one these cases resembled Eisenmenger's complex. The increase in oxygen saturation at ventricular level averaged 16%. The one distinctive feature was the similarity of aortic (or arterial), pulmonary artery, and ventricular samples. The arterial oxygen saturation was no lower than in other members of the Eisenmenger group, averaging 82%. Three such cases were proved at necropsy.

Transposition of the Great Vessels.—These cases also resembled Eisenmenger's complex in all major respects but one. The distinctive feature was the higher oxygen saturation of samples from the pulmonary artery compared with those from the aorta and right ventricle. In the three cases studied the difference was 32, 17, and 5%. The rise in oxygen saturation at ventricular level averaged 20%. Three cases in the series resembled Eisenmenger's complex in all respects except that the catheter took a left antero-lateral convex course as it entered the ascending aorta (Plate,

Fig. 1, *Journal*, September 20, facing p. 709), characteristic of one type of corrected transposition. The pulmonary artery is not readily entered in such cases.

Persistent Truncus.—There were three characteristic features in the two cases studied. (1) The physiological situation was similar to that in aorto-pulmonary septal defect with the addition of a second left-to-right shunt at ventricular level. As the catheter passed from the right atrium, through the right ventricle, into the truncus, the oxygen saturation of respective samples rose first by 10 and 12.5%, and then by a further 10 and 14%. (2) The catheter entered the pulmonary arteries from the "aorta," instead of vice versa as in aorto-pulmonary septal defect. (3) Samples from the "aorta" and pulmonary arteries were identical.

Atrial Septal Defect.—(1) The catheter passed through the defect in two-thirds of 18 proved cases. (2) The pulmonary artery pressure was less than the systemic pressure by an average of 27/34 mm. Hg in 70% of the cases; in 10% it was higher; and in the remainder about the same. When mean pressures were similar the pulse pressure was usually greater in the pulmonary artery, the systolic pressure being higher and the diastolic lower than in the systemic arteries. Agents affecting pulmonary or systemic flow or resistance selectively usually altered the pressure relationship between the two circulations. (3) A direct shunt at atrial level was demonstrated in 84% of the cases, right atrial samples being on the average 13% more saturated than samples from the superior vena cava (range 6 to 21%). (4) The oxygen saturation of left atrial samples averaged 81% in the eight cases in which they were obtained (range 72 to 88). Left ventricular samples were similar when secured, and arterial samples likewise (average 82% saturated; range 70 to 88%).

Persistent Ostium Primum.—The physiological findings in four cases could not be distinguished from a combination of low atrial septal defect and ventricular septal defect, there being bidirectional shunts at both atrial and ventricular levels. The rise in oxygen saturation averaged 10% in the right atrium and 7.5% in the right ventricle. The lie of the catheter when it entered the aorta was similar in both groups to that in Fallot's tetralogy and Eisenmenger's complex.

Common Atrioventricular Canal.—A single proved case that came to necropsy had virtually both a single atrium and a single ventricle. The rise in oxygen saturation resulting from the left-to-right component of the bidirectional shunt occurred at atrial level and measured 23%. Samples from the common ventricle, pulmonary artery, and femoral artery were similar at around 80% saturated.

Anomalous Pulmonary Venous Drainage.—As a cause of the Eisenmenger reaction both total and hemianomalous pulmonary venous drainage must be rare, for no case was recognized amongst the 127 studied in this paper. One of

*Conclusion of the Croonian Lectures delivered before the Royal College of Physicians of London on May 15, 1958. See last week's *Journal* (p. 701) for first part.

the additional necropsies, however, previously diagnosed as an ostium secundum type of atrial septal defect, was found to have total anomalous pulmonary venous drainage into a relatively small vein joining a locally dilated right superior vena cava. This female infant died at the age of 1 year with a pulmonary artery pressure of 105/60. No wedge pressure was recorded, but the pulmonary venous pressure must have been high in view of the small calibre of the single vein joining the superior vena cava, and this must have excited reactive pulmonary hypertension as described by Johnson *et al.* (1958) in four similar cases in which the single anomalous vein carrying all the blood from the lungs was stenosed where it joined the inferior vena cava or porta hepatis.

Dye-dilution Curves

The best method of identifying the site of the reversed shunt in Eisenmenger's syndrome is to inject a suitable dye first into the root of the pulmonary artery, then into the right ventricle, and finally into the superior vena cava, and

FIG. 10.—Dye-concentration curves from the radial artery after injecting cardio-green first into the superior vena cava, then into the right ventricle, and finally into the pulmonary artery: the double hump in the top tracing is due to the early appearance (time) of the dye when it has been injected proximal to the reversed shunt. Eisenmenger's syndrome associated with an atrial septal defect in a man aged 30.

has passed through the lungs in normal time (Fig. 10). In the case illustrated the double hump so formed appeared only when the dye was injected into the superior vena cava, proving that the reversed shunt was at atrial level.

While offering a highly satisfactory method of determining the site of a reversed shunt in Eisenmenger's syndrome, dye-concentration curves do not distinguish between individual members of each group, at least when the shunt is at atrial or ventricular level.

