Ventricular Septal Defect

A Review of Current Thoughts*

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Ventricular septal defect, alone or in combination with other cardiac malformations, is the commonest form of congenital heart disease in man. Morphogenically, the ventricular septum is composed of three parts: (a) the conal septum, (b) the septum of the endocardial cushions, and (c) the muscular septum proper. Consequently, most cono-truncal abnormalities (transposition of the great arteries, tetralogy of Fallot, common truncus arteriosus) include a defect of the ventricular septum and, similarly, most endocardial cushion defects (and all complete AV canals) have a ventricular component. Isolated ventricular septal defects may occur in any of the three parts. The majority of the complex intracardiac malformations are associated with a ventricular septal defect.

The purpose of this clinical review, however, is to discuss problems relating to patients whose principal, even exclusive, problem is a defect of the ventricular septum. We will, therefore, exclude from consideration patients with tetralogy of Fallot, truncus arteriosus, transposition of the great arteries, as well as endocardial cushion defect. Furthermore, because of its invariable association with other serious malformations of the endocardial cushion as well as cono-truncal regions, we will exclude from this discussion patients with single ventricle who in our view do not simply represent very large ventricular defects but a more profound developmental abnormality (Van Praagh, Ongley, and Swan, 1964). Patients with dextrocardia will not be considered either, partly because the occurrence of a solitary ventricular defect in this setting is rare and partly because they represent unique diagnostic and surgical problems. Finally, and rather arbitrarily, we will exclude from consideration patients with ventricular septal defect

and associated coarctation of the aorta, absent pulmonary valve, atrial septal defect, and patent ductus arteriosus beyond the neonatal period.

Our discussion of ventricular septal defect will include, however, patients with associated pulmonary vascular obstructive disease, aortic regurgitation, minimal pulmonary stenosis (peak gradient of less than 30 mm. Hg), and mitral valve disease (outside of the framework of endocardial cushion defect). The first three of these should be considered because their development, in the course of time, represents part of the natural history of ventricular septal defect. Coexisting mitral valve involvement will also be discussed briefly, since its recognition is difficult and may influence surgical decision in regard to ventricular septal defect.

Within this review, we will cite the incidence, restate the diagnostic criteria, discuss the anatomy and physiology, emphasize more recent information referable to the clinical picture, survey the data available on the natural course of the disease, propose indications for surgery, and present the results of operation.

Incidence

Patients with solitary ventricular septal defect, or those with pulmonary vascular obstruction, minimal pulmonary stenosis, aortic regurgitation, or mitral valve involvement, represent about 20% of the total congenital heart disease population (Keith, Rowe, and Vlad, 1967; Nadas, 1963) in series dominated by the paediatric age-group. An even higher incidence in infants is suggested by Hoffman and Rudolph (1965); the absolute incidence in their series was 1.35/1000 live births in New York hospitals. If one accepts MacMahon's data (MacMahon, McKeown, and Record, 1953) that the over-all incidence of congenital heart disease is 3/1000 live births, then this would suggest that in

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the newborn group almost 50% of the patients with congenital heart disease have solitary ventricular septal defect. We think this figure is too high. Somewhat more recent data on over-all incidence are closer to 6/1000 (Harris and Steinberg, 1954; McIntosh *et al.*, 1954). Thus, 1.35/1000 (or 2/1000 as Hoffman and Rudolph suggest may be the true figure) would represent about 30% incidence among newborn cardinals.

Interestingly enough, in surveys limited to school children (Weber, 1918; Rose and Keith, 1966) and this, of course, has a great deal of bearing on the natural history of ventricular septal defect, a much lower incidence was found (2.8 to 5.6/10,000). An interesting Table in Bloomfield's paper (1964) indicates that even in case material 'usually limited to age three and beyond', first visits for ventricular septal defect are rare over the age of 30 (48/424). The same author's necropsy data also attest to the rarity of isolated ventricular septal defects over 15 to 20 years of age (0.37/1000).

These figures are cited only to indicate that isolated ventricular septal defect is relatively common in infancy and becomes rarer with advancing age. Obviously three things may underlie this trend: (1) death; (2) spontaneous cure; (3) change in clinical or pathological profiles so that the lesion is not classified in later life as ventricular septal defect.

The discussions to follow will attempt to shed some light on this disappearance of ventricular septal defects.

Diagnostic Criteria

The diagnosis of ventricular septal defect seems, superficially, to be on firmest grounds if made at necropsy. This obviously is true in a positive sense; if the pathologist finds a defect in the ventricular septum there is very little room for argument. On the other hand, it is equally clear that small ventricular defects, giving rise to the characteristic clinical profile and proven unquestionably by physiological or angiographic data, may be missed by a less than first-class pathologist. The diagnosis of a ventricular defect indeed may be made easily at necropsy, but it cannot be excluded by anything but the most painstaking search by expert hands probing diligently behind trabeculae and papillary muscles. Despite the reported incidence of spontaneous closure of ventricular septal defects, the pathological recognition that a defect existed and later closed is rare. It seems clear that while small defects may be overlooked, evidences of a closed defect are almost invariably unrecognized, even by the most sophisticated observers.

