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Congenital heart disease—changes in form and function[1]

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The relation between form and function is the relation between anatomy and physiology; change in one leads to change in the other.

By the time of birth, in babies born alive with cardiac malformations, some adaptive changes in the cardiovascular system already may have been superimposed upon the basic structural abnormalities. These alterations in pathological anatomy continue throughout postnatal life but time is needed for the changes to evolve and show their physiological effects. Such alterations may occur as part of the predetermined natural history and may continue after early palliative surgery has extended the time of survival and thus allowed the abnormal heart to change further its form and function. The interdependence of form and function can be examined in the living from either initial aspect. Congenital heart disease is an ideal model and spontaneous alterations in cardiac form can be detected from changing symptoms, signs, and the use of invasive and noninvasive techniques. With growing experience, many changes are predictable from knowledge of the basic disturbance in cardiac morphology.

In this lecture it is shown how spontaneous change in form influences the natural history of the common anomaly, ventricular septal defect, and the clinical management of patients with this lesion. The various pathological changes which can develop in malformed hearts are then discussed and it is shown how their occurrence influences the signs and symptoms in patients with specific congenital cardiac anomalies, particularly complex malformations.

Ventricular septal defect

Ventricular septal defect (VSD) is the commonest of all congenital cardiac abnormalities (Mitchell *et al.*, 1971). The importance of altered form and function in this condition was recognised by Herbert French, when in 1918 describing a baby with heart failure which later improved he noted that 'the bruits of congenital malformations of the heart may disappear as the child grows up'.

To find out how often this happens, the clinical course of 84 infants in congestive heart failure from large ventricular septal defects was observed for up to 12 years. Initial cardiac catheterisation in 79 showed raised pulmonary artery pressures greater than 50 per cent of the systemic arterial pressure in 76 and large left-to-right shunts at ventricular level in all. Angiography confirmed the presence of an apparently large VSD. None had surgical treatment in infancy for various reasons. The study revealed that there was spontaneous diminution in the size of the VSD in 56 patients and complete closure in 11 (Table). Such changes were documented by phonocardiography (Fig. 1), electrocardiography, chest radiographs, and cardiac catheterisation. As defects became smaller and haemodynamically insignificant the murmur, which was initially pansystolic or long ejection, became early systolic or late systolic before disappearing completely. In some, the late systolic murmur was preceded by a late click (Fig. 1) loudest at the upper left sternal edge and when noted near the apex mimicking the signs of mitral valve prolapse. Indeed, this was often the initial diagnosis when such patients were examined later in life. The late click probably originated from the bulging tricuspid

Table *Fate of 84 infants who presented in heart failure, followed for up to 12 years*

	No.	*Per cent*	
Clinical state same (2 died in first year)	6	7	
Severe increase PVR	5	6	
Became 'Fallot'	6	7	Change in form
Severe inf. stenosis + smaller VSD	2	2	Change in form
VSD small	54	65	Change in form
VSD closed completely	11	13	Change in form
	84		

PVR, pulmonary vascular resistance.

[1]St Cyres Lecture, 1976.

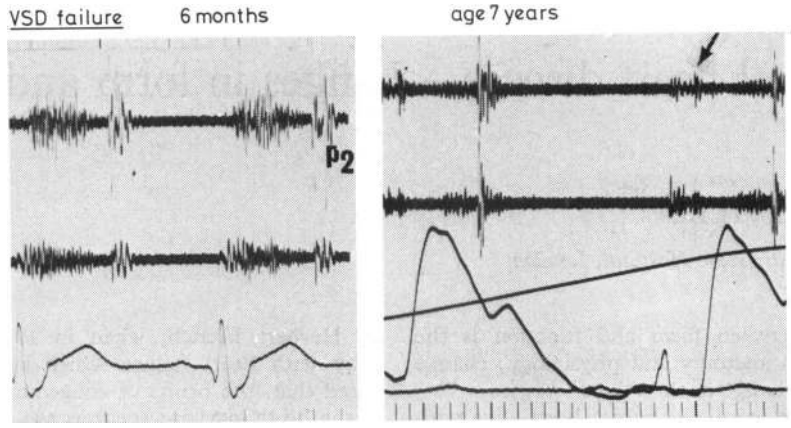


Fig. 1 *Phonocardiograms from a child in failure with large ventricular septal defect (VSD) at 6 months. He improved after 1 year and was a normal child by age 4 years, with signs of a minute VSD. At age 6 months, on the left, there was a long ejection systolic murmur, closely split second sound, and loud pulmonary valve closure (P2). By age 7 years there was only a late systolic murmur at the left sternal edge, a late click (arrow) probably from bulging tricuspid cusp tissue closing the defect, and normal splitting of the second heart sound.*

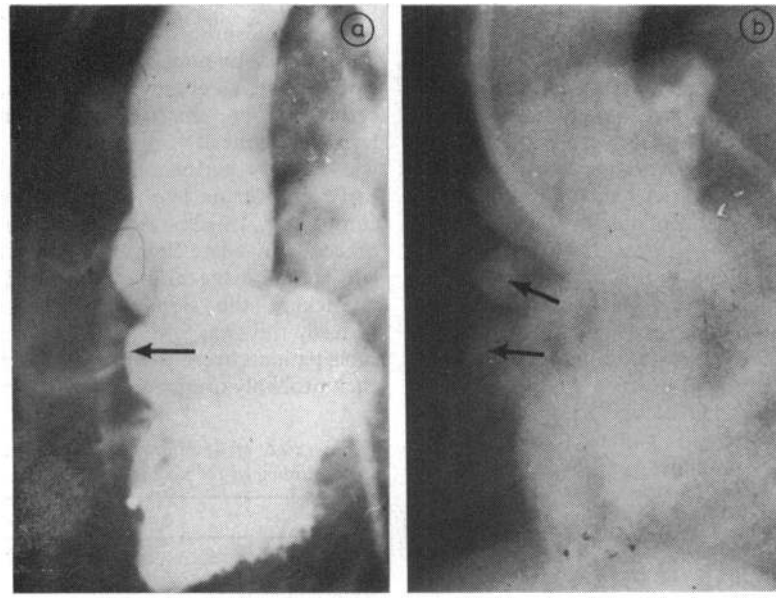


Fig. 2 *Left ventricular angiograms (lateral view) from two children with large ventricular septal defects documented in infancy which had almost closed (a) or completely closed (b). (a) At age 9 years, the tricuspid cusp tissue forms a smooth aneurysmal bulge leaving a small jet where the VSD is still patent (arrow). (b) Age three years. The once large VSD has closed leaving an irregular appearance caused by cusp and fibrous tissue, in the cephalad portion of the ventricular septum beneath the aortic valve (arrows).*

tissue which formed the acquired 'aneurysm' of the membranous ventricular septum seen on the lateral or left anterior oblique views of the left ventricular angiogram (Fig. 2a). Sometimes around the closed or minute defect was an irregular cauliflower like appearance from folds of tricuspid cusp tissue (Fig. 2b). In 5 patients whose defects closed or became very small, disproportionate enlargement and hypertrophy of the left ventricle persisted without any structural lesion to account for it. It is believed that these patients may also have congenital myocardial disease together with a VSD and as such are simple examples of 'diffuse cardiovascular disease' with the VSD being only one part of the congenital problem (Somerville and Becú, 1977). Whether the muscular abnormality progresses or causes symptoms in later life is another problem.

From the Table it is seen that 87 per cent of patients with large ventricular septal defect can change their clinical state as the result of spontaneous alteration of form. Since so many defects become small it is important to know which type of ventricular septal defect is associated with such clinical improvement and to see if this can be recognised at the time the child is ill.

Pathological evidence about spontaneously closed defects is difficult to come by because when improvement in a clinical state occurs, the patient does not usually die. I have seen 2 patients who died after later surgery for associated mitral regurgitation but in whom a large ventricular septal defect, which had been documented earlier, had spontaneously closed. The defects in both had been obviously sited posterior[1] (inferior) to the medial muscle of the tricuspid valve (Fig. 3a). The same was found in a larger series of hearts examined in the Pathology Department of the Children's Hospital, Buenos Aires. When the VSD in this site is viewed from the left side of the heart the upper edge (cephalad) of the defect can be seen to be separated from the aortic valve cusps above by a bar of muscular tissue (Fig. 3b). This is identified on left ventricular angiography by a narrow radiolucency between the under surface of the valve cusps and the contrast media streaming across the upper edge of this type of defect (Fig. 4). There are features on right ventricular angiography which help identify

[1]The description of cardiac structures depends on how the heart is viewed and by whom—surgeon, pathologist, embryologist, radiologist, or clinician. What is posterior to one is anterior to another and superior to one may be inferior to another. The ventricular septum lies in more than one plane which creates further difficulty in localisation and terminology. In the diagrams, I have tried to make my own terminology clear as seen from inside the right ventricle by a physician looking through the eyes of a surgeon!

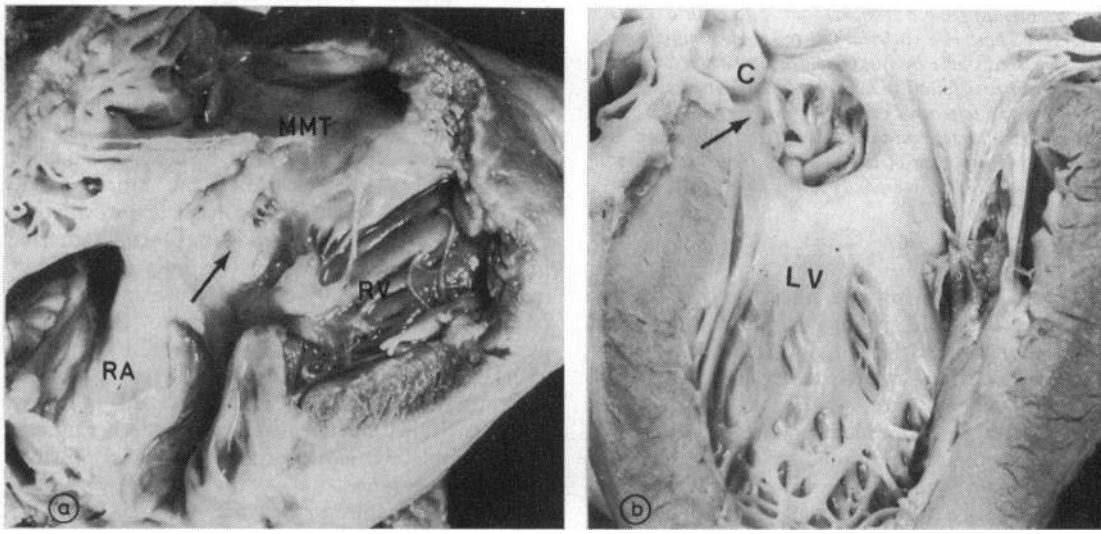


Fig. 3 *Necropsy specimens of heart from patients aged 6 years (a) and 15 years (b) in whom large VSDs have closed. Both had thriving difficulties and failure requiring digitalis in infancy. RA, right atrium; RV, right ventricle. (a) The heart is viewed from the right ventricular side. An arrow marks the site of the 'aneurysm' of the membranous septum formed by cusp tissue of the tricuspid valve which has closed the large VSD sited posterior (inferior) to the medial muscle of the tricuspid (MMT) valve (arrow) also known as the muscle of Lancisi or papillary muscle of the conus. (b) Heart viewed from the left side. Crenations of the cusp tissue can be seen closing the large defect in the ventricular septum. The VSD is separated from the aortic valve cusps (C) by a bar of tissue (arrow). LV, left ventricle.*