Angiocardiography

Selective angiocardiography may also resolve the site of a reversed shunt, and not infrequently distinguishes between individual members of each group. With atrial septal defect, for example, diiodone appears in the aorta and pulmonary artery more or less simultaneously only when injected into the superior vena cava (or high right atrium), not when injected into the right ventricle or pulmonary artery. Angiocardiography usually distinguishes patent ductus, transposition, corrected transposition, and persistent truncus from ventricular septal defect, and retrograde aortography separates aorto-pulmonary window from ventricular

septal defect (Fig. 11). Selective angiocardiograms, however, give no information about pressure, and reversed shunts are encouraged by transient overfilling of the chamber into which the contrast medium is injected; moreover, the danger of an overdose of x rays may limit the number of angiocardiograms to which a patient should be exposed, especially after cardiac catheterization. Dye-dilution curves have no such disadvantage.

FIG. 11.—Retrograde aortogram in a case of Eisenmenger's syndrome associated with an aorto-pulmonary window (with acknowledgments to Mr. Walter Somerville).

Necropsy Findings

Death occurred in 18 of the 127 cases of Eisenmenger's syndrome, and necropsy was carried out in 15 of them. Details of 38 additional necropsies of cases studied during life were sent to me by many kind colleagues in Britain, making a total of 53.

Mode of Death

The cause of death was known in 42 of these cases. Haemoptysis was the commonest natural cause, and was responsible in 29%; it was usually profuse and caused death within a few minutes, as in Eisenmenger's case. The nature of the collapse has already been discussed. Necropsy proved that the cause of the haemoptysis was usually pulmonary infarction from arterial thrombosis. In some cases, however, this was not established, and rupture of a thin-walled dilated arteriole immediately distal to the end of a thick muscular artery, as described by Dammann and Ferencz (1956) and Edwards (1957), could not be excluded. In a case described by Selzer and Lewis (1949) death was due to rupture of an aneurysm of the pulmonary artery, but this is most unusual.

Surgical repair of the defect was responsible for 26% of the fatal cases, and congestive failure for 17%; death was abrupt, presumably from ventricular fibrillation, in 14%. No other single cause, such as bacterial endocarditis, cerebral abscess, cerebral thrombosis, or pregnancy accounted for more than 5%.

Accuracy of Diagnosis

Of the 15 necropsied cases in the series fully analysed, the clinical diagnosis was wholly correct in nine, wholly wrong in two, and correct in respect of the site of the shunt but wrong in respect of the nature of the defect in four. A 40% error after full investigation is embarrassing; it was no less in the 38 borrowed cases nor in published reports in the literature. What is even worse is the high frequency of false pathological reports. The last two patients that died, for example, were diagnosed clinically as ? total anomalous pulmonary venous drainage in one case, and persistent ostium primum with bidirectional shunt

at atrial and ventricular levels in the other; the pathological reports from the hospitals where they died concluded that the first had nothing more than a simple atrial septal defect of the secundum type, and that the second had a single ventricle with intact atrial septum.

When a pathologist more accustomed to congenital heart disease examined the specimens he showed conclusively that the first had total anomalous pulmonary venous drainage into a normal right superior vena cava and the second a common atrioventricular canal with a functionally single atrium and virtually single ventricle. This is salutary experience, and emphasizes the very great care and knowledge that are needed to work out the precise physiological and anatomical situation in the Eisenmenger syndrome.

Size of the Defect

It has been stated, not infrequently, that the size of the defect is less important than the pulmonary vascular resistance in determining the Eisenmenger syndrome. This is a half-truth, for the size of the defect may very well determine the pulmonary vascular resistance. A major difficulty here is that measurements of the size of the defect vary considerably according to the circumstances under which the measurements are made. Surgical estimates in the live heart during repair work, for example, are always larger than post-mortem measurements; and post-mortem measurements are larger when made immediately after death, when the heart is fresh, than when made subsequently after the heart has been fixed. Discrepancies relating to the size of defects in reported cases, therefore, are bound to arise. Nevertheless, the following statements are secure. (1) No case of patent ductus with the Eisenmenger reaction has ever been reported with a lumen less than 5 mm. in diameter. (2) No case of Eisenmenger's complex has ever been reported with a ventricular septal defect less than 1 cm. across. (3) The size of an atrial septal defect has relatively little bearing on the presence or absence of a high pulmonary vascular resistance, and varies freely between 3 and 8 cm. in both uncomplicated and pulmonary hypertensive groups.

The size of the defect in the 53 necropsies under review is given in Table VI, where it is compared with the common size of defects in uncomplicated cases as given by Abbott

TABLE VI.—Size of Communication

	Normal Resistance. Usual Range	Eisenmenger Range
Duct.	0.1 to 1.0 cm.	0.7 to 1.5 cm.
V.S.D.	0.1 to 2.0 cm.	1.5 to 3.0 cm.
A.S.D.	3 to 8 cm.	3 to 8 cm.

(1927), Taussig (1947), and Brown (1950). The figures agree fairly closely with those given for ventricular septal defect by Selzer and Laqueur (1951).