Cardiac catheterization is today the procedure of

choice in establishing, or excluding, the diagnosis of ventricular septal defect. The most widely accepted oximetric definition of a left-to-right shunt through the ventricular septum is a minimum of 10% increase in oxygen saturation from right atrium to ventricle in one set of samples, or a minimum of 5% increase in each of two sets of samples. A more sensitive, *in vivo*, oximetric method is afforded by the fiberoptic catheter responding instantaneously to phasic changes in oxygen saturation within the cardiac cycle; the jet of highly oxygenated blood may be detected by this instrument if skilfully placed in the vicinity of the defect (Fig. 1). Other indicators of high sensitivity for detection of left-to-right shunts include hydrogen ion (the gas inhaled through a mask and detected by a platinum electrode in the ventricle) (Fig. 2) and Cardiogreen injected through a catheter in the left ventricle, with sampling in the right ventricle. Radiopaque material injected through a catheter into the left ventricle and traced by radiographs or cinefluorograms is another excellent and highly sensitive method of detection of a left-to-right shunt through a ventricular septal defect (Fig. 3). A phonocatheter registering a pansystolic murmur in the right ventricle with little or no murmur in the right atrium or the main pulmonary artery (Fig. 4) may serve as an excellent, indirect, qualitative tool for demonstrating a ventricular septal defect.

The localization of right-to-left shunts may be accomplished by injection of an indicator (ascorbic acid or Cardiogreen) in the right ventricle (Fig. 5) and sampling from the left ventricle, or by selective angiocardiography from the right ventricle.

Of course, the clearest, and many times the simplest, way of demonstrating a ventricular defect at cardiac catheterization is by passage of the catheter from right ventricle to left ventricle or aorta.

In our opinion, the hydrogen ion method, fiberoptic oximetry, and good quality left ventricular angiograms are probably the most sensitive detectors of ventricular defect. Shunts as small as 5% of the cardiac output may be detected by these techniques. Preference among the three will depend on the experience of the individual catheterization laboratories; used optimally their sensitivities are about the same. Although *in vitro* oximetry is not as sensitive as the three methods cited above, one can state with assurance that this method, with multiple samplings, will probably uncover all the surgically significant defects.

Surgical exploration of the right ventricle, in our opinion, is an inappropriate method for the diagnosis

FIG. 1.—FO O₂ = fiberoptic oxygen. RA = right atrium. RV = right ventricle. Upper ECG = intracardiac electrocardiogram obtained from fiberoptic catheter. Lower ECG = external electrocardiogram. Note the distinct systolic rise in oxygen saturation in the right ventricle establishing the presence of a left-to-right shunt into the right ventricle.

FIG. 2.—RA = right atrium. RV = right ventricle. HR = heart rate. Note the rapid, early upswing of the hydrogen trace in the right ventricle as compared to the right atrium, establishing the presence of a ventricular septal defect.

FIG. 3.—A lateral left ventricular angiogram with contrast injection via the retrograde route. The arrow indicates a jet of contrast material from the left ventricle into the right ventricle, establishing the presence of a small ventricular septal defect.

of ventricular defect. Cardiotomy, with its inevitable emotional tensions, poor visibility, limited time, and associated morbidity is not a diagnostic procedure. Open-heart surgery ought not to be undertaken in an institution not equipped with a competent, diagnostic team.

The final, remaining, question is how accurate is the clinical diagnosis of ventricular septal defect. The clinical profile is certainly characteristic enough to suggest the diagnosis in all cases worth considering for corrective surgery. Difficulties may arise with defects so small that the murmur lacks its usual characteristics, and in patients with pulmonary vascular obstructive disease or congestive heart failure, where the flow dynamics are severely altered. In case of the mini-defect, with normal heart sounds, x-rays, and electrocardiograms, the precise diagnosis is only of academic interest. In the patient with pulmonary vascular obstructive disease—Eisenmenger's syndrome—cardiac surgery is contraindicated; thus the accurate anatomical diagnosis is again only of marginal interest to the patient though it contains great fascination for the cardiologist. Finally, infants and children with left-to-right shunts and congestive heart failure have to be catheterized anyhow, to exclude the presence of a patent ductus arteriosus. Thus, one may say that the clinical diagnosis of ventricular septal defect may be made quite accurately, in over 90% of the cases where it is of practical importance to the patient. At the same time, the fact that the

FIG. 4.—RA = right atrium. RV = right ventricle. BA = brachial artery tracing. SM = systolic murmur. The uppermost tracing from the phonocatheter shows the presence of a murmur in the ventricle which is not seen in the atrium.

FIG. 5.—SVC = superior vena cava. RV = right ventricle. The first arrow indicates the timing of ascorbic acid injection into (a) superior vena cava, and (b) right ventricle. The second arrow indicates the appearance of ascorbic acid as obtained from a systemic artery sensor. The earlier appearance of ascorbic acid following right vena caval injection as compared to right ventricular injection establishes the presence of a right-to-left shunt at a point proximal to the sampling point in the right ventricle. Thus, an atrial defect with a right-to-left shunt is present.

ventricular septal defect is present, and is diagnosed clinically, does not mean that this represents a satisfactory workup from the point of view of our surgical colleagues. The propensity of ventricular septal defects to occur in association with conotruncal and endocardial cushion abnormalities has already been alluded to; as cardiologists we owe it to our surgical brethren to give them, pre-operatively, as precise an outline of the intracardiac anatomy and haemodynamics as possible. In this centre, at the present time, all patients with a clinical diagnosis of ventricular septal defect of presumed surgical importance, undergo cardiac catheterization and angiocardiology before they are submitted to operation. Particular effort is made to obtain information on the following points: (1) position of the great arteries; (2) anomalies of systemic venous return; (3) presence of patent ductus arteriosus; (4) presence of other, unrecognized, associated defects (shunt from left ventricle to right atrium, cleft tricuspid valve, mitral valve disease, atrial septal defect); (5) size and location of the ventricular septal defect; and (6) estimation of pulmonary-systemic flow ratio and pulmonary-systemic pressure ratio.

