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Thoughts on concepts of development of the heart in relation to the morphology of congenital malformations

R. H. Anderson and A. C. G. Wenink

Department of Paediatrics, National Heart and Lung Institute, Brompton Hospital, Fulham Road, London SW3 6HP (England), and Department of Anatomy and Embryology, State University of Leiden, Wassenaarseweg, Leiden 2300 RC (The Netherlands)

Summary. In the past, it has often been the case that congenital malformations have been categorized in terms of their presumed embryologic development. The knowledge of development, however, has itself often been derived from studies of the normal heart during its development coupled with inferences drawn from the morphology of the abnormal hearts. This can lead to circular thinking which, often, has little basis in fact. It is our belief that cardiac embryology is an important science which should stand in its own right, but that knowledge of abnormal development should be derived from observation rather than inference. The potential dangers of concepts derived by extrapolation are illustrated with reference to hearts having deficiencies of atrioventricular septation ('endocardial cushion defects') and those with double inlet left ventricle ('single ventricle'). It is shown that description of these hearts is greatly facilitated by eschewing those concepts derived from 'armchair embryology'. Once a clear description is established, the scene is set to understand the real mechanisms underscoring the maldevelopment of these lesions.
Key words. Embryology; atrioventricular septal defect; endocardial cushions; double inlet left ventricle; conduction tissues.

Introduction

For many years, it has been presumed that knowledge of cardiac embryology will contribute to an understanding of the mechanics of development of congenital cardiac malformations. As an extension of this principle, it has also been frequent that investigators of congenital lesions would discuss presumed morphogenesis. This approach would be entirely justified if, first, we were fully acquainted with the details of normal development of the heart and, second, we were sure that the malformations could appropriately be interpreted in the light of such normal development. Regrettably, neither of these premises can be presumed. Furthermore, recent revisitations of the anatomy of the normal heart reveal features which call into question several concepts which are widely applied in the interpretation of normal and abnormal cardiac development [5].

This preamble should not be construed as suggesting that we are opposed to the use of studies of cardiac embryology as a means of understanding congenital cardiac malformations. Far from it, we are convinced of the need to establish such relationships. It is our belief, however, that this goal can be achieved only if the anatomy of the lesions themselves is taken as the starting point. Often, this has not been the case. We will illustrate this by reference to two specific lesions: hearts with deficient atrioventricular septation [9] and those with double inlet ventricle [6]. We will show in each case how, in our opinion, either the understanding of the anatomy of these lesions or their description has been hindered by approaches which have used presumed concepts of normal development as their starting point. At the same time, we will show how alternate approaches based upon the anatomy of the lesions themselves lead to an enlightened view of cardiac development.

Hearts with deficient atrioventricular septation

Basic anatomy

There are a group of hearts unified by a complete absence of those septal structures which, in the normal heart, separate the left ventricle from the right atrium. These atrioventricular septal structures, in part made of fibrous tissue and in part of muscle, exist by virtue of two essential features of normal anatomy. The first is the position of the subaortic outflow tract, wedged deeply between the mitral valve and the septum (fig. 1 a). This arrangement permits the membranous septum to interpose between the left ventricular outflow tract and the right-sided chambers, the attachment of the tricuspid valve dividing the fibrous septum into atrioventricular and interventricular components. The second feature is the normal off-setting of the attachments of the leaflets of the mitral and tricuspid valves to the septal structures. In this respect, the mitral valve is attached to the septum over a very limited area, the remainder of the apparently 'septal' attachment being separated from the septum by the subaortic outflow tract as discussed above. In the limited area where the attachment of the tricuspid leaflet does face that of the mitral valve, the overlapping between the off-set attachments produces a muscular atrioventricular septum (fig. 1 b). A normal heart can be dissected to show the location of these two atrioventricular septal components. (fig. 2 a). It is a deficiency within this part of the septum which underscores the existence of the various lesions under discussion, including the so-called ostium primum 'atrial' septal defect (fig. 2 b). In reality, there is little wrong with the atrial septum itself in many of these hearts. The major problem is a deficiency of atrioventricular septation followed by an abnormal formation of the leaflets of the atrioventricular valves [27].

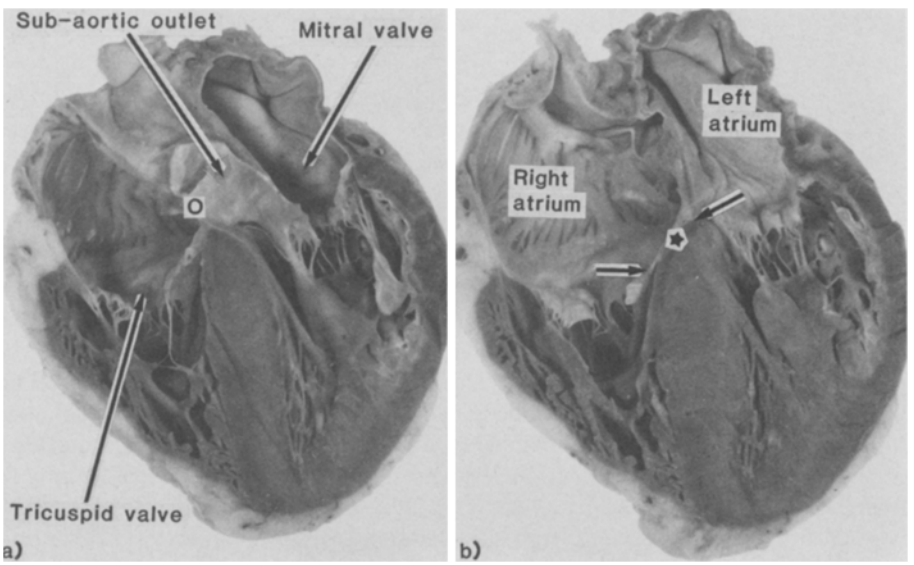

Figure 1. These simulated 'four chamber' sections through the normal heart show the position of a) the membranous component (open circle) and b) the muscular component (asterisk) of the atrioventricular septum.