Ducts under 1 cm. across with the Eisenmenger reaction were short, and the smallest were specifically stated to have had no length. Aorto-pulmonary windows are usually large—up to 5 cm. or so in their long diameter—but probably need to be no larger than the smaller ducts, since they have no length. That ventricular septal defects averaged twice the diameter of the ducts is attributed to the fact that aorto-pulmonary shunts continue throughout the whole cardiac cycle, whereas interventricular shunts are believed to be chiefly systolic.

As pointed out by Selzer and Laqueur (1951), there is no gradual transition between a large ventricular septal defect and single ventricle. The former rarely, if ever, exceeds 3 cm. in diameter and occupies no more than 10% of the septal area in a fully grown heart; the latter has a ridge where the septum should be, but that is all. Single ventricles are always complicated by pulmonary stenosis, as in the six cases described by Campbell *et al.* (1953), or by a high pulmonary vascular resistance (Rogers and Edwards, 1951). Transposition of the great vessels may be associated, but is obviously unimportant physiologically.

Elastic Arteries

Atheroma of the large elastic arteries was common, as reported by all writers, and as originally described by Eisenmenger. Secondary thrombosis and pulmonary infarction were increasingly common after the age of 20.

Of exceptional interest is the state of the elastic fibres in the main trunk of the pulmonary artery itself. Heath (1958) pointed out that in the foetus and newborn babe these elastic fibres were long and densely packed as in the aorta. As the pulmonary artery pressure falls the fibres seem to break up, shorten, and become loosely arranged, so that they no longer resemble the aortic pattern. Heath found that sections of the pulmonary artery in Eisenmenger's complex and patent ductus with reversed shunt always resembled the foetal (or aortic) pattern, whereas in atrial septal defect with pulmonary hypertension and reversed shunt, and in all forms of pulmonary hypertension known to be acquired, the appearances were more like those in a normal pulmonary artery. He concluded that pulmonary hypertension in the Eisenmenger syndrome must be present from birth with ventricular septal defect and patent ductus, but must be acquired in atrial septal defect—at least in the great majority of cases. It should be understood that the function of elastic fibres is to prevent distension from high pressure.

Muscular Arteries

In Eisenmenger's complex pulmonary arteries with a diameter of less than 1 mm. have a thick muscular media very similar to their structure in the foetus. Civin and Edwards (1950, 1951) suggested that it was the persistence of the foetal type of muscular artery that was responsible for the high resistance, and that this saved infants with large ventricular septal defects from dying as a result of an inadequate blood flow into the aorta. In their own words, "the pulmonary vascular bed of patients with the Eisenmenger complex who survive infancy maintains its foetal function." They assumed that the thick muscular arteries of the foetus were responsible for the high pulmonary vascular resistance necessary to deflect blood from the right ventricle away from the lungs into the descending aorta via the ductus arteriosus.

Thick muscular arteries have been demonstrated also in children with a single ventricle (Edwards and Chamberlin, 1951; Heath, 1957), large patent ductus (Whitaker *et al.*, 1955), and all other members of the Eisenmenger group (Edwards, 1957).

During the first two years of life the intima usually remains normal; thereafter, however, and with varying degree and tempo from case to case, progressive intimal fibrosis develops (Edwards, 1957). This is the pulmonary vascular disease that has been regarded by some as the chief cause of Eisenmenger's syndrome—for example, Whitaker (1958). Subscribers to this hypothesis do not say how these intimal changes have come about.

Arterioles

The arterioles of the lung are vessels less than 100 μ in diameter, and consist of endothelium, a single elastic layer, and adventitia; they are not supplied with muscle. Dammann and Ferencz (1956) support Edwards in his belief that the arterioles are usually thin-walled and dilated in Eisenmenger's syndrome, and that thick-walled vessels within the usually accepted compass of an arteriole are really muscular arteries in a state of contraction, an interpretation which has been extended by Short (1957) to embrace larger arteries with thick muscular coats.

The Overriding Aorta

The following observations may clarify the position in respect of the override.

1. Ventricular septal defect is but one of a total of some 12 kinds of communication between the two circulations, all of which may be complicated by a high pulmonary vascular

resistance and reversed shunt of similar magnitude. An overriding aorta or its physiological equivalent is absent in seven of these conditions.

2. When the pulmonary vascular resistance is high the arterial oxygen saturation averages close to 80% in transposition with ventricular septal defect, persistent truncus, single ventricle, the so-called Taussig-Bing syndrome (in which the pulmonary artery is supposed to be overriding the defect in cases of transposition), and Eisenmenger's complex with or without apparent override.

3. Eisenmenger's complex with all the classical features may be associated with a defect in the muscular part of the interventricular septum as in the cases described by Weiss (1927) and Heath *et al.* (1956). There can be no overriding of the aorta in such instances.

Experimental Physio-pathology

The reaction of the pulmonary circulation in Eisenmenger's syndrome to pulmonary vasoconstrictor and vasodilator drugs seemed worth investigating.

Oxygen

In adults and in the great majority of children over the age of 5, 100% oxygen fails to lower the pulmonary artery pressure (Fig. 12) or to influence the magnitude of the shunt, as first demonstrated by Burchell *et al.* (1950).