Anatomy

Most students of cardiac anatomy divide ventri-

cular septal defects into two broad categories: (a) outflow, and (b) inflow defects. The *outflow defects*, when perceived from the right ventricle, may lie anywhere between the papillary muscle of the conus (muscle of Lancisi) inferiorly, to the pulmonary valve superiorly. Most ventricular septal defects are situated in the lower portion of the area extending from the crista down to the papillary muscle of the conus. These are the subaortic defects and, if viewed from the left ventricular side, are situated underneath the posterior and/or right aortic cusps, and are referred to commonly as membranous defects, though they almost invariably also involve the muscular septum anterior to it. These defects make up the large majority. Another and considerably rarer outflow defect is supracristal, at various distances below the pulmonary valve when viewed from the right ventricle, and under the right coronary leaflet if inspected from the left ventricle.

The *inflow defects* are muscular, all proximal to the papillary muscle of the conus as viewed from the right side. They may be single lesions in the posterior portion of the septum, close to the mitral anulus if viewed from the left side, or situated antero-inferiorly near the apex. Multiple inflow defects, often referred to as Swiss cheese variety, are nightmares to surgeons. The so-called AV

commune defects are large posterior openings to the right of the muscle of Lancisi beneath the septal leaflet of the tricuspid valve.

It is perhaps easiest to remember, and is not too far from the truth, that the membranous outflow defects adjoining the right and/or posterior aortic cusps make up 70% of the defects, and the high outflow lesions, the inflow lesions, and the AV canal defects contribute probably about 10% each to the total.

The size of the defects may vary from pinpoint size to virtual absence of the septum. Defects with diameters of at least one-half the aortic diameter are referred to as 'large' (Selzer, 1949).

Physiology

The direction and magnitude of flow across the ventricular septal defect depends on the size of the defect and the pressure gradient between the two ventricles. Savard *et al.* (1960) found this relation accurate enough to suggest that the pressure gradient between the two ventricles, in mm. Hg divided by the left-to-right shunt in l./min. per m.² body weight, the so-called resistance index, could predict with reasonable accuracy the size of the defect at surgery, up to 1 cm./m.². Any defect greater than this would still give the same index. This then could be used as a definition of a 'large' defect, in a physiological sense, and is not too far removed from the anatomical definitions cited above, i.e. half the aortic diameter.

The timing of the left-to-right shunt, within the cardiac cycle, has recently been studied in our laboratory with the fiberoptic catheter (Gamble *et al.*, 1965) and by Levin *et al.* (1967) using biplane cine-angiography. It seems that the flow occurs in early systole in small defects, throughout systole in large defects without pulmonary vascular obstructive disease, and in systole as well as diastole, with a double peak, in patients with ventricular septal defect and pulmonary vascular obstructive disease (Fig. 1).

That the physiology of ventricular septal defect depends on the status of the pulmonary arterioles as well as the size of the defects, has been amply discussed by Rudolph and Nadas (1962) in the past and will not be repeated here. Suffice it to say that the large defects (over 1 cm./m.² in diameter physiologically, or over half the aortic diameter pathologically) result in pressure equalization between the systemic and pulmonary circuits. Applying Ohm's law, $P = F \times R$, it seems clear that the systemic, or near systemic, pressure levels in the pulmonary circuit, associated with large septal defects, may be high pulmonary flow or

high pulmonary resistance situations or, most likely, a combination of both.

The changes in the muscular pulmonary arteries and pulmonary arterioles from newborn period to adulthood and the parallel changes occurring in pulmonary haemodynamics have also been amply described within the past decade (Dammann and Ferencz, 1956). Briefly, the normal involution of the media of the muscular arteries becomes evident within the first couple of months of life but is not normally completed till sometime within the first year. The precapillary arterioles normally have no muscular media, except at their branching off from the muscular arteries. In patients with large ventricular septal defects and pulmonary artery hypertension, the normal involution does not usually take place, anatomically, according to the normal time-table. Medial hypertrophy is present in infancy and, with the progressive intimal changes developing in early adulthood, pulmonary vascular obstruction results (Naeye, 1966).

In the normal fetus, right and left ventricular pressures are equal due to the high resistance offered by the unexpanded lung and the muscular arteries. With the first few breaths the lungs expand, resistance drops dramatically, and a pressure gradient develops between the two circuits, now separated by the closure of the ductus arteriosus and the foramen ovale. Further drop in pulmonary resistance occurs through the ensuing months with the normal involution of the muscular arteries. The course of events in the patients with small ventricular septal defects, though not well documented, is surely not too different. In babies with large ventricular septal defects, however, the drop in resistance does not occur with the same speed as in the normal infants or in those with small defects. The drop in resistance due to expansion of the lung does occur indeed, but the further drop due to medial involution occurs probably only transiently if the size of the defect stays the same. Taking these anatomical and physiological changes into consideration, one may easily explain the following clinical facts: (1) the murmur of the ventricular septal defect is usually not heard well within the first days of life, because resistances in the systemic and pulmonary circuits are similar enough that no significant pressure gradient between the two circuits exists; thus no significant left-to-right shunt, to give rise to a murmur, occurs; (2) in almost all cases a significant murmur appears within the first month of life because, when a defect is present, enough involution of the pulmonary vasculature occurs within this period to give rise to a sizeable shunt; (3) congestive heart failure in babies with large

ventricular septal defects almost invariably occurs within the first 6 months, and mostly within the first 3 months, of life, but almost never in the first week, because the ratio of R_p/R_s does not usually permit a large left-to-right shunt in the first week of life, but will certainly, with a large defect, be conducive to congestive heart failure within the first few months; (4) the appearance on the newborn chest x-ray of pulmonary vascular engorgement cannot be the result of increased pulmonary blood flow. Rather, other factors such as pulmonary venous congestion or pulmonary parenchymal disease are more likely causes of this x-ray appearance; the reason is that the ratio of pulmonary to systemic resistance is such that a large left-to-right shunt is not possible in the first days of life.