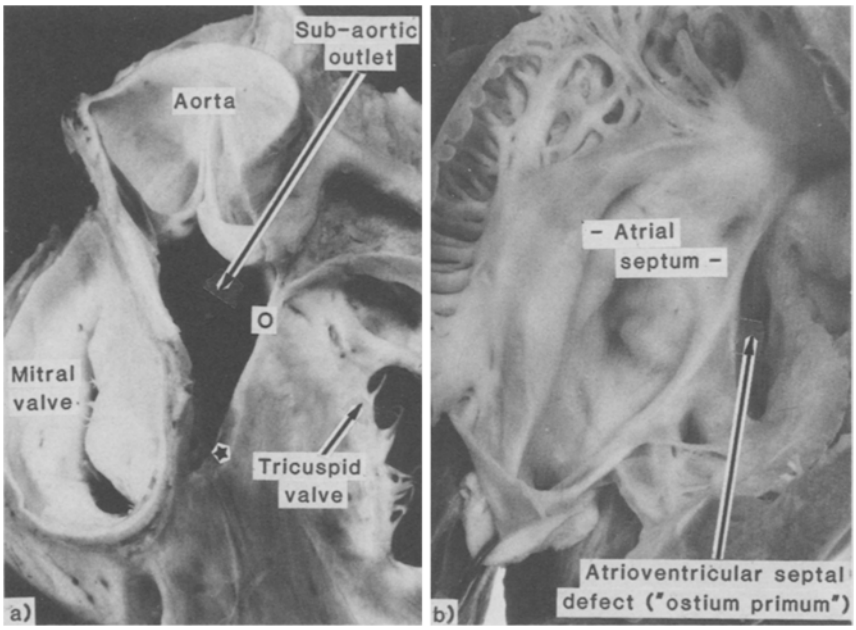

Figure 2. The left panel (a) shows a dissection of the normal heart illustrating the location of the muscular (asterisk) and membranous (open circle) components of the atrioventricular septum. The photograph of an 'ostium primum' defect seen in the right-hand panel shows that the hole between the chambers is at the anticipated site of the atrioventricular septal structures.

Since the normal off-setting of the septal attachments is missing, there is no atrioventricular septum, hence our preferred term of atrioventricular septal defect[9].

The absence of the atrioventricular septal structures, however, does not exist in the setting of the normal heart. Instead, it underscores four additional but fundamental morphologic hallmarks of the group. These are, first, a common atrioventricular junction. This common junction is guarded by the second hallmark, a valve with leaflets common to both right and left ventricles (fig. 3a). The third feature is unwedging of the outflow tract of the left ventricle so that it no longer interposes between the left atrioventricular valve and the septum (fig. 3c). In keeping with this is an abnormal arrangement of left ventricular papillary muscles when compared with the normal[4]. The fourth (and final) feature is a marked disproportion between the inlet and outlet dimensions of the left ventricular aspect of the ventricular septum (fig. 3b). All atrioventricular septal defects possess these fundamental features but there are important variations within the overall group.

Variable morphology within the group

The major differences are related to those leaflets of the common valve which are connected by tension apparatus within both right and left ventricles: the bridging leaflets. These structures may be discrete and separate structures, in which case there will be a common valve orifice (fig. 3a). Alternatively, a tongue of leaflet tissue can join together the facing surfaces of the leaflets, converting the common orifice into separate right and left ventricular components (fig. 2b). The other important feature of the bridging leaflets is their relationship to the septal structures. At the expected site of the normal atrioventricular septum, a large hole is present between the arching borders of the atrial and ventricular septal structures (fig. 3b). The anatomic potential for haemodynamic shunting through this defect is governed by the location of the bridging leaflets. If the leaflets are attached to the crest of the ventricular septum, shunting will be possible only at atrial level (fig. 4a). If the leaflets are attached to the underside of the atrial septum, however, shunting will be possible only at ventricular level (fig. 4b). If, in contrast, the leaflets are attached to neither atrial nor ventricular septal structures, shunting will be possible at both atrial and ventricular levels (fig. 4c). The potential for shunt will be governed by the extent of the communication between the leaflets and the septal structures along with the prevailing haemodynamic conditions. A third significant variation within the overall group depends on the relationship of the common junction to the ventricles. Usually the common junction is equally shared (balanced arrangement) but, sometimes, there may be either right or left ventricular dominance[10].