On the other hand, breathing 10% oxygen raises the pulmonary vascular resistance and increases the reversed shunt, at least in cases with patent ductus (Burchell *et al.*, 1953).

FIG. 12.—Failure of 100% oxygen to lower the pulmonary artery pressure in a case of Eisenmenger's complex.

In infants under 2 and occasionally in small children, when intimal fibrosis in the pulmonary circulation is negligible, breathing 100% oxygen almost halves the resistance and increases the pulmonary blood flow (Edwards, 1957).

Acetylcholine

Acetylcholine, when injected direct into the pulmonary artery in a dose of 0.5 to 1.5 mg., is an ideal selective pulmonary vasodilator, for this quantity is usually inactivated by cholinesterase by the time it reaches the systemic circulation (Wood *et al.*, 1957).

FIG. 13.—Failure of acetylcholine to lower the pulmonary artery pressure in a case of Eisenmenger's complex.

When severe pulmonary hypertension was primary, or due to mitral stenosis or cor pulmonale, acetylcholine lowered the pulmonary artery pressure and resistance, and raised the cardiac output in 85% of cases (Wood, 1958). In 13 cases of Eisenmenger's syndrome, however, no such effect could be demonstrated in a single instance (Fig. 13). The youngest patient in the series, however, was 5 years old, and it is probable that infants under 2, without intimal fibrosis, would react differently. This belief is founded on the different response of these infants to 100% oxygen, as described previously, and on the fact that acetylcholine lowers the pulmonary vascular resistance sharply in the foetal lung (Dawes, 1958).

Negative reactions to tolazoline hydrochloride ("prisol") and aminophylline have also been without exception in cases of Eisenmenger's syndrome in patients over the age of 5.

Protective Effect of Stenosis

One case of aorto-pulmonary septal defect had moderate stenosis of the origin of the right branch of the pulmonary artery (Fig. 14). The pressure fell from the systemic level of 85/55 mm. Hg in the pulmonary artery to 60/40 beyond the stricture in the right branch. The nature of the defect

FIG. 14.—Pressure pulses in a case of Eisenmenger's syndrome associated with an aorto-pulmonary septal defect and stenosis of the right pulmonary artery near its origin.

FIG. 15.—Pressure pulse from right pulmonary artery beyond the stricture, showing a marked reduction of pressure following the injection of acetylcholine. The pulmonary vessels have been protected by the stenosis and are functioning normally.

was demonstrated by passing the catheter through it. When acetylcholine was injected into the right pulmonary artery the pressure fell sharply from 55/38 to 30/18 (Fig. 15). It is true that the child was also the youngest in the series investigated, being only 3 years old, but that does not alter the conclusion that vessels which are protected from extreme pulmonary hypertension, or which have not had time to develop serious intimal fibrosis secondary to the hypertension, respond briskly to acetylcholine. This disposes of the idea that there is anything fundamentally wrong with the pulmonary vessels at birth in the Eisenmenger syndrome.

This functional evidence stands solidly side by side with the anatomical observation that when the origin of the left pulmonary artery is atresic in Eisenmenger's syndrome its distal branches and muscular arteries, which are not subjected to high pressure, are perfectly normal, whereas the vessels on the other side have all the features characteristic of Eisenmenger's complex (McKim and Wiglesworth, 1954).

Similar anatomical evidence was provided by Civin and Edwards (1950) in a case of large ventricular septal defect (2.5 cm.) with marked overriding of the aorta associated with mild infundibular stenosis of the fibrous diaphragm type, the orifice being 1.5 cm. in diameter and above the level of the shunt. This man died from carcinoma of the bladder at the age of 47, and at necropsy the pulmonary vascular tree was normal.

The protective effect of stenosis is the basis of modern surgical therapy in the Eisenmenger group (Civin and Edwards, 1950; Dammann and Ferencz, 1956).

Course and Prognosis

As previously stated, the Eisenmenger syndrome is commonly established at birth or during the first two years of life when the shunt is aorto-pulmonary or interventricular, but is typically acquired when the shunt is interatrial. In the present series, for example, cyanosis dated from infancy in 80% of those with ventricular septal defect, but did not start until adult life in 92% of those with atrial septal defect. The onset of reversed shunt in patent ductus is more difficult to establish, because differential cyanosis is usually overlooked. Aorto-pulmonary septal defects, however, behave like ventricular septal defects.

The majority of those who have studied the Eisenmenger syndrome at all closely have come to the same conclusion. Thus 8 out of 13 acceptable cases of Eisenmenger's complex collected from the literature by Selzer and Laqueur (1951) dated their cyanosis from infancy, as did at least 50% of 29 clinical cases studied by Donzelot *et al.* (1949), and all except 2 out of 20 cases reported by Kohout *et al.* (1955).

As a general rule neither cyanosis nor breathlessness changes appreciably during childhood or adolescence, but deterioration sets in sooner or later in adult life. The onset of recurrent haemoptysis may signal the downward trend, which is due in many cases to the development of thrombo-obstructive lesions.