Clinical Picture

The clinical profile of ventricular septal defect, of course, depends principally on the size of the defect and the status of the pulmonary vasculature. We should also stress that the description as briefly presented here, and as discussed many times in various publications and in textbooks (Keith *et al.*, 1967; Nadas, 1963), pertains only to ventricular septal defect with left-to-right shunts. Those with right-to-left shunts present with the clinical picture

FIG. 6.—This child was proved to have a small ventricular septal defect. Note the atypical, early, decrescendo, systolic murmur recorded at the lower left sternal border (4LIS) on phonocardiography. 2LIS = 2nd left intercostal space. CAR = external carotid tracing. The second tracing is the reference electrocardiogram.

of the Eisenmenger syndrome, or pulmonary vascular obstructive disease, and are indistinguishable, for practical purposes, from pulmonary vascular obstruction associated with atrial defect or aorto-pulmonary communications (Cutler *et al.*, 1954).

The group characteristics of congenital heart disease with a left-to-right shunt are present in more or lesser degrees in all patients with a ventricular defect as defined above. There is left chest prominence, a hyperkinetic impulse, diastolic flow rumble, and active pulmonary plethora x-ray film.

The following additional clinical findings are specific for ventricular defect and may help in assessing the severity of the disease. The cardiac impulse is biventricular; the larger the pulmonary systemic flow ratio, the more prominent is the apical impulse; the higher the pulmonary resistance, the more the xiphoid heave dominates. The pansystolic, loud murmur maximal at the xiphoid process and transmitting along the left sternal border (but in contrast to mitral regurgitation murmur not too far to the posterior axilla) is characteristic of ventricular defect with a sizeable left-to-right shunt; as the shunt diminishes in size, due either to the development of vascular disease or, more favourably, to diminishing size of the defect, the systolic murmur becomes fainter and shorter, losing its pansystolic character (Fig. 6). The mid-diastolic rumble usually follows the third sound and thus is separated appreciably from the pulmonary closure; though, by and large, the louder the rumble, the greater the left-to-right shunt, this relation is far from linear (Fyler *et al.*, 1958). It should also be mentioned that mid-diastolic rumbles due to increased mitral valve flow alone, seldom, if ever, assume a presystolic crescendo configuration (Fig. 7). The intensity of the pulmonary valve closure is roughly related to pulmonary arterial pressure, but in young children with thin chests this may prove to be an unreliable guide. Better assessment of pulmonary artery pressure may be furnished at auscultation by the inverse relation of A_2-P_2 distance, and phonocardiographically by the P_2-V interval (Gamboa *et al.*, 1965) (Fig. 8); the closer the second sound is split, the nearer pulmonary artery pressure is to systemic artery pressure.

The over-all heart size and the left atrial size in the x-ray are excellent measures of the size of the left-to-right shunt and prove to be more dependable in our hands in this regard than the estimation of degrees of pulmonary plethora. The relative size of the left and right ventricles may give some impression as to whether the ventricular defect is princi-

FIG. 7.—External phonocardiogram. Note the loud systolic murmur (SM) and prominent mid-diastolic rumble (MDM) recorded at the apex.

FIG. 8.—Schematic representation of the right ventricular, pulmonary artery, and right atrial pressure tracings. The right ventricular isovolumetric relaxation period is defined as that period of time between pulmonary valve closure and opening of the tricuspid valve. The isovolumetric relaxation period may be measured from the pulmonary valve closure to the V wave of the jugular venous pulse. The higher right ventricular pressures are associated with a delayed opening of the tricuspid valve and consequently a prolonged P_2 —V interval.

pally a high-flow or a high-resistance type. A prominent main pulmonary artery, in a patient without pulmonary stenosis, suggests pulmonary artery hypertension but does not differentiate by any means the hyperkinetic from the obstructive type.

The electrocardiogram is an excellent tool for the assessment of right ventricular, and thus indirectly, pulmonary arterial hypertension as well as the contribution of high pulmonary blood flow to the pulmonary arterial pressure. DuShane *et al.* (1960) and Vince and Keith (1961) have repeatedly stressed the importance of the electrocardiogram in the pre-operative assessment of patients with ventricular septal defect. It may be said with considerable assurance that ventricular defect patients without right ventricular hypertrophy in the cardiogram will not have appreciable pulmonary hypertension, and also that those without adequate left ventricular potential in the ECG probably will not have a significantly increased pulmonary blood flow. Of course these criteria, and they may be obtained from the scalar as well as the vectorcardiographic representations of the electrocardiogram, should not be relied upon independently but rather in conjunction with other clinical findings. It may be stated, however, that all patients with large ventricular defects will show some degree of right ventricular hypertrophy and that most patients who will benefit from closure of ventricular defects will show some left ventricular hypertrophy in the electrocardiogram.