The conventional concept of morphogenesis

The usual means of explaining the development of hearts with deficient atrioventricular septation is enshrined in the popular alternative title for the lesions namely 'endocardial cushion defect'. It cannot be denied that, in the final analysis, a failure of fusion of the atrioventricular endocardial cushions most probably will be seen to ac-

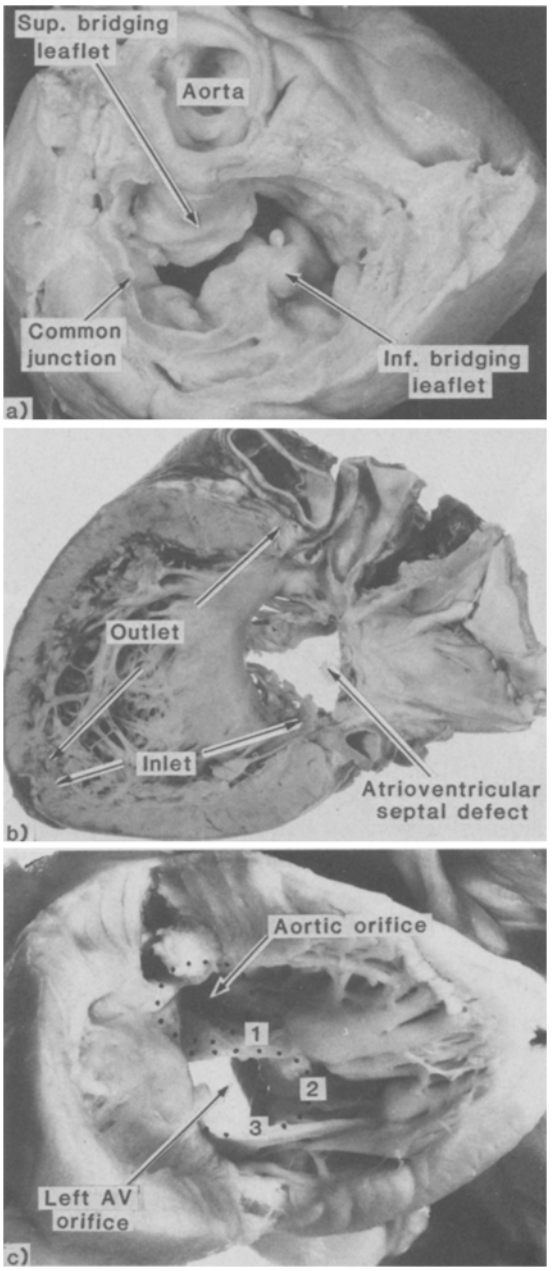

Figure 3. These three panels show the salient morphologic features of atrioventricular septal defects. The upper panel (a) shows the common atrioventricular junction and the bridging leaflets of a common valve. The middle panel (b) demonstrates the site of the septal defect and the inlet/outlet septal disproportion. The lower panel (c) shows the unwedged subaortic outflow tract along with the trifoliate left atrioventricular valve (1,2,3).

count for the malformations. It can be stated with reasonable certainty, however, that the mechanics of maldevelopment are not in accord with traditional accounts, such as that provided by Netter in the Ciba atlas[15]. These accounts presume, first, that failure of fusion results in clefts of the 'septal' leaflets of both atrioventricular valves. This is particularly the case for the mitral valve since, on the basis of this embryologic premise, some workers categorize an isolated cleft of the anterior (aortic) leaflets of the mitral valve as a 'forme frust' of endocardial cushion defect[12]. The second presumption made in this 'classical' concept is that the endocardial cushions themselves contribute materially to the formation of the lower component of the atrial septum and the upper part of the ventricular septum (see the diagrams in the Ciba atlas!). Neither of these assumptions has any factual foundation. The concept of a 'cleft mitral valve' underscoring the valvar morphology of hearts with deficient atrioventricular septation can be readily discounted. Study the morphology of the so-called 'cleft' and compare it, first, with an artificial cleft produced in a normal mitral valve and, second, with the anatomic arrangement in hearts having congenital clefts of an otherwise normal mitral valve[9]. In the first instance, the artificially produced cleft 'points' to the subaortic outflow tract while the so-called cleft in hearts with deficient atrioventricular septation is orientated towards the ventricular septum. The congenital cleft also 'points' to the subaortic outflow tract (or outlet component of the right ventricle in the setting of double outlet ventriculo-arterial connexion) rather than towards the ventricular septum. Thus, it is *not* analogous to the so-called cleft seen in atrioventricular septal defects. These facts are reinforced by examination of the left atrioventricular valve in atrioventricular septal defects and by morphometric comparison with the mitral valve in hearts with normal atrioventricular septation. Measurements of the extent of the leaflets reveal a fundamental difference so great that it makes little sense to consider the left valve in hearts with deficient atrioventricular septation as a 'mitral' valve[16].

Concerning the presumed contribution of the cushions to the musculature of the septum, no factual evidence has ever been marshalled to substantiate this notion. Indeed, examination of serial human embryos produces evidence that the cushions contribute very little[18]. It has now been shown[25] that the central cushions do not grow beyond the 25-mm stage, which is at the age of 6 weeks. By then, they have reached their total volume of 0.074 mm^3. Additional circumstantial evidence points to this minimal material role for the cushions. This comes from the location of the atrioventricular conduction axis in the normal heart. It is well established that this axis, prior to completion of septation, is located on the crest of the muscular ventricular septum[8, 22]. The cushions, at this stage, occupy the space between the potential atrioventricular junction and the septal crest. If the cushions *did* contribute materially to the ventricular septum then, of necessity, the conduction axis in the definitive heart would be sandwiched between that part of the muscular septum derived from the cushions and the primary component of the muscular septum. It is not. The axis in the formed heart retains its location astride the crest of the muscular septum, indicating that the contribution of the cushions, irrespective of its size, must be confined within the central fibrous body.