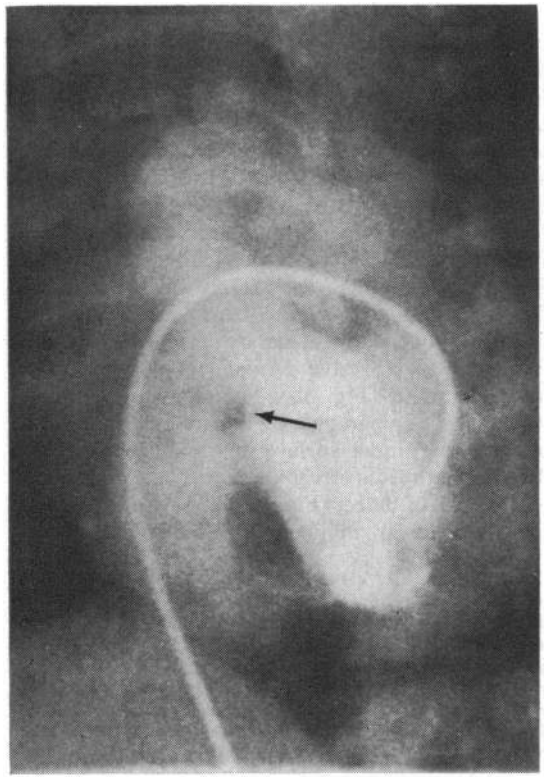


Fig. 4 *Left ventricular cineangiocardiogram (left anterior oblique) from a 9-month-old child with a VSD proven to be posterior (inferior) to the medial muscle of the tricuspid valve by inspection at operation 2 years later when it was found to be closing. The jet of contrast passes from the left across the VSD in the cephalad part of the ventricular septum but the upper edge of the VSD is separated by an area of radiolucency from the aortic valve (arrow). This corresponds to the bar of tissue shown (Fig. 3b).*

this defect by showing the intact convex fossette above the tricuspid valve; this investigation is not usually done in left-to-right shunting ventricular septal defects and so the value of the sign cannot be assessed here.

Many such posterior defects do not close completely but remain surrounded by fibrous and cusp tissue (Fig. 5a) which gives rise to irregularity on the left ventricular angiogram (Fig. 5b) and may be associated with a left ventricle to right atrial shunt. Though these defects do close sometimes in adolescence or adult life they are the ones which are prone to bacterial endocarditis. When associated with a significant shunt and cardiomegaly surgical closure is justifiable particularly if there has been an episode of endocarditis. Hence the reason to identify the anatomy of clinically small or moderate sized VSDs in the 'healthy' child, adolescent, or young adult.

Further evidence about the type of VSDs which close spontaneously comes from the group of infants who presented in failure in the first 3 months with VSD, duct, and coarctation. In 10 such infants who survived surgery for coarctation and left hospital after the first admission, the documented large VSD closed or became very small in 7 with or without banding of the pulmonary artery. It could be argued that these infants were selected by survival and that the anatomy in them was not representative of the whole group of patients with VSD and coarctation as they may not have included certain forms of VSD with a bad prognosis. Despite this theoretical argument, something can be learnt from them. In order to find out what type of VSD occurred in association with this coarctation syndrome a series of 43 hearts was examined from children aged 1 day to 10 weeks who died from cardiac and other causes before or after surgery. In 34 (79%), the defect was posterior to the medial papillary muscle (Fig. 6)—the same incidence as those of the living who improved spontaneously from closure of the defect. Since this posterior defect is so common in the coarctation syndrome presenting in failure in infants under 3 months and this is the defect which shrinks spontaneously, the wisdom of recommending early closure of the VSD or even banding of the pulmonary artery must be questioned, and thus the anatomical definition of the exact site and anatomy of the defect in this group is vital.

There is evidence that other VSDs can also close spontaneously. For example, the small single muscular VSD (Fig. 7) may leave a pit when it closes and the small or moderate sized anterior infundibular subpulmonary (supracristal) defect may be physiologically closed by prolapsing aortic cusp tissue. The VSD anterior to the medial papillary muscle (Fig. 8a) bordered by muscle (marked with a ?) and separated from the aortic valve, may be found at operation and necropsy to be encircled by fibrous tissue; whether it can close completely is uncertain but it is possible from its appearance.

Perhaps more important are the VSDs which cannot close or reduce in size (Fig. 8b). The large posterior inlet septal defect (Fig. 8b (a)) which extends completely to the posterior border of the atrioventricular valve ring beneath the attachment of the whole septal leaflet of the tricuspid valve remains large, causing symptoms. This uncommon defect, sometimes referred to as a 'canal' type VSD

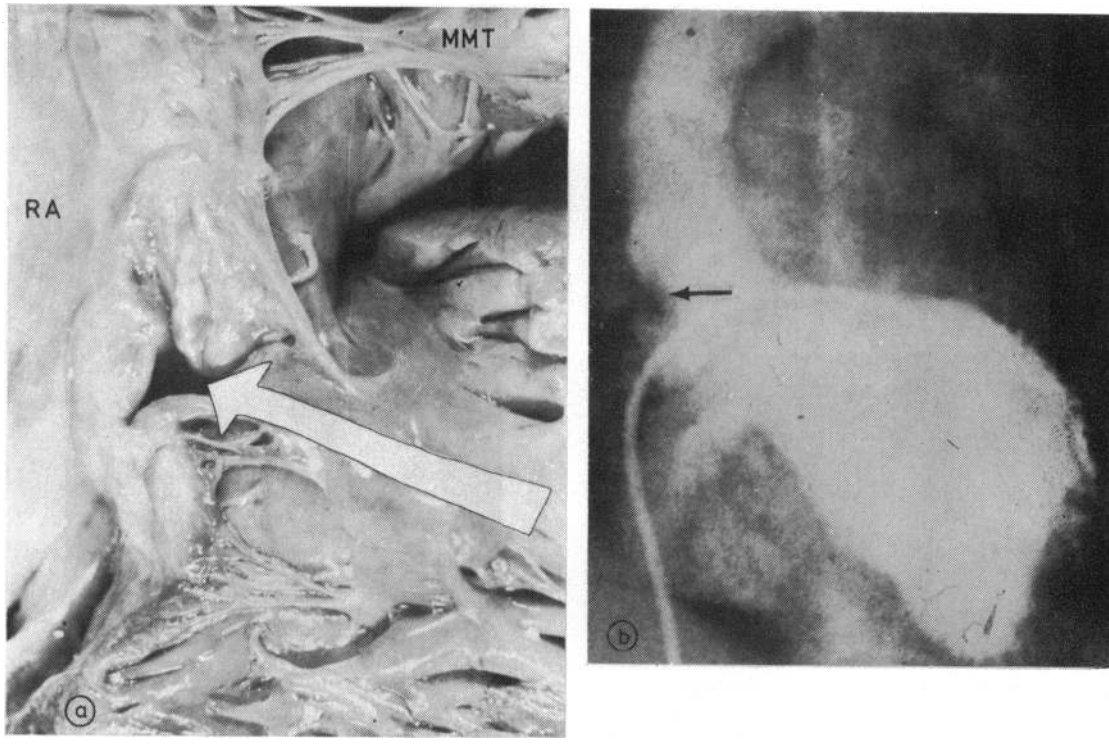


Fig. 5 *(a) Necropsy specimen from a girl aged 14 years viewed from the right ventricle showing a partially closed VSD (white arrow) posterior to the medial muscle (MMT). The VSD is surrounded by irregular cusp tissue and associated in life with a left ventricle to right atrial shunt. RA, right atrium. (b) Left ventricular angiocardiogram (left anterior oblique view) from a living patient with the same defect as shown in (a). The irregularity in the region of the defect is obvious as is the separation from the aortic valve (arrow).*

(Neufeld *et al.*, 1961), can be identified on the left ventricular angiogram not only by the wide separation of its cephalad edge from the aortic valve but also by the broad irregular jet of contrast medium which spreads through the chordal and cusp tissue into the body of the right ventricle. Patients with this VSD frequently have left anterior hemiblock on the electrocardiogram, but since the atrioventricular septum is not absent as it is in persistent atrioventricular canal from which it should be differentiated, the mitral valve is not displaced apically and does not with the deficient ventricular septum, form the characteristic 'gooseneck' appearance of the left ventricular outflow tract on the anterior-posterior view of the left ventricular angiogram (Baron *et al.*, 1964).

The most frequent large ventricular septal defect which does not close (Fig. 8b (b)) lies anterior (superior) to the medial muscle of the tricuspid valve, immediately beneath the aortic valve cusps which forms its cephalad border (Fig. 9a). The attachment of the septal cusp of the tricuspid valve posterior (or inferior) to this defect has a variable relation to it particularly when the lesion is part of the tetralogy of Fallot where the normally formed medial papillary muscle may be absent and its function is taken over by other identifiable septal muscles. This subaortic defect cannot close with its moving upper border of opening and closing cusps. The recognition of this VSD on angiography is simple because the dye outlines the aortic cusps which form the superior border (Fig. 9b). The defect is large and with the aortic root grows as the heart grows during postnatal life. Indeed, the aortic root has a characteristic shape quite different from the small root associated with other forms of equally large VSDs. The size and shape of the aortic root is mainly related to the type of VSD beneath it rather than the size of the left-to-right shunt.

This type of superior subaortic VSD is commonly associated with congenital anterior displacement of the infundibular septum (Fig. 9a) which leads to pulmonary stenosis. However, the

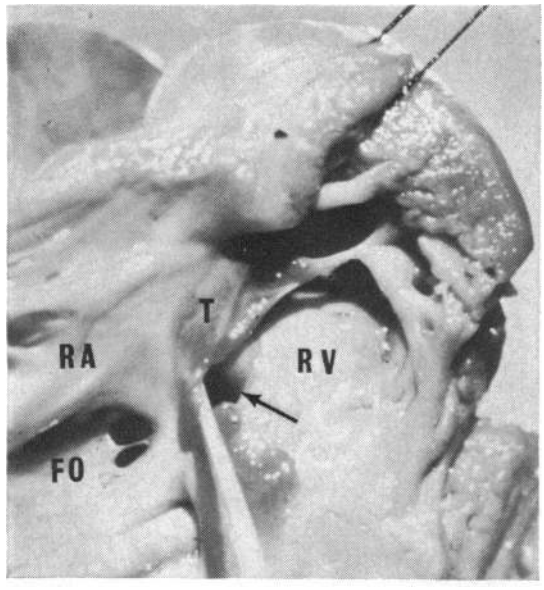


Fig. 6 *Clinically large VSD (arrow) posterior to the medial muscle of the tricuspid valve (T) from a 3-week-old infant and associated with coarctation and duct who died before surgery for the coarctation. There is no evidence of closure because there has not been time. RV, right ventricle; RA, right atrium; FO, fossa ovalis.*