Natural History

We have alluded already, in the section devoted to the discussion on incidence, to the 'case of the disappearing ventricular septal defect'. To paediatricians and paediatric cardiologists, ventricular septal defect is probably the commonest congenital cardiac malformation (2/1000 live births); in contrast, in the school surveys, incidences of only 0.3–0.6/1000 are cited. Looking at the problem in another way, the figures for newborns suggest that at this age about 30% of the patients with congenital heart disease have ventricular septal defect, data obtained from cardiac clinics dominated by the paediatric age-group suggest a 20% incidence, whereas from units frequented by adults an 8% figure is reported. These figures, difficult to obtain and harder to interpret, gain validity from the common-sense observation that in paediatric cardiac clinics ventricular defects are present in large numbers, whereas they are as rare as hens' teeth in adult clinics and offices.

What happens then to the patients with ventri-

cular septal defects? Our more surgically-oriented colleagues suggest, if not in writing but in formal and informal meetings, that they obviously die on account of the lack of surgical correction. The record does not seem to bear out this contention. In our own material (Fyler *et al.*, 1958), less than 5% of ventricular defects died and most of them with bronchopneumonia, prematurity, and associated anomalies. An 18% 'medical death rate' was found and contrasted with 25% 'surgical death rate' by Ritter *et al.* (1965), but in only half of the 18% was death attributable to congestive failure; in the others pneumonia, prematurity, and arrhythmias were the underlying causes of death. It is also interesting to note that in this carefully analysed series only one of the 85 patients who belonged to well-defined severity groups died without operation; 19 out of 20 deaths belonged to a category designated as 'remainder', by which the authors mean that the diagnosis was made at necropsy or on the basis of non-classifiable incomplete data. The vast majority of these deaths, then, were in patients who probably did not receive optimal care for any length of time. Walker *et al.* (1965) cite a mortality of 7/415 (less than 2%); but one of these occurred in an unexplained fashion in a baby with a defect of less than 1 cm./m.² and right ventricular pressure of 45 mm. Hg, and another one had congenital heart block.

It is clear then that death can account for only a small percentage of the disappearing defects. It is also uniformly accepted that the vast majority of the few deaths occurred within the first year, and probably within the first six months of life (Zacharioudakis, Terplan, and Lambert, 1957). Bloomfield (1964) could find only 25 ventricular defects in patients of over 20 among 67,000 necropsies, and 16 of these died from causes unrelated to their defects. Combining several series, this author found a 3.7/10,000 incidence among 142,000 necropsies of patients over 15 to 20 years, and death in most of these was probably not attributable to the ventricular defect itself.

The final consideration of the discussion of deaths in patients with ventricular septal defect should relate to the type of defect and to the nature of their demise. There seems to be no evidence whatsoever that small defects, less than 1 cm./m.², are likely to prove fatal. Bloomfield (1964) states that, 'pulmonary hypertension has never been reported to occur or develop in small defects'. In a statement based on the analysis of 115 reported necropsy cases, Lucas *et al.* (1961) come to the same conclusion on the basis of a smaller number of clinical observations. Ritter *et al.* (1965) found no

progressive pulmonary vascular obstructive disease among any of the patients with clinically small defects (pulmonary-systemic flow ratio of less than 2.5). Kaplan *et al.* (1963) state that, 'we did not recognize any instance of progression of small ventricular defects to severe pulmonary hypertension in adult life'. So that pulmonary vascular obstruction, one of the common causes of death, does not seem to occur with small defects. Congestive heart failure in Kaplan's group never occurred with pulmonary arterial pressure of less than 30 mm. Hg and was rare under 40 mm. Hg. Hoffman and Rudolph (1965) did not find evidence of severe failure in anybody with pulmonary-systemic pressure ratios of less than 50%. One can say then that only large defects develop the two commonest fatal complications: pulmonary vascular obstruction and congestive failure. Bacterial endocarditis, another potentially fatal complication of ventricular defect, may indeed affect small as well as larger defects; the assumption that small defects are more likely to be associated with bacterial endocarditis is probably not true (Blumenthal, Griffiths, and Morgan, 1960). Finally, one should mention another possible mode of death which may strike patients with small as well as large defects in the fifth or sixth decade, i.e. cardiomyopathy. Bloomfield (1964) speculates on this but the proof as yet is not completely convincing. One can say then with assurance that the disappearance of ventricular defect, and particularly the small defect, in adult life, is not due to premature death.

The next explanation of the mystery might be spontaneous, complete, or virtually complete, closure of the defect. The disappearance of a loud systolic murmur has suggested this course of events to clinicians for a long time (Weber, 1918), but it was not clearly proven by cardiac catheterization till this decade, and its frequent occurrence was documented only quite recently (Hoffman and Rudolph, 1965). As many as 60% of newborn ventricular defects were reported closed, or almost closed, within the neonatal period. If one adds to this Bloomfield's statement that 'at least 25% of small defects among patients *surviving infancy* will close in a lifetime' this will become a sizeable figure indeed. In our clinic we have 3 patients among 73 recatheterizations in whom the defect completely closed. In addition, we have 50 in whom the defect either closed completely, or became appreciably smaller, by clinical criteria. The mode of spontaneous closure of ventricular defects has not been proven yet, but it seems likely that several mechanisms could be responsible (Hoffman and Rudolph, 1965; Bloomfield, 1964; Evans, Rowe,

and Keith, 1960). There are no data available to predict with accuracy how many and which type of defect will close spontaneously, but certain inferences can be made. First, the commonest time of closure is in the neonatal period: but we have seen it occur in the pre-school period, documented once between 6 and 9 years of age and another at 14 years of age, and have no doubt that it may occur in adults as well. Small defects are more likely to close than larger ones; Evans *et al.* suggest, and we agree, that as many as 30% of clinically diagnosed ventricular defects with small shunts, normal electrocardiograms, and short, regurgitant murmurs, will close spontaneously. It is important to emphasize, however, that not too infrequently large defects with significant pulmonary arterial hypertension will also close or at least become appreciably smaller (Hoffman and Rudolph, 1965; Bloomfield, 1964; Kaplan *et al.*, 1963; Nadas *et al.*, 1961). It seems perfectly feasible, furthermore, that the soft short murmur of a small ventricular defect, quite obvious in childhood, will become practically inaudible in an adult with a large chest.