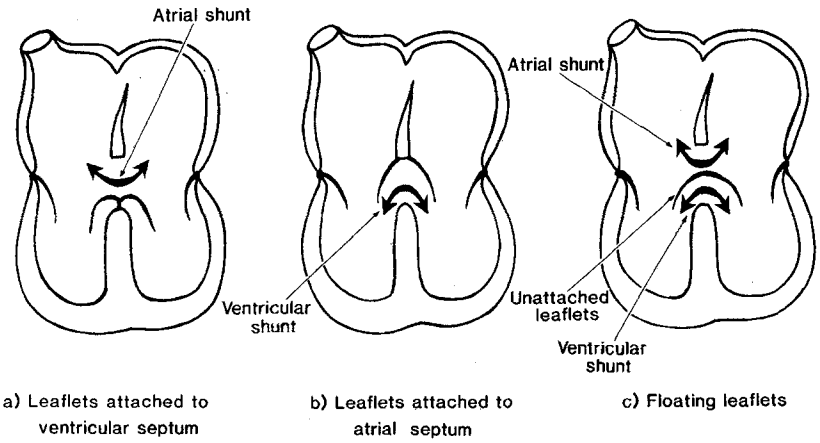

Figure 4. This diagram shows how shunting through the atrioventricular septal defect relates to the way the bridging leaflets of the common atrioventricular valve are attached to the atrial and ventricular septal structures.

The mechanics of formation of atrioventricular septal defects

If the classical concept of 'endocardial cushion defects' is unable to account for the morphologic arrangement of hearts with deficient atrioventricular septation, and is out of step with evidence concerning the development of valvar and muscular structures within the heart, are we able to provide a more rational explanation? We believe we are. Our concept of the morphogenesis of atrioventricular septal defects is founded in the notion that the real role of the atrioventricular endocardial cushion during the crucial period of cardiac development is to bind together the centrepoint of the atrioventricular junction. This notion of the fixative function of the cushions was advanced by Van Mierop[19], departing markedly from his earlier concepts which Netter had used to construct his drawings for the Ciba atlas[15]. In his later contribution, presented at the Henry Ford Symposium in 1975, Van Mierop[19] proposed that failure of fusion of the cushions in hearts with deficient atrioventricular septation permitted the atrioventricular junction to 'spring apart'. He did not, however, develop the concept to account for the valvar abnormalities so characteristic of these lesions. Nonetheless, this simple concept of failure to provide a solid cornerstone for the growing central part of the heart explains most of the features of atrioventricular septal defect. It underscores the deficiency at the anticipated site of the atrioventricular septum. It can account well for the inlet/outlet septal disproportion and the abnormal location of the subaortic outflow tract. But what of the abnormal formation of the leaflets of the atrioventricular valves? It is this final point which is the key to the entire process. Explanation of this mechanism must take note of the fact that formation of the leaflets of the atrioventricular valves is a very late event during cardiac development. Indeed, in the normal heart, the septal leaflet of the morphologically tricuspid valve does not exist until the process of septation is completed. Once it is recognized that the valve leaflets are derived by a combination of ingrowth of the atrioventricular groove and delamination of the superficial layer of ventricular myocardium[27], it is evident that the location of the leaflets will be inexorably linked with the formation of the ventricular mass. Thus, the formation of a normal mitral valve, with aortic and mural leaflets, can only occur *after* the subaortic outflow tract has been normally established within the left ventricle. In other words, sculpting of the normal mitral valve can occur in the setting of normal atrial and ventricular septation. Once the atrioventricular endocardial cushions have failed in their ordained role to seal together the centrepoint of the developing atrioventricular junction, the ventricular mass will develop so as to produce a common junction. Ingrowth of the tissue of the atrioventricular groove in this setting, along with delamination of myocardium of the developing inlet, will produce bridging leaflets along with the three-leaflet left valve so characteristic of hearts with deficient atrioventricular septation[28]. The presence of a common valve orifice versus separate right and left orifices ('complete' vs 'partial' defects) will depend upon the extent of delamination of the bridging leaflets from the ventricular septum. The extent and location of the septal deficiences will depend on the relations of the leaflets to the developing septal structures. In the reported developmental stages of the malformation[28], cushion tissue was observed to glue the superior leaflet to the septum as in the Rastelli A type. Alternative dispositions of the cushion tissue could bring the valves into relationship with other septal structures.

We submit, therefore, that the morphogenesis of 'atrioventricular canal malformations' cannot adequately be explained on the basis of normal cardiac anatomy (cleft mitral valve) nor on concepts of normal embryogenesis which invoke the atrioventricular endocardial cushions as contributing materially to septal structures. Instead, knowledge of morphogenesis must take note, first, of the characteristic morphology of hearts with deficient atrioventricular septation and, second, of the fact that valve leaflets are derived from ingrowth of the atrioventricular

groove along with delamination of the superficial layer of ventricular myocardium.