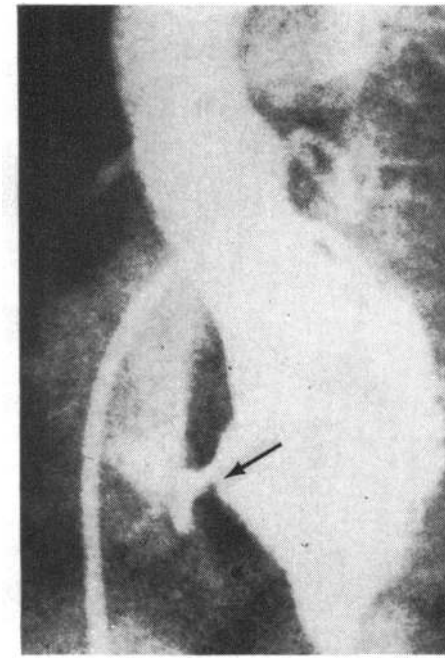


Fig. 7 *Left ventricular angiogram from a child aged 3 years with a small muscular ventricular septal defect which closed by the age of 5 years. The jet passes through the hole 'low' in the septum from the centre of a pit (arrow).*

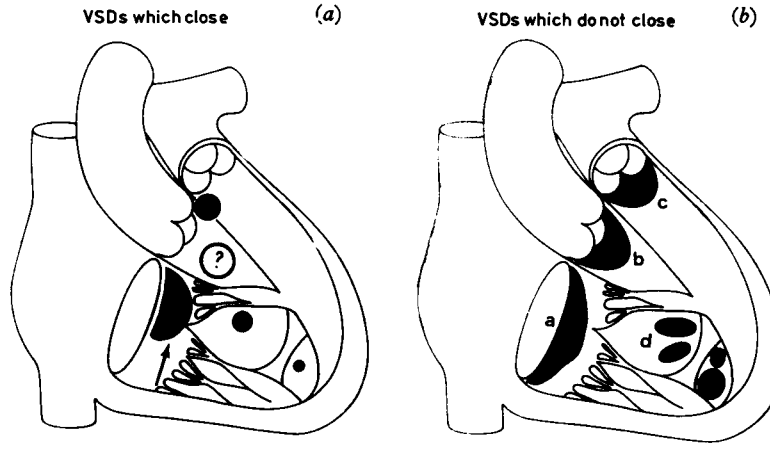


Fig. 8 *(a) Diagram of the heart viewed from the right side to show the site of ventricular septal defects which can close or diminish in size spontaneously. The arrow shows the VSD posterior (or inferior) to the medial muscle of the tricuspid valve, which most frequently behaves in this way. (b) Ventricular septal defects which do not close spontaneously. a: Complete defect which is posterior (inferior) to the medial muscle which extends to the posterior tricuspid ring—so-called inlet VSD or previously referred to as 'canal-type VSD'. b: Subaortic VSD with cephalad border formed by the aortic cusps. c: Large anterior infundibular subpulmonary VSD—may be part of Taussig-Bing complex. d: Multiple muscular VSDs (Swiss cheese).*

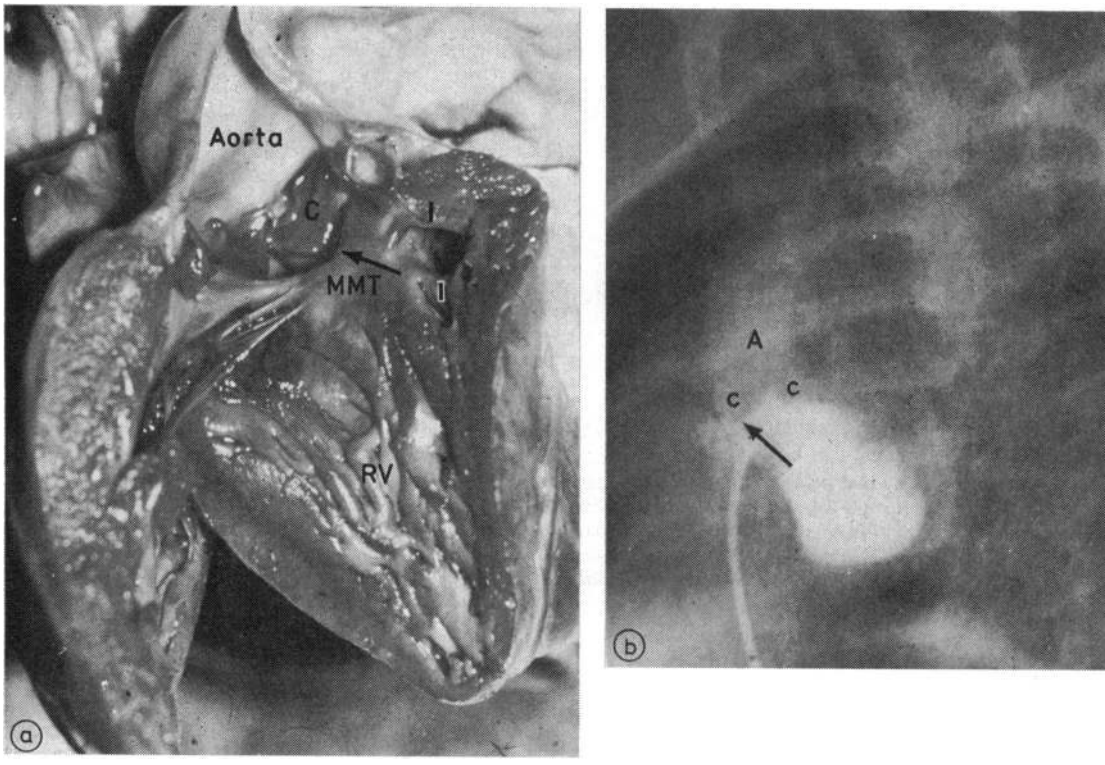


Fig. 9 *Subaortic VSD (8b (b)) which does not close. (a) Heart of a newborn who died in congestive failure, viewed from the right ventricle, the VSD (arrow) is anterior (or superior) to the medial muscle of the tricuspid valve. The aortic cusps (C) are forming the upper part of the defect. The bands of the infundibular septum (I), parietal and septal, are abnormally rotated as in tetralogy of Fallot so that in time an infundibular stenosis will form. (b) Left ventricular angiogram (lateral) from a 1½-year-old child with proven defect of the type illustrated in 9a. The catheter has been passed from the right ventricle through the VSD in the subaortic position into the left ventricle. The contrast medium outlines the aortic cusps forming the roof of the defect (arrow). The aortic root (A) is large and characteristically shaped above this type of VSD. C, aortic valve cusps.*

same defect may be associated with a hypoplastic infundibular septum and no obstruction to the right ventricular outflow either at birth or acquired later. As the defect remains large throughout life, clinical improvement can thus not occur unless pulmonary vascular disease develops. These patients are particularly the ones who develop the Eisenmenger reaction (Wood, 1958) and such was the defect in Eisenmenger's original description (1891). Thus, if this defect is detected without evidence of displaced infundibular septum (or an outflow gradient) it should be closed early. Occasionally the subaortic VSD can become partially obstructed by prolapse of aberrant redundant tricuspid tissue (Scott *et al.*, 1976) and such a complication should be suspected in tetralogy of Fallot if the electrocardiogram shows unusually severe right ventricular hypertrophy and P pulmonale or if the right ventricular pressure exceeds the aortic systolic pressure.

Other types of ventricular septal defect in which there is no evidence of spontaneous closure include the large subpulmonary infundibular defect in the right ventricular outflow tract and the large anterior infundibular defect in which part of the infundibular septum is displaced into the left outflow causing subaortic obstruction often associated with congenital aortic anomalies (Becú complex) (Fig. 8b (c)). Large multiple muscular defects ('Swiss cheese') also do not close (Fig. 8b (d)).

This account of the changes in form and function associated with ventricular septal defect shows how the natural history varies in relation not only to the size of the defect at birth but also to its site and to associated lesions. I believe now that a diagnosis of VSD alone is inadequate for correct management. The site and also size should be specified in order to predict the natural history and recommend surgical treatment at the correct time.

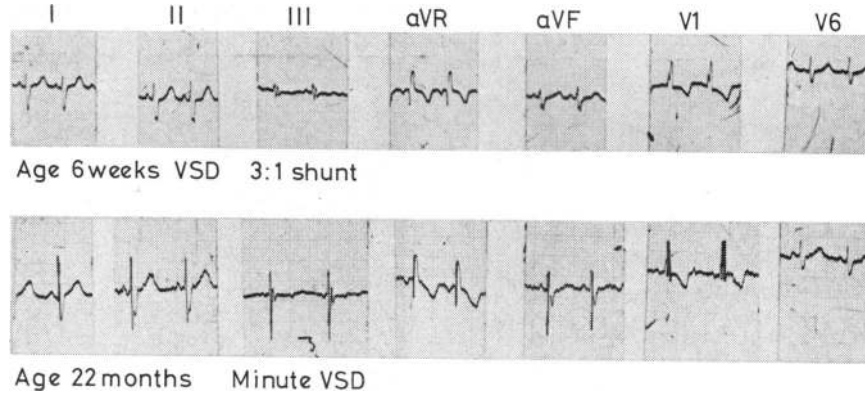


Fig. 10 *Serial electrocardiograms from a child who presented at age 6 weeks with thriving difficulties and mild heart failure. Cardiac catheterisation at age 2 months showed a 3:1 left-to-right shunt and raised pulmonary artery pressure 50/10 mmHg (systemic 60/30 mmHg). By 22 months the heart was normal in size with a short early systolic murmur at the left sternal edge. The upper record shows right axis deviation and probable right ventricular hypertrophy. By age 22 months the electrocardiogram showed left anterior hemiblock and partial right bundle-branch block with normal PR interval.*

UNWANTED SEQUELAE AFTER CLOSURE OF VENTRICULAR SEPTAL DEFECT

Spontaneous closure or reduction in size of a ventricular septal defect usually results in the improvement of the patient but occasionally the pathological process may leave residual effects on the conducting tissue or the tricuspid valve. For example, the electrical axis may become abnormal as the ventricular septal defect closes with eventual development of left anterior hemiblock (Fig. 10). Whether this can progress to complete heart block later is not known but it is theoretically possible.

In adults with small long-standing left ventricular to right atrial shunts due to the septal cusp of the tricuspid valve partly occluding the defect, premature atrial fibrillation from additional pathology such as alcohol or pulmonary emboli, etc may be associated with apparently severe tricuspid regurgitation in middle age, with a small measured shunt which does not account for the severe symptoms. Restoration of the patient to sinus rhythm, if possible, is the best solution.

Before large ventricular septal defects close, serious changes in the peripheral pulmonary arterioles may already have become established. In 2 patients, now aged 6 and 10 years, with angiographically proven closure of once large VSDs the resting pulmonary artery pressures remain at 55/30 mmHg and 45/25 mmHg. Whether this pulmonary hypertension will progress or regress is not known. It is interesting to speculate that these patients may present years later with what might appear to be pulmonary primary or thromboembolic hypertension if the early history is unknown or forgotten. When VSDs close in association with classic transposition of the great arteries serious left ventricular obstruction may result from protrusion of the 'aneurysm' below the pulmonary valve (Fig. 11a and b).