The average age of natural death in the 18 fatal cases in this series and the 38 additional cases from elsewhere, omitting three which died in infancy, was 33 for both aorto-pulmonary and ventricular defects, and 36 for atrial septal defects. The cases in which death occurred in infancy included one severe ostium primum, one common atrio-ventricular canal with what was virtually cor biloculare, and one total anomalous pulmonary venous drainage into a stenosed vessel joining the right superior vena cava.

The maximum age reached was 65 for both the ventricular and the atrial cases, and 55 for the ducts.

The downhill course was usually punctuated with haemoptyses, which when severe sometimes caused sudden collapse and death within a few minutes, as previously described.

Bacterial endocarditis occurred in only 5% when it was responsible for death; cerebral abscess from paradoxical embolism occurred once and proved fatal; cerebral thrombosis also occurred in one case, but was not fatal. An appreciable number (14%) died abruptly, presumably from ventricular fibrillation.

As many as 26% of the fatal cases died from a surgical attempt to repair the defect, mostly from ligation of a patent ductus.

Patients who survive these risks develop congestive heart failure sooner or later, and this was the cause of death in 17% of the fatal cases.

Treatment

Medical treatment aims at preventing secondary thrombo-obstructive lesions by means of permanent anticoagulants, such as phenindione ("dindevan"). Pulmonary vasodilators, such as tolazoline, aminophylline, and reserpine, fail to lower the pulmonary vascular resistance, and do not influence the course of the disease (Rudolph *et al.*, 1958). Small venesections, repeated from time to time, may be helpful in cases with gross polycythaemia, but should be

undertaken very slowly and with the utmost vigilance. Heart failure requires the usual remedies.

Surgical repair of the defect has been responsible in recent years for more deaths in the Eisenmenger syndrome than any other agent except haemoptysis. Ellis *et al.* (1956) stated that the surgical mortality in cases with reversed shunt through a patent ductus was 56%, and Anderson *et al.* (1956), after reviewing 45 such cases in the literature, could find only four good results. Similar fatalities and poor results in the survivors are now taking place with repair of ventricular septal defect and atrial septal defect complicated by pulmonary hypertension and bidirectional shunt.

Direct repair of a defect, without the special preparation that is discussed below, is justified only when it can be predicted with confidence that its closure must result in a fall of pulmonary blood pressure because a hyperkinetic factor of sufficient magnitude has been eliminated. In practice this prediction can be made when the pulmonary blood flow is at least twice the systemic flow at rest, and the pulmonary vascular resistance does not exceed 10 units (800 dynes sec./cm.²). Borderline cases have pulmonary/systemic flow ratios of 1.75 to 2, and resistances of 10 to 12 units. No case with a pulmonary blood flow less than 1.75 times the systemic flow or with a resistance over 12 units should have the defect repaired in the ordinary way, whether the shunt is reversed, direct, or bidirectional.

Observance of this law since its introduction on theoretical grounds in 1950 has resulted in a mortality rate of zero for cases of patent ductus in this class. Several of them just within the limits outlined, and with samples from the femoral artery having oxygen saturations between 82 and 85%, have been cured by duct ligation. In these instances the pulmonary artery pressure fell, and the systemic pressure rose, when the duct was compressed manually. A year later the pulmonary vascular resistance was either normal or close to normal. In cases unsuitable for duct ligation identical pulmonary artery and aortic blood pressures do not separate favourably when the duct is manually occluded. Precisely the same criteria must apply to cases with interventricular or interatrial shunt.

Synthesis

The cardiac output of the newborn babe is about 0.5 l./min. (Prec and Cassels, 1955), and is presumably much the same in the foetus at term; if the situation is similar to that in the lamb, about 0.1 l./min. passes through the pulmonary circulation (Dawes *et al.*, 1954). Since the mean pulmonary artery pressure is the same as the aortic, about 50 mm. Hg at birth, the foetal pulmonary vascular resistance must be about 500 units (40,000 dynes sec./cm.²).

During the first three hours after birth a reversed shunt through a patent ductus is invariable (Eldridge *et al.*, 1954); from 3 to 72 hours after birth the shunt may be direct, bidirectional, or reversed (Eldridge *et al.*, 1954; Prec and Cassels, 1955; Amoroso *et al.*, 1958); and by the end of the third day the duct is usually closed. It follows that in newborn infants the pulmonary vascular resistance is more or less the same as the systemic—that is, about 100 units (800 dynes sec./cm.²)—for, as previously stated, the cardiac output is about 0.5 l./min., and the mean pressure around 50 mm. Hg.

Within a remarkably short time after birth, then, probably within a few minutes of independent life, a pulmonary vascular resistance around 500 units falls to about 100. Four questions clamour for an answer: (1) What is the cause of the fantastic pulmonary vascular resistance in the foetus? (2) Why does it drop so precipitously at birth? (3) Why is the rapid fall halted temporarily more or less at systemic level? (4) What is responsible for the subsequent slower decline to normal?

In the correct answer to these four questions lies the secret of the Eisenmenger syndrome.

An answer to the first has been offered by Alan Burton (1958), who points out that resistance to flow in a tube is

greatly increased by kinking the vessel. In the fully developed foetus the pulmonary vessels are as long as they are a few minutes after birth, but since the lung is completely collapsed they must be coiled up, or kinked in innumerable places, and Burton has demonstrated their "gnarled" appearance. It can be readily understood that vessels in such a state may be highly resistant to flow.