Double inlet left ventricle

Problems and controversies

The difficulties engendered by those who have related development to the malformation of double inlet left ventricle (including one of us [2]) are of somewhat different colour from those associated with atrioventricular septal defect. The major problem in recent years with hearts having a double inlet atrioventricular connexion has stemmed from an inability to agree as to their precise morphologic nature along with whether their ventricular mass is 'univentricular'. Speculative notions derived from embryology have contributed in no small way to the uncertainty which still surrounds this debate. Resolution of the issue once more rests in anatomic descriptions. This then opens the way to highlight those mechanisms of development which still require clarification.

The morphologic nature of the lesion

The lesion under question is simply a heart in which both components of atrial myocardium (those surrounding the atrioventricular junctions belonging to the right-sided and left-sided atriums, irrespective of the morphologic nature of those chambers) are connected to only one ventricle. This ventricle possesses the apical trabecular characteristics associated usually with the morphologically left ventricle (fig. 5). Almost without exception in such hearts there is present antero-superiorly within the ventricular mass an incomplete and rudimentary ventricular chamber with the apical trabecular characteristics of the morphologically right ventricle (fig. 6). Thus, in terms of simple descriptive morphology, the anomaly has double inlet left ventricle with an incomplete and rudimentary right ventricle. Variation can then be found [6] according to the atrial arrangement ('situs'), the morphology of the atrioventricular valves (two valves, one of which may be imperforate, straddling or overriding or a common valve which may be straddling or overriding), the position of the incomplete right ventricle (right-sided or left-sided) and the ventriculo-arterial connexion (concordant, discordant, double outlet from either ventricle or single outlet from the heart). Problems were produced previously when such a heart was described as 'single ventricle'! In no way is the heart univentricular. Those who tried to describe it as univentricular (including one of us [2]) used as their justification the conventional wisdom that double inlet ventricle was the criterion for presence of a single ventricle [21]. This convention simply creates a rod for one's own back. No amount of special pleading, such as denying the rudimentary chamber its ventricular status [3], can obscure the fact that the ventricular mass in these malformations is *not* univentricular. Instead, it is unbalanced, with one dominant and another rudimentary ventricle. If the adjective 'univentricular' is to be used appropriately in description, then it can only justifiably be applied to the atrioventricular connexion [7]. If problems are resolved in terms of description by recognition of the precise morphologic nature of the lesion, they are not solved in terms of morphogenesis. The question remains as to how a heart can develop in such a way that, in the usual circumstance, the ventricular septum separates the two atrioventricular valves while, in the setting of double inlet left ventricle, both valves (or a common valve) enter a dominant ventricle which is separated by a discrete septum from a hypoplastic and rudi-

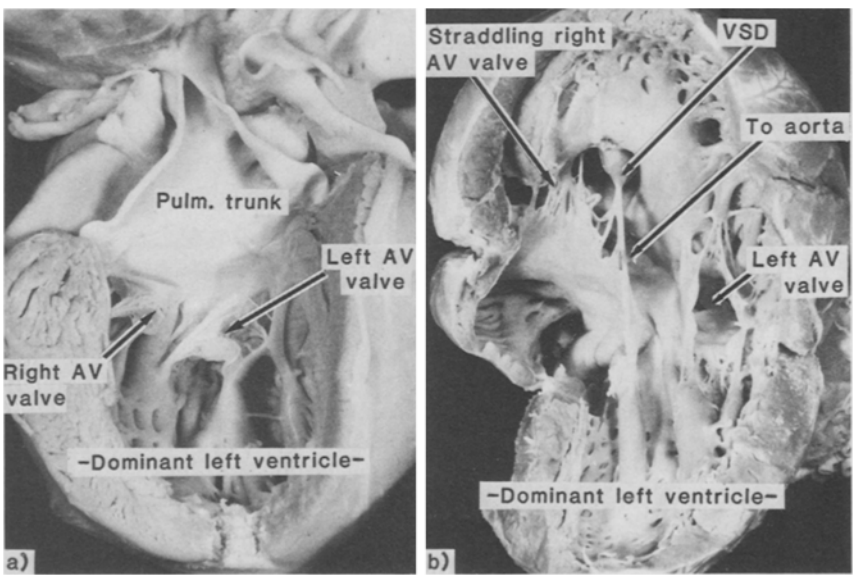

Figure 5. These photographs show double inlet to a dominant left ventricle in the setting of (a) a discordant and (b) a concordant ventriculo-arterial connexion. In panel (b), there is minimal straddling of the right atrioventricular valve.