Pathological mechanisms of changing cardiac form

Spontaneous alterations of cardiac anatomy and physiology result from several different pathological mechanisms. Fibrosis from turbulence commonly influences natural history in congenital heart disease in many ways. Another important change is hypertrophy of muscle which not only affects the whole ventricle as a response to increased work demands as in stenotic valves but it may also occur in a more irregular fashion as part of a healing process after earlier infarction or myocardial necrosis. The capacity for this to occur before the age of 5 years is remarkable as can be seen in survivors of infarction associated with anomalous origin of the left coronary artery. More influential in altering the natural history of certain congenital cardiac malformations is 'selective' hypertrophy of congenitally abnormally placed muscular bands which result in acquired obstruction to the egress of blood.

Another pathological change affects atrioventricular valves either secondary to ventricular changes or due to valvular incompetence from abnormal stresses as the result of the disturbed haemo-

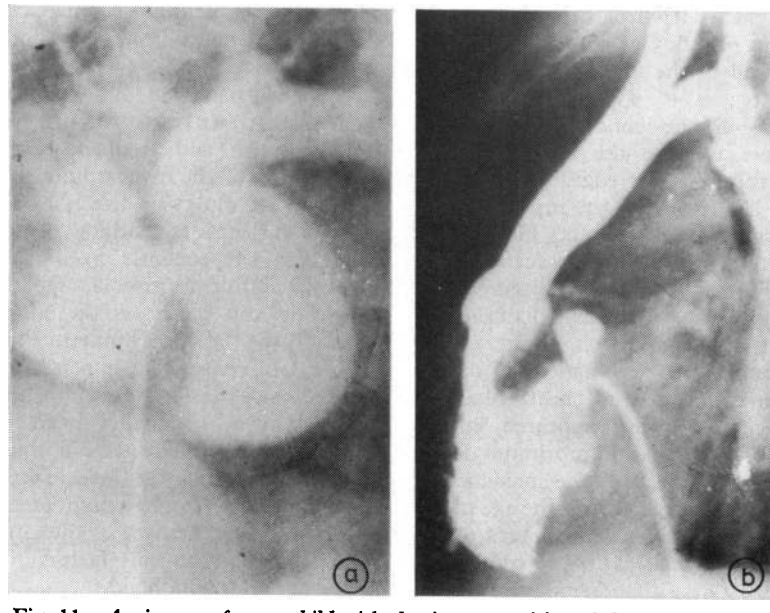


Fig. 11 *Angiograms from a child with classic transposition of the great arteries and ventricular septal defect which closed spontaneously and the 'aneurysm' of the septum protruding into the left ventricular outflow causing serious pulmonary stenosis. (a) Left ventricular angiogram (lateral) showing large VSD and no obstruction between left ventricle and pulmonary valve at age 6 months. (b) Right ventricular angiocardiogram in same patient aged 6 years, showing no evidence of VSD but there is a pouch of tissue protruding into the posterior left outflow causing serious subpulmonary obstruction with a gradient of 85 to 90 mmHg between left ventricle and pulmonary artery. It may be relevant to the morphology that a coarctation was present.*

dynamics from the underlying defect or added anatomical abnormality of the valve and attachments. The addition of mitral or tricuspid regurgitation to an already complicated heart may be disastrous.

The commonest pathological change which occurs with age is calcification. This is most often seen in semilunar valves but also appears in atrioventricular valves, in jet lesions, and myocardial scars.

FIBROSIS STIMULATED BY TURBULENCE

The basic mechanism which closes most VSDs is platelet deposition and fibrosis aided by the sealing curtain effect of the septal cusp of the tricuspid valve. Fibrosis may also develop at other sites in the heart such as in jet lesions on semilunar and atrioventricular valves, on endocardium in the ventricles opposite defects or regurgitant streams, or help late closure of the duct. Fibrosis may disturb vulnerably placed conducting tissue and affect the natural history in certain lesions such as Ebstein's anomaly, corrected transposition, and atrioventricular defects.

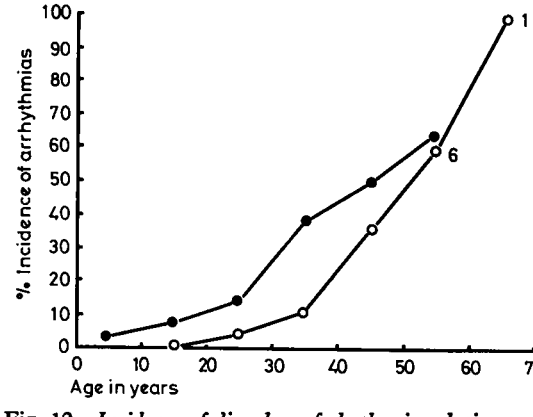


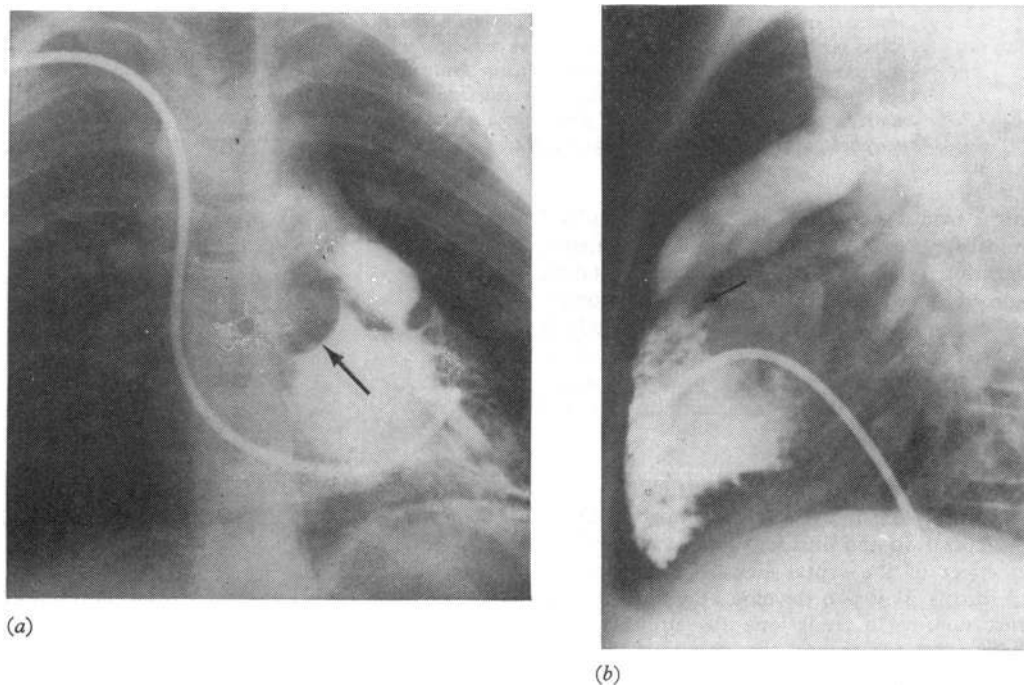
Fig. 12 *Incidence of disorders of rhythm in relation to age of 169 patients with unoperated ostium primum atrial septal defects. Black dots show those who developed spontaneous nodal bradycardia and tachycardia or heart block (including sudden asystole). Open circles show the incidence of paroxysmal and established atrial fibrillation. Nodal rhythms and block occurred occasionally in childhood and adolescence but after age 20 years were common. Atrial fibrillation was common in those who survived beyond 40 years.*

An example of such an effect can be found in the study of ostium primum atrial septal defects, a lesion where survival in the natural course to the fourth or fifth decades is possible (Somerville, 1965). In this lesion the conducting tissue is specially vulnerable because the atrioventricular node lies behind the posterior edge of the defect, and the bundle of His is close to the exposed upper border of the ventricular septum. These areas are subject to chronic turbulence associated with the left ventricular to right atrial and interatrial shunts and so one might expect that disturbances of nodal function and conduction might appear with time. The incidence of spontaneously occurring nodal rhythm disorders and heart block in relation to the age when they appeared in 169 unoperated patients with the ostium primum defect is shown (Fig. 12). As expected, the incidence of such rhythm disorders increased with the age of the patient; fibrosis has been shown in the area of the atrioventricular node as well as in the contiguous conducting bundles. There are other ways in which conducting tissue may be affected in congenital heart disease, and in the conditions where this occurs the conducting tissue may be in an abnormal site and thus more prone to secondary changes.

HYPERTROPHY IN DISPLACED OR DYSPLASTIC MUSCLE BUNDLES

An important and frequent adaptive change is hypertrophy of the myocardium. When this occurs in displaced muscular bands of the infundibular septum it leads to outflow obstruction, at first labile and subsequently fixed as fibrosis occurs. Enlargement of ventricular septal muscle, when dysplastic, can cause outflow obstruction on both sides of the heart asymmetrically or as part of diffuse left ventricular hypertrophy. The factors that influence the development of acquired muscular obstruction in congenital heart disease are the following: abnormally placed muscle bands, the amount of dysplastic muscle present and the stimuli to hypertrophy, high pressures secondary to other lesions, activity of the child, and perhaps additional biochemical factors which may be important after childhood.

Depending on the basic congenital abnormality and the site of the abnormal muscular bands, the



(*a*) (*b*)

Fig. 13 *Classic morphology of acquired infundibular obstruction shown on right ventricular angiograms in 2 patients. (a) Anteroposterior view from a 4-year-old child. The under surface of the aortic valve is outlined (arrow) where contrast medium has crossed the subaortic defect. (b) Lateral view showing a clear infundibular stenosis (arrow) composed of fibrous and hypertrophied muscle. The pulmonary valve is normal and the pulmonary arteries are large showing that they have once carried an increased blood flow or have been dilated by a raised pressure.*

obstructions will affect the cardiac function in different ways.

ACQUIRED OBSTRUCTION IN NORMALLY PLACED RIGHT VENTRICULAR OUTFLOW TRACT (WITHOUT TRANSPOSITION OR MALPOSITION)

In the original series of infants with large ventricular septal defect, it is seen that serious infundibular pulmonary stenosis developed in 8 of the 84 patients who had been in heart failure (Table). Of these, 6 developed the features of tetralogy of Fallot, first with cyanotic attacks and later with chronic cyanosis and effort dyspnoea in their first 2 years, a course described by Becú *et al.* (1961). As the infundibular obstruction in the right ventricular outflow developed, the physical signs changed. On auscultation and phonocardiography, pulmonary valve closure became delayed and diminished and the systolic murmur developed a diamond shape difficult to differentiate with the ear. The electrocardiogram maintained or developed right axis deviation and increasing right ventricular hypertrophy, with diminution of left ventricular voltage in V6. Chest radiographs were slower to change and lagged about 6 months behind in showing progressive reduction in heart size and pulmonary blood flow. The haemodynamics altered appropriately and the infundibular obstruction was confirmed angiographically (Fig. 13a and b).

In 6 of the 8 patients the ventricular septal defect was anterior to the medial muscle of the tricuspid valve and immediately subaortic and thus unable to close (Fig. 9a). In the other 2 patients who acquired severe infundibular obstruction the VSD was posterior to the medial muscle, and at surgery, age 7 years, was small in 1 and closed spontaneously forming a septal aneurysm in the other (Watson *et al.*, 1969).

Haemodynamically important infundibular obstruction can only be acquired under special circumstances. Firstly the infundibular septum (bands of the crista) must be congenitally displaced (Fig. 9a). A stimulus to right ventricular hypertrophy is then probably needed for these to enlarge. Initial obstruction is mild, reducing the pulmonary blood flow. As it increases it may respond to inotropic stimulation and cause cyanotic attacks. Subsequently fibrosis occurs to fix the obstruction and inhibit myocardial growth. The patient may lose the propensity to have cyanotic attacks, to become chronically cyanosed and disabled.