The answer to the second question follows. As the lungs expand the vessels uncoil: as the kinks straighten out the resistance falls; as the blood begins to flow through the lungs the vessels must dilate, and this also lowers the resistance (Williams, 1954); the blood that fills up the pulmonary vascular bed acts as a natural scaffolding and encourages further expansion (Jäykkä, 1957). Stepwise, and in a matter of a minute or so, and aided by lusty cries, the lungs are fully expanded (Lind and Wegelius, 1956), the vessels are wholly unfurled, and the pulmonary vascular resistance is at systemic level, at least five times lower than *in utero*.

The difficulty about accepting this explanation is that the resistance falls precipitously only when the lungs are inflated with any kind of gas, and does not do so at all when the lungs are distended with saline (Dawes *et al.*, 1953). What is clear, however, is that the initial steep fall in resistance is closely associated with full expansion of the lung.

An alternative suggestion that the astronomical resistance in the foetus is due to hypoxic vasoconstriction is untenable in view of its equally rapid fall when the lungs are inflated with nitrogen (Dawes *et al.*, 1953). Nor can the thick muscular arteries of the foetus be blamed for the high resistance *in utero*, because they could hardly be expected to change their structure in a few minutes; nor in fact do they do so, as the microscope shows clearly enough.

This brings us to the third question: Why is the rapid fall in resistance at birth temporarily halted at systemic level? This may well be a function of the thick muscular arteries just mentioned. In the foetus these have developed in relation to the systemic pressure to which they have been subjected, and, as shown by Dawes (1958), they are also in a state of active vasoconstriction, which can be released by acetylcholine. After birth a powerful right ventricle, as big and strong as the left, pumps its contents into a system of vessels which differs little from the systemic circulation; it is only natural, therefore, that pulmonary and systemic resistances should be similar.

During the first day of life, then, the physiological and anatomical findings are identical with Eisenmenger's syndrome associated with patent ductus. Two events of great importance must now be considered: the first is the relaxing effect of an increased alveolar oxygen tension on the tone of the muscular arteries; the second is the closure of the ductus arteriosus. Before the duct closes, release of vasoconstrictor tone in the muscular arteries is met by an increased flow from aorta to pulmonary artery, and this hyperkinetic factor tends to maintain the pulmonary artery pressure at systemic level. When the duct closes, and this hyperkinetic factor is eliminated, release of vasoconstrictor tone lowers the pulmonary artery pressure, and the approach to normal adult physiology begins. Just how quickly this goal is reached depends on the speed of involution of the muscular arteries. Edwards (1957) states that complete involution takes about three months.

The factors responsible for the final change to the adult arrangement, and so for the answer to the fourth question, are believed to be as follows. (1) As the pressure falls in the pulmonary circulation vasoconstrictor tone is diminished, for muscular arteries react to increased pressure by contracting and to decreased pressure by relaxing (Bayliss, 1902). This local response of the muscular arteries to any change in pressure must increase that change in either direction. (2) As the resistance declines the pulmonary blood flow increases. This must dilate the vessels and so lower the resistance still further (Williams, 1954). (3) As the pressure falls the muscular arteries atrophy and so diminish their resistance to flow.

The Eisenmenger Reaction

All that is necessary to prevent these natural forces from lowering the pulmonary vascular resistance to normal is a sufficient increase of flow to keep the pressure at systemic level. Any large aorto-pulmonary or interventricular communication will do just this, and the higher the resistance the less increase of flow necessary to maintain the pressure. If the pressure is maintained pulmonary vasoconstrictor tone must remain high, and the muscular arteries will not atrophy. This is the situation in the Eisenmenger syndrome, and it will be understood that it must be established at birth if the defect is large enough.

If the defect is not quite critical, however, the shunt flow at rest may not be sufficient to maintain the pressure at systemic level, and the forces acting in the opposite direction may win or partially win the competition. Once the resistance falls appreciably much larger flows are necessary to maintain high pressure. This brings us to the peculiar behaviour of cases with interatrial shunts.

Pulmonary Hypertension in Atrial Septal Defect

It was stated in the introduction that no hypothesis explaining Eisenmenger's syndrome was tenable unless it provided a solution to the question why cases with large atrial septal defect behaved differently. The simple answer that in atrial septal defect there is no "common ejectile force" will not do, because with a potentially large left-to-right interatrial shunt the powerful right ventricle in the newborn babe would certainly maintain the pulmonary artery pressure at or above systemic level, and so prevent both relaxation and subsequent involution of the muscular arteries. Since in fact this relaxation and involution must take place in cases with atrial septal defect, it follows that *there can be no interatrial shunt during the critical period*. That an atrial septal defect may not function for an appreciable time after birth is not at all unlikely, for the two great causes of a left-to-right interatrial shunt are a larger volume of blood returning to the left atrium than to the right (so that the shunt is self-perpetuating), and a lower resistance to diastolic filling on the part of the right ventricle compared with the left. Now, before the shunt operates it is obvious that the self-perpetuating factor inherent in an increased pulmonary blood flow may be disregarded, so that only filling resistance need be considered.