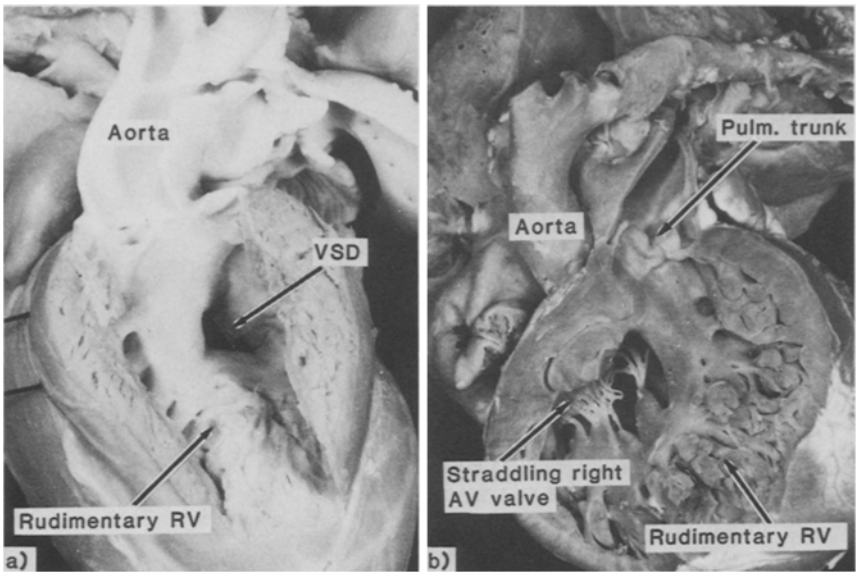

Figure 6. These panels show the complementary rudimentary right ventricles in the hearts in figure 5 with (a) a discordant and (b) a concordant ventriculo-arterial connexion.

mentary ventricle. Before broaching the topic of morphogenesis and development, the very nature of this septum in double inlet left ventricle must be clarified, along with the components of the rudimentary ventricle. This is because some authorities contend that the incomplete and rudimentary ventricle is simply the infundibulum of the right ventricle[20]. Our observations militate strongly against this contention. As we see it, the infundibulum is simply the funnel-shaped cone of musculature supporting the arterial valve of the morphologically right ventricle. The incomplete ventricle seen in double inlet left ventricle is much more complex. Almost always it possesses an infundibulum (or outlet component). This is not, however, universal since double inlet left ventricle can exist when there is also double outlet from the dominant left ventricle. In this circumstance, the rudimentary ventricle does not possess an outlet (fig. 7). What, then, is the incomplete ventricle formed by in this extreme setting of double inlet *and* double outlet? It is made up of the apical trabecular component which has characteristics of the morphologically right ventricle. In other words, the basis of the rudimentary ventricle seen in double inlet left ventricle is the apical trabecular component of right ventricular morphology. Recognition of this anatomic arrangement points, in turn, to the morphology of the septal structures. The septum in double inlet left ventricle almost always has two components, one between the outlets (the outlet or infundibular septum) and the other between the apical trabecular components. It is the apical component which is universally present and which, as would be expected, carries the atrioventricular conduction axis. The ventricular septal defect is almost always located between these septal components although, rarely, defects may be observed between the ventricular apices.

Morphogenesis of double inlet left ventricle and development of the ventricular septum

Once the anatomy is recognized, it is not too difficult, in terms of known concepts of development, to provide a rational explanation for the existence of double inlet left ventricle. Difficulties arise only when we try to correlate that explanation with concepts concerning the formation of the normal ventricular septum. Consider, first, the possible scenario which accounts for double inlet left ventricle. All students of cardiac development accept the premise of a primary heart tube as described by Streeter[17]. They acknowledge also that, at the stage of ventricular looping, the atrial component of the tube connects to the inlet component of the ventricular loop while the arterial segment is supported by the outlet component. Note that, in describing the components of the tube, we have refrained purposely from using nominative terms such as primitive ventricle, bulbus and so on. These names in themselves have contributed in no small way to existing controversies. Be that as it may, after looping of the primary tube, development proceeds with formation of the apical trabecular components of each ventricle. Formation of the two ventricular pouches proceeds with and accompanies the appearance of the septum between them. For descriptive purposes, we will refer to this structure simply as the primary ventricular septum. It is this primary septum which is known to carry part of the atrioventricular conduction tissues on its crest. After formation of these pouches and the primary septum, it is

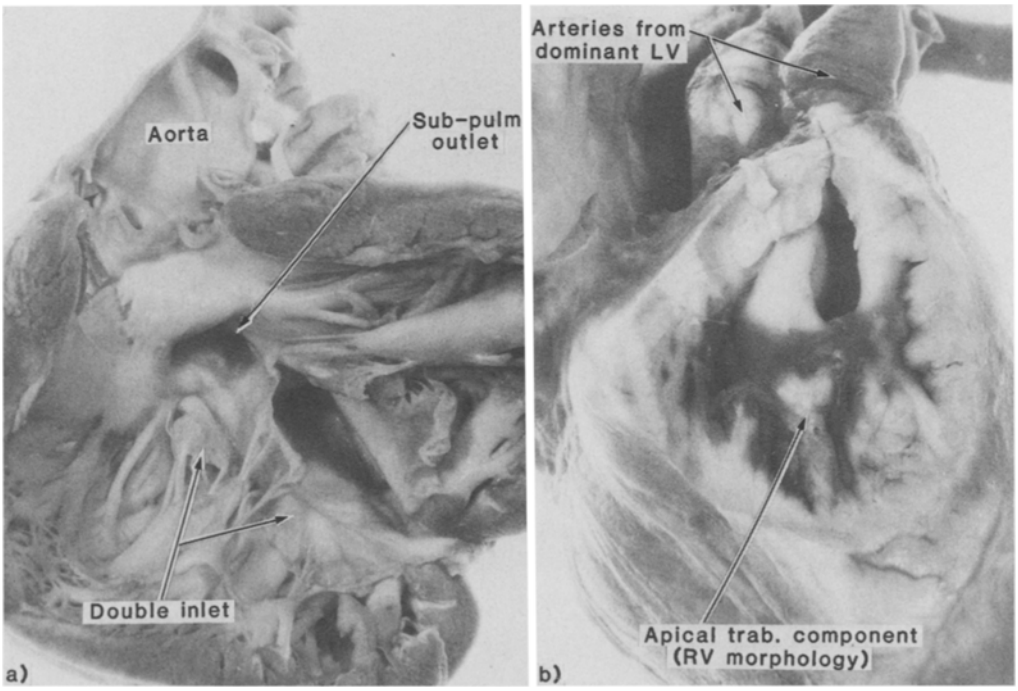

Figure 7. These photographs show (a) the dominant left ventricle in a heart with double inlet and double outlet from the same chamber. The rudimentary right ventricle (b) is represented by its apical trabecular component.