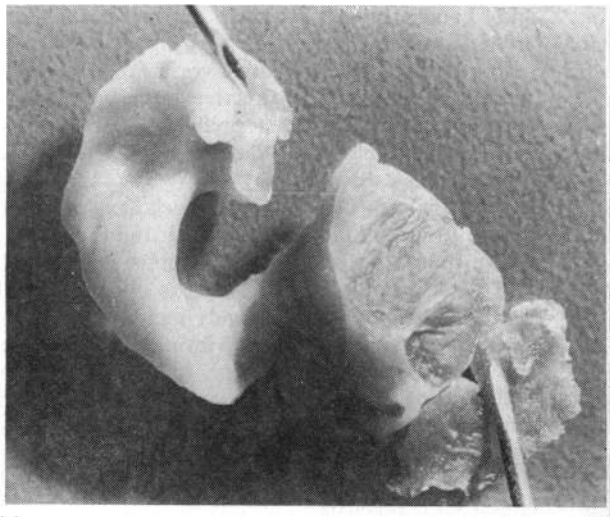


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Fig. 14 *(a) Complete infundibular stenosis removed from a child aged 5 years with fixed fibrous ring and hypertrophy of septal band of the infundibulum. (b) Acquired infundibular atresia removed from a 16-year-old girl who had bilateral Blalock anastomoses earlier. The arrow shows the atresia surrounded by a fibrous tissue ring. Extreme enlargement of displaced septal band which contains dysplastic muscle, fibrous tissue, and hypertrophied muscle is also present.*

The pathological form of the infundibular obstruction depends not only on the type of congenital disorder of the infundibulum but also on the age of the patient at operation or death. The older the child, the more the fibrosis and fixed obstruction. In infants below 2 years the muscular bands are hypertrophied and covered by thickened endocardium and later an incomplete or complete ring of fibrous tissue surrounded by muscle is found (Fig. 14a and b). In adolescents and adults huge eccentric masses of infundibular muscle invaded extensively by fibrous tissue as well as thick fibrotic endocardial rings are found. One wonders if the giving of digitalis to the infant in heart failure with this form of infundibular septal rotation hastens the onset of cyanotic attacks. Without the stimulus to hypertrophy from right ventricular hypertension, would the infundibular stenosis develop so severely? Probably not, but it does occur in patients whose VSDs close, but presumably by the time a process has reduced the size of the defect the infundibular obstruction has already become severe enough to increase the right ventricular pressure and perpetuate its own development. In small VSDs associated with aortic regurgitation, the right ventricular pressure is usually not raised from left-to-right shunts as the defects are small. However, this form of abnormal infundibular rotation is commonly present but rarely causes severe obstruction in the first decade, presumably because of the lack of right ventricular hypertension to stimulate secondary hypertrophy.

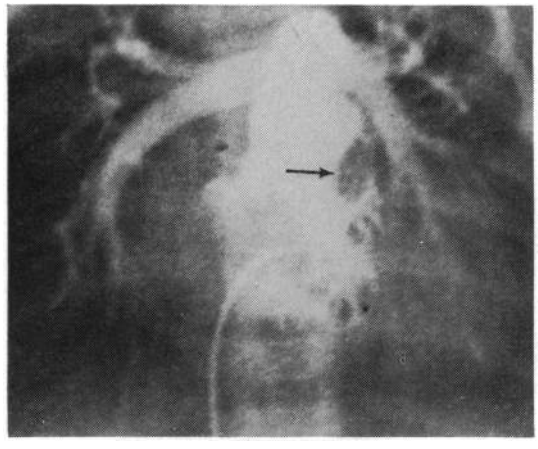


Fig. 15 *Right ventricular angiocardiogram from a week old baby in heart failure with pulmonary artery pressure 10 mmHg below the systemic pressure and a large left-to-right shunt at ventricular level. The child improved with medical treatment and at 13 months developed cyanotic attacks. The displaced abnormal infundibular septum is shown (arrow) and the pulmonary valve is slightly thickened.*

It is important to predict which patients with large ventricular septal defects in heart failure will develop such outflow obstruction so that improvement can be predicted, parents can be warned about cyanotic attacks, digitalis can be stopped early, and the ventricular septal defect can be closed at the right time. Displacement of the infundibular septum can be identified on right ventricular angiocardiography even before significant obstruction occurs, for the displaced bands are obvious in the right ventricular outflow (Fig. 15). In these babies it is worth waiting for spontaneous improvement with medical help and recommending surgery when the infant is larger. In all such patients, however cyanosed, the anatomy is favourable for radical correction as the pulmonary arteries are large. This demonstrates the important concept in congenital heart disease that size reflects use even if it has been in the past.

Infundibular stenosis with Fallot type subaortic VSD can progress to complete atresia (Fig. 14), particularly in patients who develop cyanosis early and who have never been in heart failure but have had a palliative shunt to survive. If they survive to adult life the outflow may even become calcified. Patients with infundibular atresia, however disabled and hypoxic, always have central pulmonary arteries which may stop growing; eventually secondary changes in the lung vessels can prevent a successful outcome of corrective surgery and there may still be a place for a preliminary shunt procedure to redevelop the pulmonary circulation. The infundibular septum may also be abnormally rotated in other conditions such as common atrioventricular canal, double outlet right ventricle, absent pulmonary valves, and common atrium with ventricular septal defect as well as other types of ventricular septal defect already mentioned. Eventually all such patients develop infundibular stenosis and reduction of pulmonary blood flow. This outflow anomaly does not occur with lone secundum atrial septal defect and if a patient is seen in childhood or adolescence with this combination one should assume that a VSD has been present and closed spontaneously.

When subpulmonary stenosis develops with these other lesions, the physiological and clinical effects are the same as with isolated subaortic VSD and the heart becomes smaller. However, when infundibular obstruction develops in patients with common atrioventricular canal and associated double outflow right ventricle, progressive right ventricular dilatation with increasing atrioventricular valve regurgitation appears together with

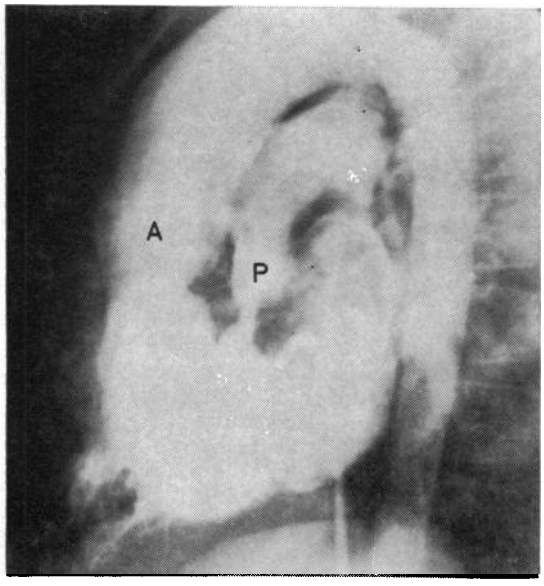


Fig. 16 *Angiogram from a 19-year-old boy with a univentricular heart and anterior aorta (A). A severe subpulmonary obstruction is present beneath a minimally stenosed pulmonary valve and a normal pulmonary artery (P). The infundibular stenosis was lined with radiologically visible calcium.*

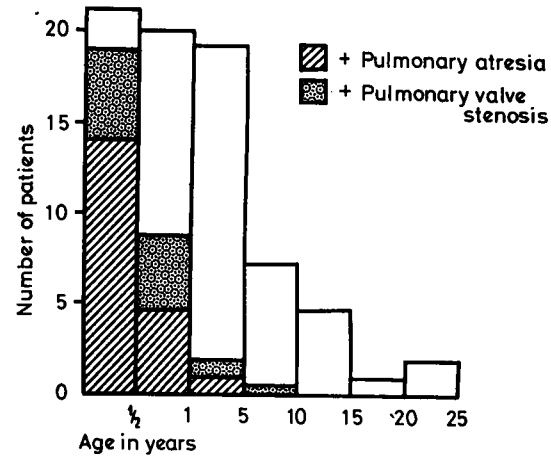


Fig. 17 *Age when hypoxia became a problem needing a palliative shunt in 74 patients with tricuspid atresia and normally related great arteries. Patients with added pulmonary atresia and pulmonary valve stenosis have been shown separately. In the majority, obstruction to pulmonary flow was the result of shrinkage of the VSD.*

cyanotic attacks and widening right bundle-branch block. Another form of acquired right ventricular muscular obstruction occurs when there are anomalously placed muscle bundles 'low' in the outflow at the entrance of the infundibulum. When they hypertrophy a two-chambered right ventricle forms, usually seen after the first decade and with or without VSDs at various sites.

Acquired subpulmonary obstruction in complex lesions

Obstruction which limits the pulmonary blood

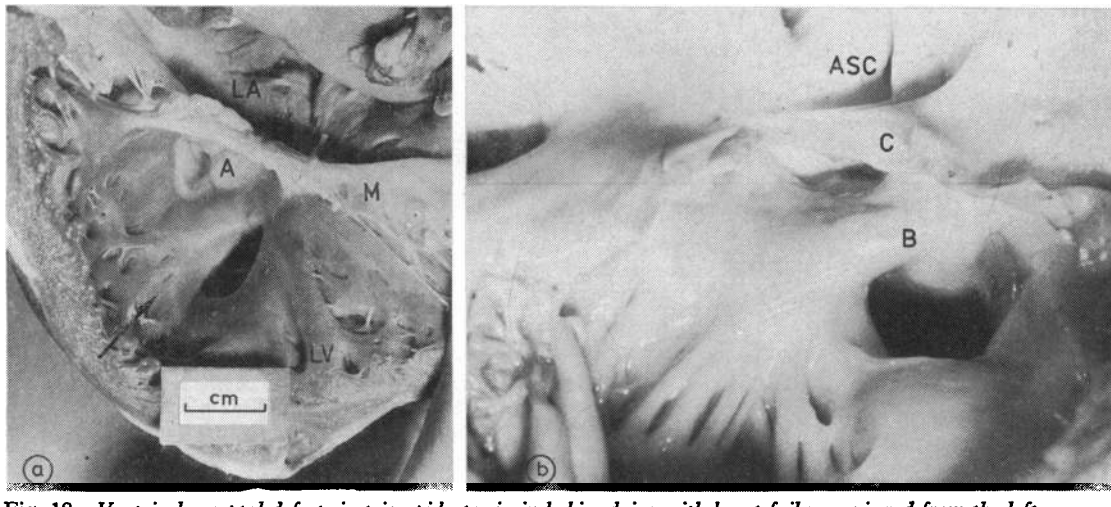
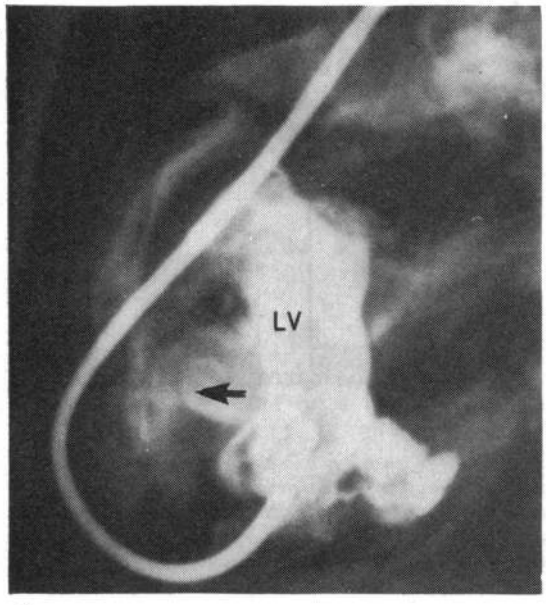