The considerations presented so far indicate that spontaneous closure or diminution of ventricular defect may explain the rarity of the defect in adults much more readily than premature death. In considering the matter further, one will have to raise the possibility that the defect does not disappear but changes its clinical appearance by developing complications. This way the same patient may have been classified under the diagnosis of ventricular defect in early life and is classified as something else by the time he, or she, starts attending an adult clinic. This consideration incidentally supports the argument of the same clinic looking after patients with congenital heart disease from infancy up to adulthood.

Among the most dreaded complications of ventricular defect is the development of pulmonary vascular obstructive disease. With the advent of medial and intimal changes in the arterioles, the patient, who, in infancy, was non-cyanotic and suffered from congestive failure due to a large pulmonary flow, becomes, as an adult, severely cyanotic, polycythaemic, and dyspnoeic. There are no overt evidences of failure, the systolic murmur becomes faint or even disappears, pulmonary incompetence murmur becomes evident, and the electrocardiogram shows pure right ventricular hypertrophy. This, then, is the clinical picture of Eisenmenger's disease, which is totally different from the profile of ventricular defect as seen in childhood. It was mentioned earlier that ventricular defects of Eisenmenger variety are almost invariably large

defects. The high incidence of pulmonary vascular obstructive disease among adults, as contrasted to infants and children, has been well documented clinically; Kaplan *et al.* found 46% in 26 patients over 20 years; the average age of patients with Eisenmenger's complex in Bloomfield's series was 22 years. In our series of paediatric patients, 25% of isolated ventricular septal defects catheterized have pulmonary vascular obstructive disease. Earlier figures from our department indicate that almost one-half of our adolescents studied at cardiac catheterization had pulmonary hypertension at systemic levels. Histological confirmation of this prevalence of pulmonary vascular obstructive changes in patients beyond the teens was provided by the work of Edwards (1957) as well as by Dammann and Ferencz (1956). Clearly, one may find some grade 4 and 5 changes in the lungs of young children, but this is rare. Over the age of 20, it becomes relatively common. So that one may say with assurance that large defects in adults are likely to be associated with pulmonary vascular disease, and thus a certain percentage of children with ventricular defect may be classified, when they become adults, as Eisenmenger's disease. The true incidence of this complication is hard to assess; among Ritter's material (Ritter *et al.*, 1965), covering all ages, 10% had Eisenmenger's disease. Figures much higher than this may have to be quoted for adults with large defects; these are the patients who as infants and children had high pulmonary blood flow and pressure, with pulmonary to systemic pressure ratio of over 75%.

The emergence of subvalvar pulmonary stenosis in patients with ventricular septal defect has been well documented for many years (Gasul *et al.*, 1957). Most of these patients present in infancy with the clinical picture of large ventricular defect. The murmur of infundibular stenosis, if present at all, is usually masked by the pansystolic murmur of ventricular defect. Findings that may suggest the presence of additional pulmonary stenosis are: (1) a degree of right ventricular hypertrophy in the electrocardiogram out of proportion to the evidence of increased pulmonary flow (pulmonary plethora, heart size, and rumble), and (2) the murmur may transmit better than usual to the supraclavicular area and the neck. With the passage of time, in these patients, evidences of a left-to-right shunt diminish and those of a right-to-left shunt begin to dominate, so that by the second or third decade, the clinical profile is indistinguishable from that of Fallot's tetralogy. This then is another way that the ventricular defect may disappear; it turns into the tetralogy of Fallot. The incidence of the

development of this complication is also unknown; our own guess is that it is about 5% of patients with large ventricular defects. One other point should be stressed, namely, that though most of the patients who in later life present as tetralogy of Fallot did have some degree of pulmonary stenosis at the time of the first catheterization in childhood, this is not invariably the case. We have seen, rarely, infants with ventricular defect without appreciable gradient across the R-V outflow tract develop, *de novo*, pulmonary stenosis by the time they are catheterized for a second time in their teens.

A third complication of patients with ventricular defect, which may alter the clinical profile over the years, is development of aortic regurgitation. Anatomically, this consists of a prolapse of the right coronary, and occasionally the non-coronary, cusp of the aortic valve into the left ventricle or even across the defect into the right ventricle or the pulmonary artery. The defect is always of the outflow type and may be unusually high, right below the pulmonary valve. The development of aortic regurgitation, due to the prolapsed cusp, may be paralleled by the diminution, or even disappearance, of the ventricular left-to-right shunt as the defect becomes plugged by the pendulous aortic leaflet. It is well documented now that clinical aortic regurgitation is acquired invariably beyond the first birthday, commonly at the end of the first decade. At first a faint, high frequency, protodiastolic murmur appears in addition to the murmur of ventricular defect; as time goes on evidences of aortic incompetence increase and signs of ventricular septal defect diminish or disappear. Not only is the accurate incidence of this complication not known, though it surely is less common than the previously discussed two, and in no case is it any higher than 1-2%, but the rate of progress of aortic regurgitation is not known either. Some observers maintain that all patients with prolapsed aortic cusps deteriorate within a few months or a year; we certainly have observed this course of events (Fig. 9) but we are also following patients at present whom we have observed for over 5 years without accentuation of the signs of aortic regurgitation. On the whole, this is a malignant complication leading to congestive failure and predisposing to bacterial endocarditis in a high percentage of cases. Ventricular septal defect and aortic regurgitation is a much more life-threatening combination than ventricular defect with pulmonary stenosis, and though potentially surgically correctable, may run a more rapid downhill course than the equally fatal pulmonary vascular obstructive disease.