Resistance to filling or diastolic myocardial tone is presumably related to the mass of relaxed muscle that must stretch in response to the filling pressure. When the mass of the two ventricles is similar—as in many cases of Fallot's tetralogy, simple pulmonary stenosis, and Eisenmenger's complex, for example—little difference between the diastolic tone in each ventricle can be detected, and if an atrial septal defect happens to be present it may permit of no appreciable shunt in either direction. Many examples of this state of interatrial balance have been encountered in the conditions mentioned. At birth the mass of each ventricle is roughly the same, and it is probable, therefore, that diastolic myocardial tone in each ventricle is also the same. If this is true there should be no left-to-right shunt of any magnitude through an atrial septal defect at this time.

Just how soon the right ventricle involutes sufficiently to permit a shunt large enough to maintain pulmonary hypertension is unknown, but serial electrocardiograms in normal infants strongly support the view that involution is slow, far slower than involution of the muscular pulmonary arteries. In practice, also, uncomplicated atrial septal defect is rarely diagnosed in infancy, and the pulmonary systolic murmur so characteristic of an increased pulmonary blood flow is not usually heard "until the child is well past the neonatal period" (Nadas, 1957).

If this reasoning is correct, and the pulmonary vascular resistance falls to normal before the interatrial shunt gains much momentum, it becomes very difficult for the Eisen-

menger reaction to develop later, for once the pulmonary vessels are fully involuted an increased pulmonary blood flow is met by further reduction in the pulmonary vascular resistance, as in the normal individual, so that flows of 24 litres per minute may be associated with a resistance of about one-third normal (0.33 unit), and a mean pulmonary artery pressure only 8 mm. Hg higher than the left atrial pressure.

Subsequent Course of the Eisenmenger Syndrome

During the first two years of life pulmonary hypertension at systemic level maintains the hypertrophied and contracted state of the muscular pulmonary arteries, and the high pressure type of elastic tissue in the larger elastic arteries. During this period the muscular arteries are capable of relaxing, at least in response to increased alveolar oxygen tension. Whether or not they relax in response to acetylcholine, aminophylline, tolazoline, or reserpine is as yet unknown, but they may well do so: if the defect were repaired at this time, and the infant treated in an oxygen tent with pulmonary vasodilators, the pressure should fall, and if it did so the pulmonary vascular resistance should gradually diminish as a result of release of local vasomotor tone and involution of the muscular arteries.

After about two years of continuous pulmonary hypertension, however, reactive intimal fibrosis tends to obliterate the lumen of the muscular arteries, and they no longer respond to vasodilating agents. The obliterative process presents a solid anatomical obstruction to flow and replaces vasoconstriction as the chief cause of the high pulmonary vascular resistance. The pulmonary blood flow at this stage may be no greater than the systemic flow, and repairing the defect is without benefit. There are borderline cases, however, in which the pulmonary blood flow is twice the systemic flow and the pulmonary vascular resistance under 10 units, and in these there is still a good chance that repairing the defect may lower the pulmonary artery pressure enough to promote the involutionary changes that must lead back to health.

As life advances, usually between the ages of 20 and 30, thrombo-obstructive lesions develop in the larger pulmonary arteries which increase the resistance considerably and herald the beginning of the downhill course. These lesions may be prevented in good measure by permanent anticoagulant therapy. Just what part thrombosis plays in the production of the intimal fibrosis of the muscular arteries mentioned previously is controversial.

Cases of atrial septal defect with a low pulmonary vascular resistance may continue to have large pulmonary blood flows until they die from congestive failure between the ages of 50 and 75. About 10% of any large series of cases of atrial septal defect confirm this statement. An increased pulmonary blood flow *per se* does not, therefore, cause obliterative pulmonary vascular disease. The Eisenmenger reaction in atrial septal defect develops gradually, however, in a relatively small number of cases in which a powerful hyperkinetic factor comes into being before complete involution and relaxation of the muscular pulmonary arteries has taken place. In childhood the pulmonary vascular resistance in this group is not as low as it should be, so that flows of 16 to 24 litres per minute cause hyperkinetic pulmonary hypertension. If the resistance is 2 units, for example, a pulmonary blood flow of 24 litres per minute must result in a pulmonary blood pressure of about 70/30 mm. Hg (mean 48). Progressive intimal fibrosis and late thrombo-obstructive lesions then develop as complications of the hypertension, and as the obliterative process continues the resistance increases, the pressure rises further, and a vicious circle is inaugurated. In the end the physiological situation is similar to that in other members of the Eisenmenger group. Such cases are usually curable if the defect is repaired before the resistance reaches 10 units, and when the pulmonary blood flow is still at least twice the systemic flow.

Protective Effect of Pulmonary Stenosis

The evidence that pulmonary stenosis protects the pulmonary circulation from developing obliterative endarteritis is overwhelming. As suggested by Edwards (1950) and as practised by Dammann and Ferencz (1956), artificial stenosis of the pulmonary artery may be created surgically in cases of Eisenmenger's syndrome in order to lower the pulmonary artery pressure and so initiate the involutionary cycle. Just how long it may be wise to maintain the stenosis before repairing the defect remains to be seen, but the post-operative course of cases of mitral stenosis with extreme reactive pulmonary hypertension suggests that a year or two should be sufficient.