Fig. 18 *Ventricular septal defects in tricuspid atresia in babies dying with heart failure—viewed from the left ventricle. (a) Linear type of VSD (arrows) in the muscular septum which diminishes in size early usually. M, mitral cusp; A, aortic valve cusps; LA, left atrium. (b) Large window type of VSD beneath the aortic valve (C) and separated from it by a bar of muscular tissue (B). ASC, ascending aorta. This defect, when large, takes a longer time to close or reduce in size.*



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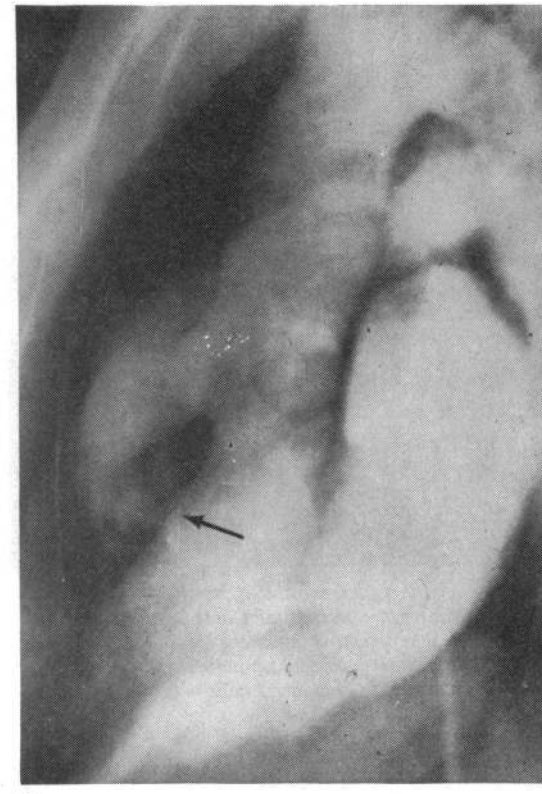

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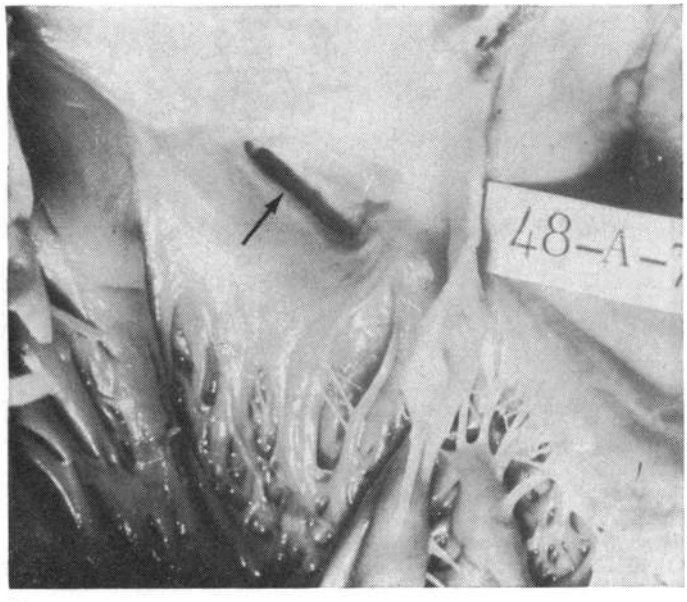

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Fig. 19 (*a*) *Left ventricular angiogram from a 4-year-old boy with severe cyanosis. The defect was vertical and low in the muscular septum (arrow) which was confirmed at necropsy.* (*b*) *Left ventricular angiogram showing a closing window type of VSD (arrow) in a 14-year-old girl with tricuspid atresia who developed hypoxic symptoms first at age 5 years.* (*c*) *Window type of VSD (arrow) in a child aged 10 years with tricuspid atresia, showing signs of closing. Same anatomy as patient shown in 19b.*

flow may develop in more complex cardiac anomalies if muscle bands encircling an abnormally placed outflow tract become hypertrophied, such as that seen in some forms of univentricular hearts without an outflow chamber (Fig. 16) or with a subpulmonary chamber and normally related great arteries (Holmes heart) where the obstruction may occur in the bulboventricular foramen (Somerville *et al.*, 1975). The same process operates in tricuspid atresia with normally related great arteries. As the bulboventricular foramen (or ventricular septal defect) through which the left ventricle communicates with the right ventricular outflow tract shrinks, the pulmonary blood flow diminishes.

Newborns with uncomplicated tricuspid atresia usually have a normal-sized pulmonary artery and a large ventricular septal defect (Kreutzer *et al.*, 1973). In the absence of pulmonary valve stenosis or atresia the size of the VSD controls the size of the pulmonary blood flow and the symptomatic state in these patients. In the early months of life babies with tricuspid atresia may present with heart failure and increased pulmonary blood flow and later cyanosis appears as the hole shrinks.

In order to find how frequently this morphological change influenced the natural history of tricuspid atresia, the age when hypoxia first developed in 74 children with tricuspid atresia and normal great arteries was studied (Fig. 17). The few patients with added pulmonary atresia or valve stenosis are shown. It can be seen that the majority had no pulmonary valve lesion and reduced pulmonary flow and hypoxia was thus the result of reduction in the size of the VSD (bulboventricular foramen), the importance of which was first recognised by Brock (1964).

It can be deduced from seeing the different ages when the patients with tricuspid atresia presented with hypoxia that the behaviour of the VSD varies. This must, as in uncomplicated VSD, be related to the basic anatomy. In tricuspid atresia the inflow portion of the right ventricle with the medial papillary muscle is absent and so the classification used in simple VSD cannot be applied in tricuspid atresia. For simplicity the defects in tricuspid atresia will be described as viewed from the left ventricle. In a necropsy study of 60 hearts there were two main types of defect (L. Becú, 1976, personal communication); either 'low' in the muscular ventricular septum surrounded by muscle (Fig. 18a) or more often cephalad where they appeared as an oval window separated from the aortic valve by a muscular band (Fig. 18b). It appeared that the lower defect, depending on its initial size, critically reduced in size (Fig. 19a) earlier than the window type nearer to the aortic valve (Fig. 19b and c). Complete closure of both types was documented in 7 patients whose lives were prolonged by palliative procedures. In 2 patients with closing of the cephalad type, subaortic stenosis developed with gradients of 35 mmHg and 45 mmHg, respectively. This appeared to be the result of hypertrophy of the superior muscle band (Fig. 20) which probably occurred as part of the progressive left ventricular hypertrophy. This complication was bad in patients who were presented for Fontan procedures and must be considered in the assessment of patients for this type of operation.

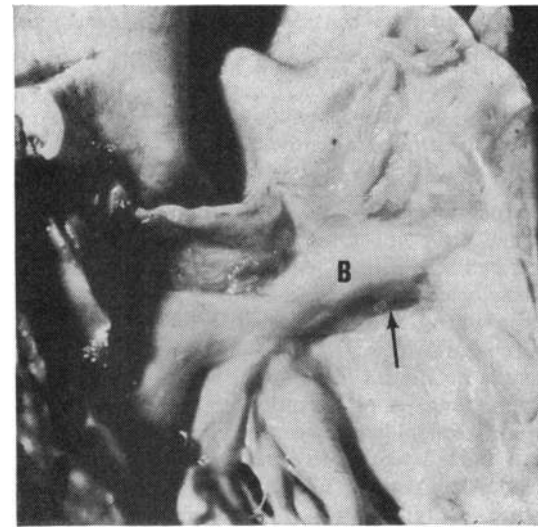


Fig. 20 *Heart viewed from the left ventricle from a boy aged 17 years who had palliative surgery for tricuspid atresia at age 6 years and died after a modified Fontan procedure. The window type VSD has closed spontaneously but hypertrophy of the muscular bar (B) above the defect has caused mild subaortic obstruction with a gradient of 35 mmHg. Arrow shows where VSD has closed.*

It was rare for the 'VSD' in tricuspid atresia with normal great arteries to remain large throughout postnatal life and be associated with persistent pulmonary hypertension. Thus, banding of the pulmonary artery in such infants in failure with tricuspid atresia is probably contraindicated in view of the natural history.

Once the VSD (bulboventricular foramen) reduces in size and limits flow, the once normal right outflow and pulmonary arteries will not grow. If this occurs early these hypoplastic structures cannot be used in these modifications of Fontan operations and so this change in mor-

phology must be considered in the management of such patients.

Acquired left ventricular obstruction in normally placed outflow tracts

Obstruction can also develop in the left ventricular outflow tract appearing as a fibrous ring, rarely described as a membrane. The fibrous obstruction is usually eccentric, attached to the anterior cusp of the mitral valve, and usually associated with severe septal hypertrophy. This type of collagen tissue is not found in newborn hearts, presumably because there is no turbulence in the fetal heart and this lesion has never been reported to cause death under 1 year. There are, therefore, grounds to consider that this 'fixed' subaortic obstruction is thus acquired and not congenital. However, despite its probable absence in the newborn, I believe that fixed subaortic obstruction develops in relation to the presence of some congenital abnormality perhaps in the cardiac muscle. In a consecutive series of 39 patients with fixed subaortic stenosis other congenital lesions in the cardiovascular system were present in 22 (56%); this supports the likelihood of the influence of some congenital disorder in the aetiology.

Perhaps more relevant is that as well as simple myocardial hypertrophy in the left ventricle areas of myocardial dysplasia identical to hypertrophic obstructive cardiomyopathy (or asymmetrical septal hypertrophy) are present low in the ventricular septum in infants who die from other diseases in whom mild fixed subaortic stenosis has been found (L. Becú, 1976, personal communication). After complete surgical removal of the fixed part of the obstruction leaving only small pressure gradients across the left outflow at rest, the left ventricle responds to inotropic stimuli and ectopic beats as if hypertrophic obstructive cardiomyopathy were present in many patients, suggesting that the muscle is very abnormal (Somerville and Montoyo, 1971; Somerville and Becú, 1977). Perhaps this abnormal muscle in the septum contracts abnormally, develops secondary changes and causes turbulence in the abnormal outflow, and stimulates the formation of fixed subaortic stenosis which in turn further stimulates the abnormal muscle.