also generally accepted that the entirety of the atrioventricular junction remains connected to the inlet component of the heart tube. It is from this inlet component that the trabecular component will grow which, after formation of valves and tension apparatus [26], will achieve left ventricular characteristics. The arterial segment of the developing tube, in contrast, is supported by the outlet component. It is this outlet part which gives rise to the trabecular portion destined to be of right ventricular morphology. Here, then, is the setting of double inlet left ventricle. If the heart develops in such a way that the atrial chambers retain this developmental relationship with all of the inlet component (in other word, that portion that will achieve left ventricular characteristics) then all variations of the recognized lesion are easily explained in terms of further development of the atrial and arterial segments. The simple retention of the atrioventricular junction in connexion solely with the developing inlet component will certainly ensure that this chamber of left ventricular morphology achieves dominance in terms of size. The developing right ventricle will remain hypoplastic and, in absence of its inlet component, will, of necessity, be incomplete and rudimentary. The position of the outlet septum will depend on the formation and further growth of the two ventricular outlets.

This explanation of events is simple and clear cut. It accounts well for the presence of the apical trabecular (primary) septum between the apical ventricular components in an antero-superior position relative to both atrioventricular valves (or a common valve). The outstanding question is how this concept can be related to development of the normal heart. This is particularly so concerning the mechanism of formation of the inlet septum. This part of the septum normally separates the inlet of the right ventricle (containing the tricuspid valve) from that of the left ventricle (and the mitral valve) and, self-evidently, is absent in double inlet left ventricle. The answer to this question is that we have no proof as to its formation. Our own prejudices are to argue that the inlet component of the normal ventricular septum has a different embryological origin from the primary (apical trabecular) septum. We believe that the study of developing human embryos supports this view, since a condensation of embryonic myocardium is to be found in the developing inlet component of the primary heart tube positioned so as to separate the ventricular inlets [24]. Our belief, therefore, is that the inlet component of the normal right ventricle is derived from the inlet of the primary heart tube, and that it is allotted to the definitive ventricle by means of fusion of the developing inlet septum with the primary septum. The extent of the embryonic outlet portion of the right ventricle, forming the apical trabecular and infundibular components (along with the subaortic outlet of the left ventricle) is then marked by the septomarginal trabeculation (the rightward extension of the primary ventricular septum). Observations on the disposition of the conduction tissues in double inlet left ventricle [1, 23] support this view [26, 27] that the component of the conduction tissues which is carried by the primary septum could never achieve its contact with a normally situated atrioventricular node without the interposition of an inlet septum. Indeed, in double inlet left ventricle an