Bacterial endocarditis is a dreaded but, fortunately

FIG. 9.—Two chest x-rays in a child with ventricular septal defect and aortic insufficiency. Note the increase in heart size due to increasing aortic insufficiency over a seven-year period.

nowadays, very rare complication of ventricular septal defect. It is difficult to express accurately the risks of bacterial endocarditis in any patient at a given age. Available figures vary from 1/2000 to 1/1000 patient years (Keith *et al.*, 1967). There seems to be a strong suggestion that neither the very young infants nor patients beyond 30 are likely to acquire this disease. Anatomically, vegetations may be found on the right ventricular side of the defect itself, or on the wall of the right ventricle opposite the defect, or even on the septal leaflet of the tricuspid valve. Among 15 patients with ventricular defect and bacterial endocarditis treated in our own institution out of a total of 93 children with endocarditis, 10 had complicated lesions; 4 of these with aortic regurgitation (A. G. Zaver and A. S. Nadas, unpublished data).

Very rarely, a child will be encountered with a ventricular septal defect and a mitral valve deformity which is not an endocardial cushion anomaly. More often mitral valve obstruction rather than insufficiency has been recognized. In clinical terms, a diastolic rumble in the presence of a minimally increased pulmonary flow suggests mitral obstruction; while in physiological terms, a high pulmonary capillary wedge pressure in association with a small left-to-right shunt is also suggestive. The clinical and physiological diagnosis is, of necessity, somewhat

uncertain, but, in our hands, clinical suspicions have been confirmed at necropsy. The overlap of the clinical observations between this combination of defects and isolated ventricular septal defect is such that only the most wary clinician will suspect that more than an isolated ventricular defect is present.

In summary then, one may say that the natural history of ventricular defect is a complex one. There seems to be general agreement by most workers in the field that small defects are relatively innocuous, are likely to close spontaneously, and may cause trouble only through the development of aortic regurgitation and/or bacterial endocarditis. Although large defects may also improve spontaneously, they may prove to be fatal or severely debilitating in infancy on account of congestive failure, and in the third or fourth decade because of pulmonary vascular obstruction and/or failure. Patients with large defects may also be plagued by bacterial endocarditis and aortic regurgitation.

Operative Indications

Certain tentative conclusions, in regard to operative indications, may be drawn from the foregoing remarks on the natural history of ventricular septal defects. It should be stressed that the thoughts expressed are the policies of our unit at the present time (late 1967), and may very well have

to be modified as new information from current studies on the natural history of the disease become available and the long-term results of surgery are assessed.

First, we find absolutely no justification, on the basis of present knowledge, for the thesis proposed in the past to the effect that all ventricular defects should be closed. Only certain rather well-defined categories of patients should be submitted to cardiac surgery. The deciding factors are the pressures and blood flow in the pulmonary artery.

Expressed in an oversimplified way one could say that children with small shunts (pulmonary systemic flow ratio less than 1.5) should not be treated surgically; if they have normal pulmonary arterial pressures, the defect is not worth closing; if the pressure is significantly raised the risks become prohibitive and the benefits questionable.

Operations on patients with large shunts (pulmonary-systemic flow ratios of over 3) are mandatory. If a large shunt is associated with significant pulmonary arterial hypertension (pulmonary artery mean pressure/systemic artery mean pressure/0.75) in a child, closure is recommended as soon as possible. In asymptomatic young infants, in whom the defect may become smaller, or the pulmonary artery pressure may drop, we follow Hoffman's suggestion (Hoffman and Rudolph, 1965) of recatheterizing within 6 months. If no improvement occurs, pulmonary artery banding is our procedure of choice at the present time. We fully realize that with technical advances closure of the defect may very soon be the preferred technique even in the very young. Children with large shunts and smaller, if any, increases in pulmonary artery pressure, should be operated upon electively at an age preferred by the surgical and medical teams, which, in our institution, is somewhere between 8 and 10 years.

Children with intermediate flow ratios (1.5-3) present the most difficult decisions. If these flow ratios are associated with significant pulmonary artery hypertension, as defined above, surgery is mandatory. Since for any given pressure level these flow ratios represent a high degree of obstruction, surgery, banding or closure, depending on the surgical preference, is perhaps more imperative and more urgent at any age. We do not at present operate on infants with intermediate flow ratios and pressure ratios of less than 0.5. In childhood these may be done electively depending on heart size, the electrocardiogram, the symptomatology, parental attitude, and surgical skill.