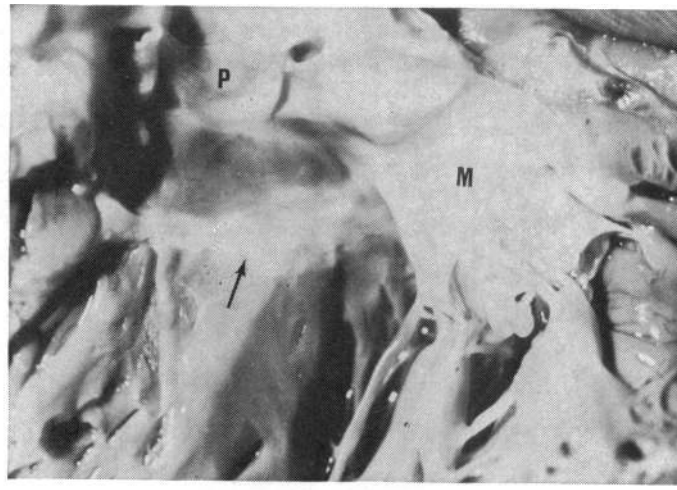
This type of fixed subaortic stenosis may also form with certain ventricular septal defects anterior to the medial muscle of the tricuspid valve. If the subaortic obstruction is not recognised when the ventricular septal defect is closed from the right ventricle the patient may die from untreated left ventricular outflow obstruction. Sometimes a fixed subaortic stenosis forms as a VSD closes spontaneously.

The subpulmonary obstruction from the accumulation of fibrous tissue in the left ventricular outflow tract in certain patients with classic transposition of the great arteries (TGA) is also acquired, not congenital, when it has the same anatomical and histological form as the fixed subaortic stenosis described above. Its presence limits pulmonary blood flow, increasing the central cyanosis in TGA, adding signs of pulmonary stenosis, and increasing left ventricular hypertrophy. The opportunity to examine the left ventricular outflow stenosis presents earlier in transposition than in fixed subaortic stenosis and thus we know more about its pathogenesis.

The obstruction begins as a deposition of fibrous tissue on the ventricular septum opposite the anterior mitral cusp (Fig. 21a). This fibrous area becomes crescentic and eventually forms a complete ring (Fig. 21b and c). Careful histological sectioning of the ventricular septum beneath these obstructions in 5 such patients, aged 5 months to 20 months at the time of death, has shown dysplastic myocardium (Somerville and Becú, 1977) but we do not know how much muscle dysplasia must be present to be associated with significant obstruction or why only some patients develop it. The speed and extent at which left ventricular outflow obstruction develops in transposition must depend upon factors other than the presence of dysplastic muscle in the ventricular septum, such as abnormal septal movement and altered haemodynamics, particularly left ventricular hypertension associated with an added lesion. There are other anatomical forms of subpulmonary obstruction in TGA but this ring form is the most common. It is easily removed during arterial correction for transposition (Ross *et al.*, 1976), but we do not yet know whether it continues to progress when the aorta is restored to its correct position.

Acquired subaortic obstruction in complex anomalies

Subaortic stenosis can develop as the bulboventricular foramen ('VSD') shrinks in certain complex anomalies. This may occur in some univentricular hearts with a subaortic chamber (Somerville *et al.*, 1974) or subaortic conus, tricuspid atresia with transposition particularly when associated with coarctation, double outflow right ventricle (Fig. 22a and b), and occasionally in classic transposition (Fig. 23a and b) where the anterior aorta is connected to the physiological and anatomical right ventricle. The formation of such an obstruction



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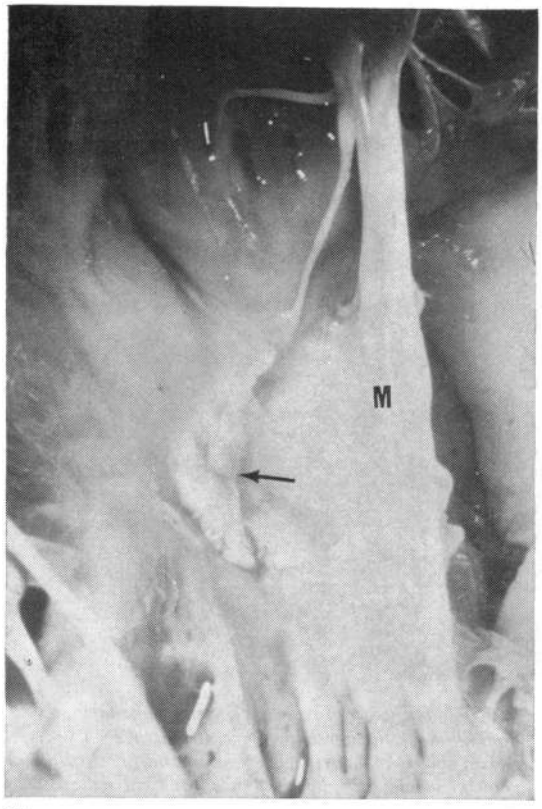

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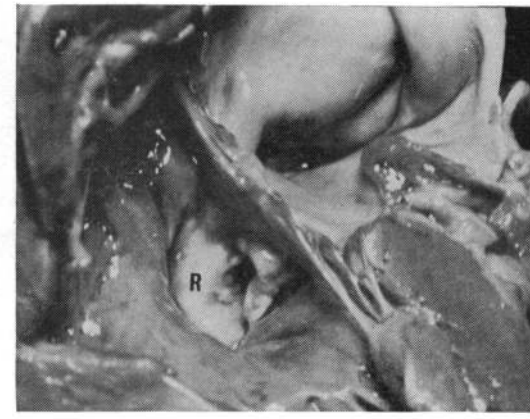

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Fig. 21 *Formation of subpulmonary obstruction in classic transposition of the great arteries (TGA). (a) From a baby aged 5 months who died after a Mustard procedure. Viewed from the left ventricle, the start of a fibrous ridge on the ventricular septum can be seen forming (arrow) opposite the mitral anterior cusp (M) and beneath the pulmonary valve (P). A gradient of 5 mmHg had been recorded between pulmonary artery and left ventricle. (b) Crescentic obstructing ridge on ventricular septum in a 4-year-old child with TGA and ventricular septal defect, viewed from the apex of the left ventricle with anterior cusp of the mitral valve to the right (M) and subpulmonary ridge on the left (arrow). (c) Fully developed fibrous (collagen) subpulmonary ring obstruction (R) in the left outflow in a 6-year-old patient with TGA, viewed from the apex of the left ventricle.*

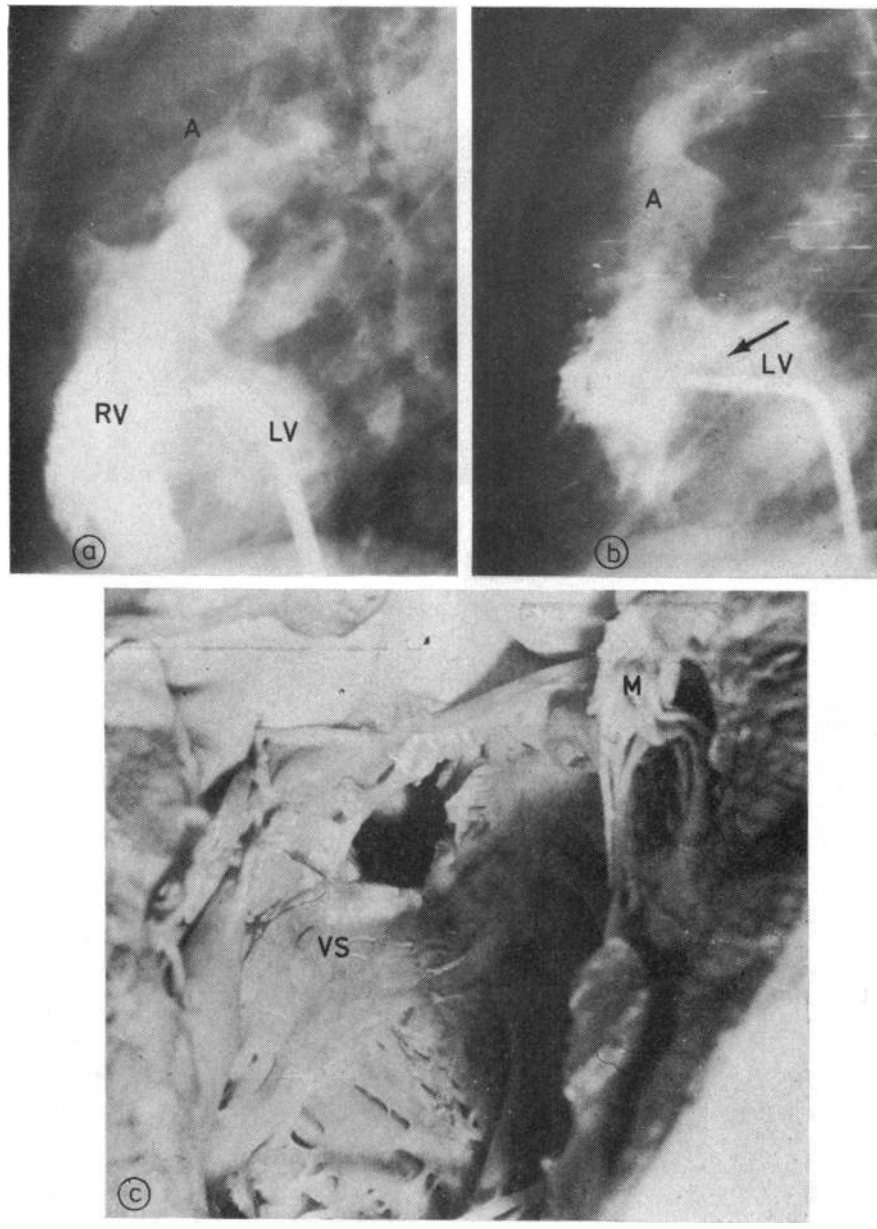
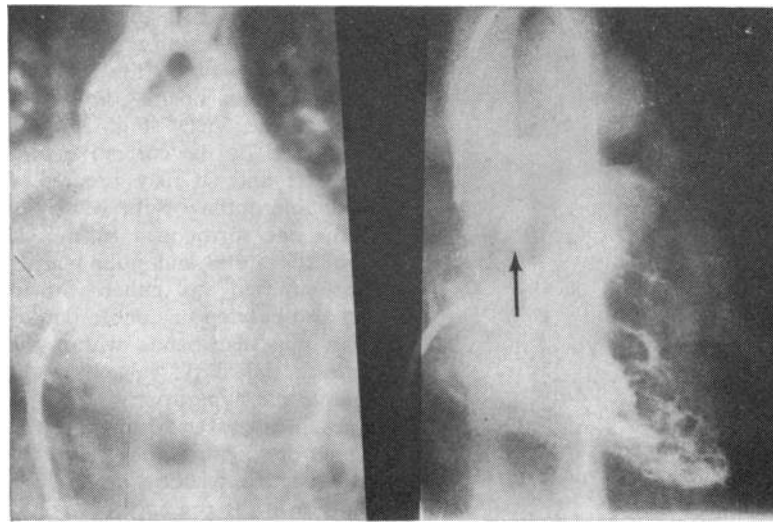


Fig. 22 *Serial right ventricular angiograms from a patient with double outflow right ventricle and pulmonary stenosis. (a) At age 4 years, the left ventricular pressure was 10 mmHg above the aortic pressure. (b) At age 15 years, the left ventricular pressure (165/0 mmHg) was 75 mmHg higher than the right ventricular pressure and fibrous lips can be seen around the defect (arrow). A, ascending aorta; RV, right ventricle; LV, left ventricle. (c) Ventricular septal defect in double outflow right ventricle, viewed from the left ventricle. Between mitral cusp (M) and ventricular septum (VS) is a fibrous ring around the VSD. A systolic gradient of 75 mmHg was present between the left ventricle and the right ventricle.*

depends upon the distribution of the displaced muscular bands and how quickly enlargement takes place in them. Banding of the pulmonary artery may accelerate the development of this obstruction (Freedom *et al.*, 1977) and should not be done as a palliative procedure when the anatomic potential