Summary

Eisenmenger's syndrome may be defined as pulmonary hypertension due to a high pulmonary vascular resistance with reversed or bidirectional shunt at aorto-pulmonary, ventricular, or atrial level.

It may be caused by patent ductus, aorto-pulmonary septal defect, persistent truncus, transposition with ventricular septal defect, corrected transposition with ventricular septal defect, ventricular septal defect, single ventricle, common atrioventricular canal, persistent ostium primum, atrial septal defect, single atrium, and hemianomalous or total anomalous pulmonary venous drainage into the right side of the heart.

These conditions have in common a large communication between the two circulations exceeding 0.7 cm. in diameter when aorto-pulmonary, 1.5 cm. when interventricular, and 3 cm. when interatrial. If the pulmonary vascular resistance were normal, such defects would cause a pulmonary/systemic flow ratio of at least 3.5, and the usual range would be 4 to 6.

The clinical and physiological features of 127 cases of the Eisenmenger syndrome are analysed and presented with special emphasis on the distinguishing characteristics of each type.

A total of 53 necropsies from cases well investigated during life were studied in relation to the clinical and physiological data. Thirty-eight of these do not belong to the series, but were used to check certain interpretations that needed more pathological support.

When the shunt was aorto-pulmonary or interventricular the Eisenmenger reaction was initiated and maintained from birth in at least 80% of the cases; when the shunt was interatrial the reaction was chiefly acquired in 90%.

The key to the physio-pathology of Eisenmenger's syndrome lies in the behaviour and structure of the pulmonary circulation in the foetus, newborn babe, and during the first three months of infancy.

The fantastic resistance of the foetal pulmonary circulation is attributed to the contorted state of the vessels in fully collapsed lungs.

The thick muscular arteries of the foetus and newborn babe represent a functional and structural reaction to high pressure.

Expansion of the lung after birth unfurls the pulmonary vessels and lowers the resistance precipitously to around systemic level (about 100 units).

Subsequent reduction of the pulmonary artery pressure is gradual, and depends on the relaxing effect of an increased alveolar oxygen tension on vasomotor tone, the inhibition of vasomotor tone that results from a fall in pressure *per se*, early closure of the ductus preventing

an adverse hyperkinetic factor, and gradual involution of the muscular pulmonary arteries.

In Eisenmenger's syndrome with aorto-pulmonary or interventricular shunt, this favourable cycle is prevented by a powerful hyperkinetic factor which maintains the pulmonary artery pressure at systemic level. So long as pulmonary hypertension is maintained vasoconstrictor tone is not inhibited and the muscular pulmonary arteries do not involute.

Obliterative pulmonary vascular disease due to reactive "endarteritis fibrosa" is secondary and is rarely found in infancy.

Thrombo-obstructive lesions are relatively late and may not be demonstrable before adult life.

The different behaviour of cases with atrial septal defect may be explained by the relatively slow involution of the right ventricle after birth. The pulmonary vascular resistance may well fall to normal before right ventricular diastolic tone is reduced sufficiently to allow a critical interatrial shunt, and, once the resistance is truly normal, flows up to 24 litres per minute do not cause pulmonary hypertension.

The practical application of these observations to the treatment of the Eisenmenger syndrome is discussed.

This analysis was begun in 1948 and two attempts at synthesis were made previously; the first in conjunction with Dr. J. B. Lowe in 1950, the second with Dr. H. Gilmour in 1953; and, though both attempts proved unsatisfactory owing to lack of sufficient data, I want to express my great indebtedness to these two colleagues.

Details of necropsies on cases well investigated during life were sent to me by Drs. I. M. Anderson, D. Evan Bedford, Wallace Bridgen, Maurice Campbell, William Evans, Frances Gardner, C. J. Gavey, Ronald Gibson, Frederick Jackson, and Walter Somerville; I am very grateful to all of them for their trouble and generosity.

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LOCAL TREATMENT OF BRONCHIAL ASTHMA WITH HYDROCORTISONE POWDER

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The fact that bronchial asthma can be greatly improved by systemic treatment with cortisone and its derivatives is well established. This treatment, however, demands high dosage and thus has the disadvantage of causing cortical atrophy, and of other risks. Its continued use must therefore be limited to patients whose life is endangered by the asthma or where invalidism is threatening.

If a similar therapeutic effect could be achieved by local instead of systemic treatment the dosage could be expected to be much lower, and the risks connected with high dosage would be avoided. A local effect of hydrocortisone has been well known for some time in allergic disorders of the eye and of the skin. In hay-fever a similar effect has been reported more recently and has been confirmed (Herxheimer and McAllen, 1956; Godfrey, Maunsell, and Pearson, 1957; Lake, Logan, and Peters, 1957; Morris-Owen and Truelove, 1958; Findeisen, 1958). Some of these reports include a number of cases in which pollen asthma was present and which were benefited by the treatment. Apart from