The surgical treatment of ventricular defect with aortic regurgitation is a subject of great controversy at the present time; an intelligent decision is difficult

since we do not know the natural history of this combination of defects, and since the results of surgery are far from ideal. Enthusiastic surgeons recommend that ventricular defects, even with trivial aortic regurgitation, should be treated surgically, irrespective of the size of the defect. This proposal is based on the optimistic assumption that closure of the defect will eliminate, or at least arrest, aortic incompetence. Unfortunately, at the present time, we have no conclusive data to support this thesis, nor do we know what would have happened to the aortic regurgitation had the ventricular defect not been closed. The conservative ones among us advocate that this lesion should not be corrected surgically except as an emergency when the consequences of severe aortic regurgitation become manifest. In addition, patients with marked cardiac enlargement and severe aortic incompetence are poor surgical risks. We believe that if a patient, when first seen, already has severe aortic regurgitation, closure of the defect with insertion of an aortic valve prosthesis or homograft is indicated. If aortic incompetence is trivial or even moderate, careful, at least six-monthly, follow-up examinations with x-ray, electrocardiogram, and possibly with cardiac catheterization, with left ventricular volume studies performed every 2 years, are advisable, to demonstrate any significant progression. Only if these are manifest would we recommend operative intervention on account of aortic regurgitation. Of course, the indications for surgical treatment of the ventricular septal defect are the same as mentioned earlier.

Ventricular defect with pulmonary stenosis and a right-to-left shunt should be treated surgically according to the principles appropriate to the treatment of tetralogy of Fallot, i.e. shunt operations, Brock procedure, or complete repair according to prevalent surgical skills. Ventricular defect with pulmonary stenosis without a right-to-left shunt may be treated conservatively for a long time; these are benign lesions, and surgery is indicated for asymptomatic patients only if the right ventricular pressure is at systemic range.

Lest one be accused of abandoning clinical judgement in favour of a physiological numbers game, we hasten to state that the above considerations are strongly modified all the time by the clinical picture. Babies in intractable congestive failure need operation if they have a sizeable shunt almost irrespective of pulmonary arterial pressure. Poor growth and development, again in the presence of a large shunt, would hasten surgical intervention in our institution, everything else being equal. A large heart by x-ray often modifies the significance

of flow ratios. Change in clinical parameters, symptomatology, electrocardiogram, and x-ray appearances, all should influence surgical decisions. Our psychiatrically oriented colleagues prefer, everything being equal, that cardiac surgery be performed after 8 years of age; individual family situations may justify postponement of operation even longer. All these factors should not cancel out intelligent physiological evaluation but should supplement it and result in better care for a larger number of patients.

Operative Results

Operative closure of a ventricular septal defect in patients beyond infancy may be accomplished with an over-all mortality of 5–10% in most first-rate centres. Figures lower than this (1%) may be cited for patients with low pulmonary vascular resistance, and a 25% risk may have to be accepted for those with high pulmonary resistance (more than two-thirds systemic) and a net left-to-right shunt. As mentioned earlier, the risks are prohibitive for those who have near systemic levels of pulmonary resistance and a bidirectional shunt.

What is accomplished by the surgical closure of ventricular septal defects? Under ideal circumstances, the murmur disappears, there is no residual shunt, the pulmonary arterial pressure is low, the heart size and the electrocardiogram return to normal. Unfortunately, this perfect result does not occur in more than 50% of the survivors. Post-operatively, many of the children have some residuum; the heart size may not be entirely normal, the electrocardiogram may show right bundle-branch block, a murmur may remain, and sensitive indicators may demonstrate a small residual shunt at catheterization, and even the pulmonary arterial pressure may not return to normal. Any of these residual features may be quite disturbing to parents who were promised, in return for the agony of cardiac surgery, that the child's heart would be 'normal'. The wise cardiologist will be careful to point out before operation the likelihood of residual abnormalities and the desirability of post-operative recatheterization in certain situations. The presence of these, hopefully minor, abnormalities does not negate the helpfulness of the operation—the parents themselves often note the increase in growth rate, the quiet sleep, the steady slow heart rate, and the increased exercise tolerance after operation. The heart just is not 'normal' and this fact cannot and should not be glossed over.

What happens to the increased pulmonary resistance in the survivors of operations for hypertensive ventricular septal defect? In most instances

the pulmonary arterial pressure falls commensurately with the decrease in pulmonary flow, but the calculated resistance, whatever that means, remains unchanged in about 75% of the cases. In the lucky half of the remaining, the resistance drops significantly, but in the other unfortunate ones, the resistance continues to rise. At this time, the authors are not aware of any diagnostic tool that could identify the latter group.

Infants with ventricular defect represent a difficult group from the operative point of view. Attempts at complete closure in infants under 6 months of age are considered to be too hazardous, entailing a mortality of anywhere between 25 and 50%. Consequently, in situations where surgery is mandatory (intractable failure), almost all surgeons in America prefer pulmonary artery banding which carries a 10% risk in skilful hands. This approach is the preferred one in our institution and in many other centres in the United States, for infants up to 2 years of age, but some especially skilful surgeons can accomplish complete repair in the 6- to 24-month age range with mortality figures of 10% or less (Cartmill *et al.*, 1966). Obviously, this is preferable to banding if it can be accomplished safely.

The results of pulmonary artery banding in the survivors is highly satisfactory. Congestive heart failure disappears, the heart becomes smaller, and growth and development improves. We have seen patients banded in infancy in whom the ventricular defect, in the course of the first two years, decreased in size and even closed. Others become cyanotic and present as tetralogy of Fallot patients 3 to 6 years after banding. The majority, however, continue to do well, with a physiological picture of ventricular defect with moderate pulmonary stenosis and a small left-to-right shunt. Elective closure of the ventricular defect with removal of the band can be accomplished at 5 to 10 years of age with a risk probably no higher than 5–10%.

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