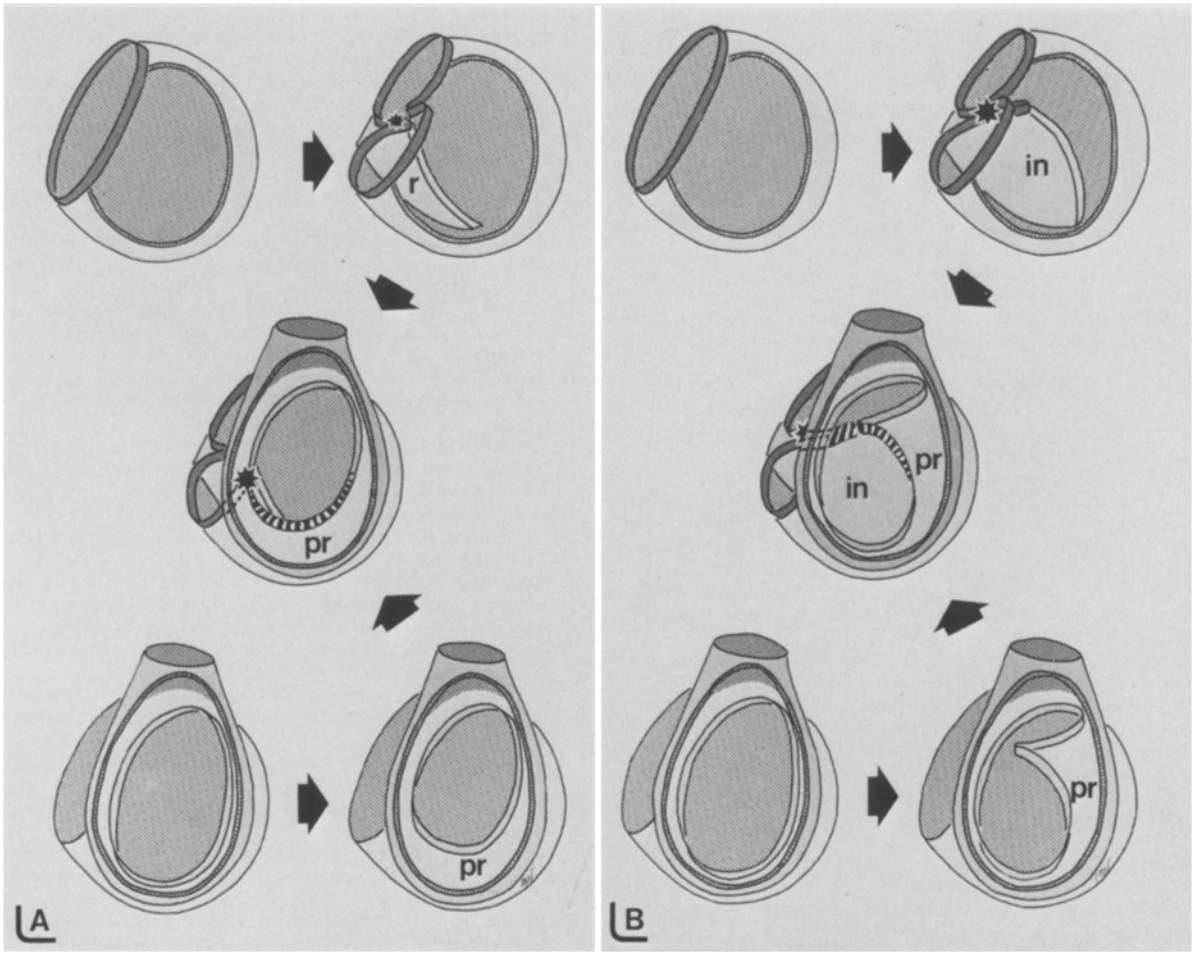

Figure 8. Diagrams to show the developmental backgrounds of the conduction system in double inlet left ventricle (A) as opposed to the normally septated heart (B). Top row: The developing inlet septum (in) carries part of the conduction tissues which is continuous with the atrioventricular node (asterisk). Since, in a double inlet left ventricle, only a small muscular ridge (r) develops, there is no posterior conduction axis and the posterior node is hypoplastic. Bottom row: In both cases a primary septum (pr) develops, which on its free rim carries part of the conduction tissues. Central figures: In the normal heart the posterior node and the conduction tisues on top of both septal components are continuous. In double inlet left ventricle the conduction tissues on the primary septum are continuous with an anomalous anterior node (asterisk), because the normal continuity on top of an inlet septum is missing.

abnormal anterior node has developed to guarantee an alternative route for atrioventricular conduction (fig. 8). Others suggest that the right ventricle derives in its entirety from the outlet component of the developing heart tube (the 'bulbus') and that the ventricular septum somehow migrates to position itself between the atrioventricular valves [11]. But do we have to choose between the concept of 'migration' of cardiac structures or that of individual development of an inlet septum? In the case of double inlet left ventricle, the anatomy can readily be described in terms of absence of an inlet septum. Any arguments on a possible 'shift' of the atrioventricular canal over the inlet septum are, therefore, non-productive.

Conclusions

It has not been our purpose, in constructing this chapter, to decry the science of embryology. Indeed, we see huge fields reopening for the study of the intrauterine development of the heart. Techniques such as fetal echocardiography are themselves developing with sufficient speed that, already, we can chart the growth of malformed hearts from about the twelfth week of gestation. The acquisition of large numbers of specimens from therapeutic abortions also provides the opportunity for studying the developing heart (both normal and abnormal) with techniques such as scanning electron microscopy. It is our intention to become deeply involved ourselves with all these advances. Our reasons for presenting this review in its constructed fashion is to point out the multiple dangers which have existed, and (continue to exist) in what can pejoratively be termed 'classical' embryology. From our position, admittedly biased, we see grave dangers in extrapolating from presumed knowledge of normal embryology and anatomy to account for congenitally malformed hearts. There are even worse dangers in using observations on congenital cardiac abnormalities

to provide concepts of normal and abnormal development. There is no longer the need for extrapolation. Each of these vital avenues can be explored and described in its own right. Only in this way will we finally unravel the mysteries of development and maldevelopment of the human heart.

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From the head to the heart: Some thoughts on similarities between brain function and morphogenesis, and on their significance for research methodology and biological theory

P. Grobstein

Department of Biology, Bryn Mawr College, Bryn Mawr (Pennsylvania 19010, USA)

Summary. A broad review of the phenomena of morphogenesis and of brain function, and of the history of research in these two areas, suggests that there are quite striking similarities between the two sets of biological phenomena. Among other things, both reflect the interaction of internally complex components at several levels of organization, display variance as an essential characteristic, and incorporate information from the environment. It is argued that reductionist approaches are inadequate to deal with fundamental problems of either morphogenesis or brain function, and alternative foundations for research strategy and tactics are discussed. Attention is also given to the question of why morphogenesis and brain function are so similar, and it is suggested that this may reflect the existence of rules of information acquisition, transmission, and storage to which both are subject. Variance, it is argued, is an essential component of information acquisition processes, and hence of biological integrity, at all levels of organization.
Key words. Morphogenesis; regulation; localization; variation; levels of organization; autonomy; homeostasis; distributed function; experience dependence; brain development; brain function; information.