(*a*) (*b*)

Fig. 23 *Serial angiograms from a child with TGA, VSD, and coarctation who developed severe subaortic obstruction from hypertrophy of displaced bands in the right ventricle beneath the aortic valve. (a) Age 3 months, before resection of coarctation. Bands visible beneath the aortic valve. Right ventricular pressure 10 mmHg above the ascending aortic recorded pressures. (b) Age 4 years, 3 years after resection of coarctation and banding of the pulmonary artery. There was a gradient of 100 mmHg between the ascending aorta and right ventricle. The increase in the size of the bands forming the subaortic obstruction is recognisable (arrow).*

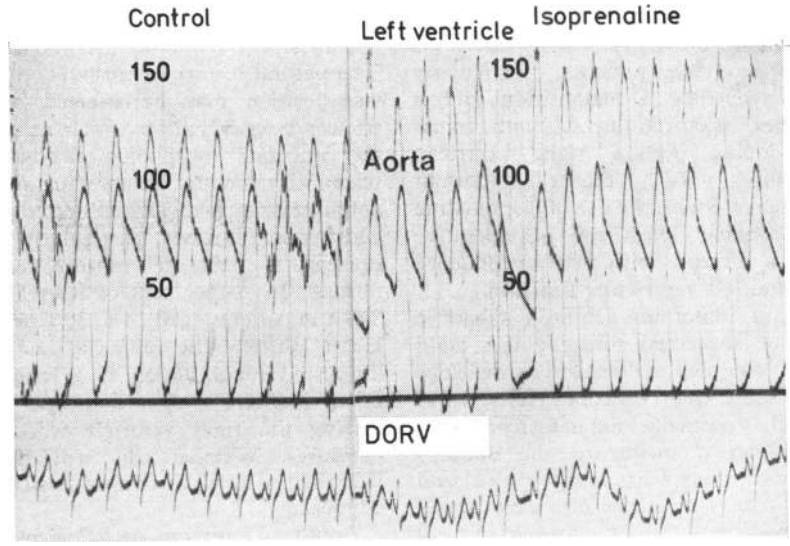


Fig. 24 *Left ventricular and aortic pressures in a 7-year-old boy with double outflow right ventricle and pulmonary stenosis. At rest there was a gradient of 28 mmHg. After isoprenaline the gradient rose to 60 mmHg and the postectopic beat showed an increase in gradient with falling of the aortic pressure as in a labile muscular obstruction.*

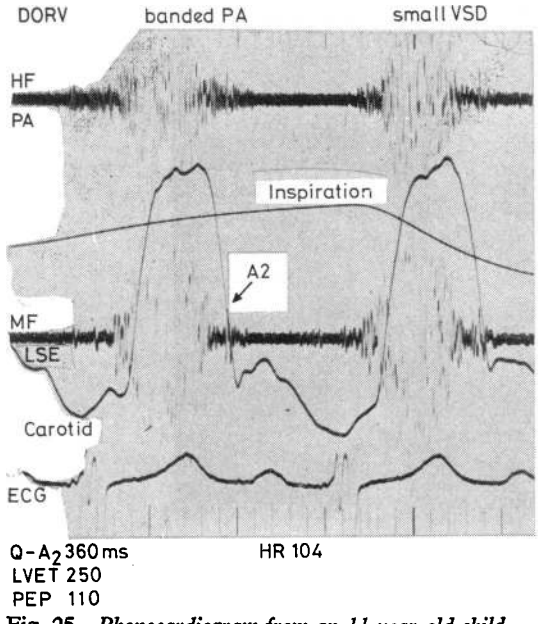


Fig. 25 *Phonocardiogram from an 11-year-old child with severe subaortic stenosis caused by shrinkage of the VSD in double outflow right ventricle. The gradient between the ventricles was 100 mmHg. Aortic valve closure (A2) was diminished with slight prolongation of ejection times.*

for subaortic stenosis to develop is recognised. Both clinicians and investigators must be aware of this serious complication and routinely search for gradients when studying patients, particularly those with one ventricle L-malposition and a subaortic chamber, tricuspid atresia with transposition, and double outflow right ventricle. The documentation of small gradients is important since they may increase with the use of isoprenaline (Fig. 24) and adversely affect the postoperative course. They also increase with time to influence both symptoms and left ventricular function.

The presence of important acquired subaortic stenosis should be suspected clinically if a child with one of these complex malformations develops angina, effort giddiness, or syncope. Aortic valve closure (A2) which is normally loud in many of these pathological complexes, owing to the anterior position of the aorta, may become diminished and even delayed with the appearance of a new carotid thrill (Fig. 25). Adding to the difficulties of clinical assessment is the fact that after banding of the pulmonary artery a thrill in the carotid area is often felt. Unexpected severe left ventricular hypertrophy may develop over the years in double outlet right ventricle with stenosing 'VSD' but this is not seen in univentricular hearts. In double outflow right ventricle the surgeon must be warned of even mild obstruction between the left and right ventricles since a fibrous lip may lie on the left ventricular side of the VSD (Fig. 22c) and may remain untouched by the corrective surgery in the right ventricle and so may progress later. The VSD in double outflow right ventricle which obstructs is the one surrounded by muscle, well separated from the aortic and pulmonary valves and often 'uncommitted' to either. Subaortic obstruction can also develop in double outflow right ventricle from muscular bands within the right ventricle beneath the aortic valve (subaortic conus) which enlarge and hypertrophy.

In all cases seen with this problem, the potential for its development has usually been ignored and retrospective scrutiny of the early investigations has shown the presence of appropriately displaced muscle bands around the foramen, subaortic region, or circling the ventricular septal defect.

Other postnatal pathological changes

The other basic pathological mechanisms which change the cardiac form and function deserve brief mention. Firstly, atrioventricular valve regurgitation either on the right or left side of the heart may be acquired causing failure in sinus rhythm in univentricular hearts, double outflow ventricles, atrioventricular defects, and classic or corrected transposition. This may lead to atrial fibrillation, usually after the first decade, and a downhill course. The natural history of treated and untreated classic transposition may be affected by the onset of tricuspid regurgitation which results mainly from the congenital morphological abnormalities of the tricuspid valve and its attachments (Fig. 26). The abnormal tricuspid valve subjected to high pressures and unusual stresses, particularly when a VSD is present, is liable to rupture, calcification, and fibrosis. In 20 per cent of Rastelli procedures for TGA in patients aged 14 to 30 years in the National Heart Hospital the valve has had to be replaced. Tricuspid regurgitation is a serious complication in a Mustard's operation and encouraged by leaving the right ventricle working at systemic pressures. Whether this will affect those who have had arterial correction must await long-term studies.

Another common pathological ageing change is calcification which affects congenitally abnormal semilunar and atrioventricular valves. Calcification of the congenitally abnormal aortic valve is inevitable and common but its timing depends upon the severity of the obstruction, athletic activities,

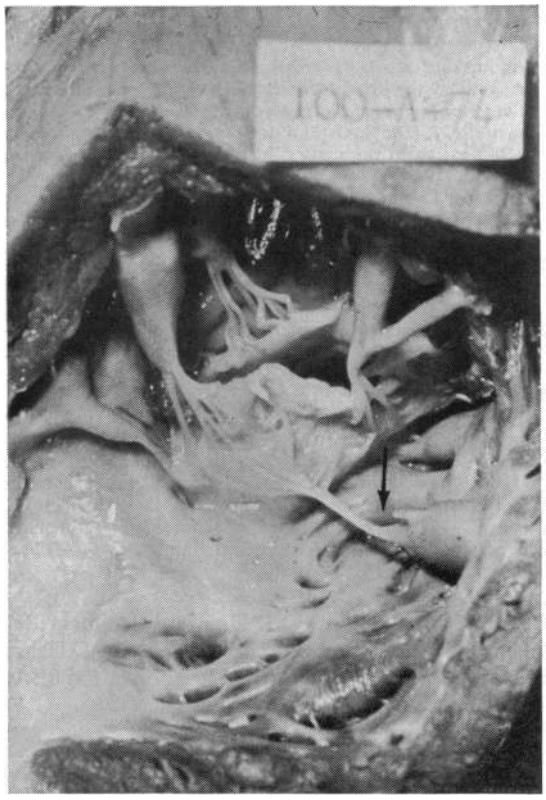


Fig. 26 *Undersurface of tricuspid valve and attachments from a child aged 4 years with TGA and Rashkind septostomy who had a successful Mustard operation one year previously and died from sudden pulmonary oedema. The papillary muscles and chordae are abnormal and one has ruptured (arrow).*

metabolic disturbances, and infection. The congenitally stenosed pulmonary valve also calcifies eventually and features of pulmonary regurgitation usually develop when this occurs. The stenosed pulmonary valve calcifies earlier in adults with cyanotic congenital heart disease and calcium may also be deposited on the tricuspid valve and ring in adults with unrelieved congenital pulmonary valve stenosis. Identification of the calcified pulmonary valve on the chest *x*-ray film of the adult with cyanotic heart disease may aid the correct clinical diagnosis.

Conclusions

Knowledge of the relation between changing form and function must underlie any understanding of the natural history of congenital heart disease. The same principles apply to all forms of heart disease.

Such clinico-morphological correlations were first established in human pathology by Theophilus Laennec (1781-1862) who not only invented the first noninvasive instrument, the stethoscope, but also confirmed his findings by performing necropsies on his patients.

Since then our knowledge of how function alters in response to changing form has been greatly extended by electrocardiography, angiography, radioisotope scanning, and echocardiography. Prolonged survival, often the result of heroic surgery, has added a new dimension of time to our studies of congenital heart disease. What Laennec discovered at necropsy we can now detect in the living and, though Laennec could not follow the changing anatomy by recording the changing physiology as the patients live, we can and must.

I have used congenital heart disease as a model for the study of changing form and function. Correlating the two is the basis of modern cardiology. Progress in medical understanding and surgical dexterity has produced a new medical community, namely the survivors of congenital heart disease. Correct management of these is not ideal unless the predictable effects of changing cardiac form and function for each anomaly are understood within the framework of time.

Some of these ideas were first expressed in an invited talk on 'changing morphology in congenital heart disease' at the World Congress of Cardiology, 1974, and subsequently in the first Stacy White Lecture, Atlanta, 1975.

I am particularly grateful to Luis Becú, Chief of the Department of Pathology, Hospital de Ninos, Buenos Aires, for all the pathological illustrations shown here and for teaching me much about basic morphology in congenital cardiac anomalies. I am indebted to Donald Ross for encouragement, instruction in living anatomy, and many special biopsies, and to the radiologists, Simon Rees and the late Dr Keith Jefferson.

To my associates in the Thoracic Unit, The Hospital for Sick Children, Dick Bonham-Carter, David Waterston, James Taylor, and Fergus Macartney, I am specially grateful for the opportunity to follow survivors with congenital heart disease, and for allowing me access to patients with large ventricular septal defects and tricuspid atresia. I am indebted to James Taylor for Fig. 11b.

Finally, I cannot adequately express my thanks to the teachers who profoundly influenced my thinking, Lord Brock, the late Dr Evan Bedford, and the late Dr Paul Wood.

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