Morphogenesis of bulboventricular malformations

I: Consideration of embryogenesis in the normal heart

R. H. Anderson,¹ J. L. Wilkinson, R. Arnold, and K. Lubkiewicz²

From the Department of Anatomy, University of Manchester; and the Department of Child Health, University of Liverpool

The results are described of a microscopical study of 17 embryos between the 14th and 22nd horizons of Streeter. The investigation has been concentrated upon the development of the ventricular outflow tracts, and the establishment of the crista supraventricularis of the right ventricle. During the 14th horizon the atrio-ventricular orifices both open into the primitive ventricle, which in turn communicates with the bulbus via the bulboventricular foramen. The truncus is directly continuous with the bulbus and is unseptated. Thus, both presumptive outflow tracts originate above the bulbus. The bulbotruncal ridges which fuse to septate the truncus are arranged in spiral fashion at first; however they fuse in straight fashion after detorsion of the truncus. After fusion of these ridges the aorta is still present above the bulbus, but during the 16th and 17th horizons it migrates to lie above the primitive ventricle, after the absorption of posterior distal bulbus. This process also brings the proximal edge of the bulbotruncal septum into the cavity of the newly formed right ventricle, and reorients the primary bulboventricular foramen as the aortic outflow tract. The secondary interventricular foramen is restricted anteriorly by the proximal margin of the bulbotruncal septum, and is finally closed by growth from the inferior cushion which forms the membranous septum. The crista supraventricularis is formed in part by the right hand margin of the bulbotruncal septum, but this tissue underlies the right hand portion of the bulboatrioventricular ledge, which therefore constitutes an important part of the crista. The significance of these processes of differential bulbar absorption and truncal rotation are discussed in relation to previous theories of cardiac embryogenesis, and the structure of the crista supraventricularis is discussed in relation to cardiac malformations.

It appears reasonable to propose that a detailed knowledge of cardiac ontogenesis will provide a sound platform on which to base hypotheses concerning the morphogenesis of congenital cardiac malformations. While careful studies such as those of de Vries and Saunders (1962), Van Mierop and his associates (1963), and Los (1968) have helped elucidate many problems of normal cardiac growth, other aspects remain controversial. This is particularly true of the formation of the ventricular outflow tracts. Attention has been focused upon this area by the careful morphological observations of Van Praagh and Van Praagh (1966), which showed that the generally accepted 'straight septum' hypothesis of transposed arteries (de la Cruz *et al.*, 1959; Van Mierop *et al.*, 1963) was not entirely satisfactory. Though they had considered a conal

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¹ Present address: Department of Cardiology and Experimental Physiology, Wilhelmina Gasthuis, Eerste Helmerstraat 104, Amsterdam, Netherlands.

² Present address: Montreal Children's Hospital.

absorption hypothesis such as previously espoused by Keith (1909) and Lev and Saphir (1937), they considered that this was not possible in view of the fact that Harris and Farber (1939) had declared the hypothesis untenable (Paul, Van Praagh, and Van Praagh, 1968). They therefore postulated their hypothesis of differential conal growth (1966). However, the recent study of Goor, Dische, and Lillehei (1972) has suggested that differential conal absorption is an embryological fact, and these workers quote much supporting evidence to substantiate their concept. In view of the uncertainty surrounding this topic we have, therefore, attempted to ascertain the method of development of the ventricular outflow tracts in embryonic material, and to use this information to consider the possible morphogenesis of bulboventricular anomalies. We shall present our findings in two parts, considering first the normal development of the outflow tracts and the crista supraventricularis of the right ventricle.

Materials and methods

The embryos studied were all obtained from the serially sectioned specimens in the embryological collections of the Department of Anatomy, University of Manchester, and the Institute of Child Health, University of Liverpool. In all, 17 specimens were studied, which covered the developmental horizons XV to XXII described by Streeter (1942, 1945, 1948). During this period the bulboventricular loop becomes septated and the ventricular outflow tracts are established. Details of individual embryos are given in the Table.

The conclusions reached from the embryological study were verified by careful examination of normal neonatal and infantile hearts. These specimens were obtained from routine necropsies performed at the Alder Hey Children's Hospital, Liverpool.

Comparison of the timing of certain events observed in this study with those described by Goor and his associates (1972) reveals several discrepancies. Since these workers were studying the specimens previously investigated by Streeter (1942, 1945, 1948) it appears that our staging is only approximate. However, it serves to form a basis for describing temporal events, but must be considered as an approximation to the original study of Streeter (1942, 1945, 1948).

In describing structures within the embryos we have attempted to correlate to definitive appearances. Thus the embryo is considered as if it were in the anatomical position. The atria are therefore described as lying superiorly to the ventricles, while the truncus is considered to be anterior to the atrioventricular canal. Finally, since there is some confusion surrounding the term 'conus' (Goor *et al.*, 1972; Lev, 1972), we have avoided this term, and considered the heart tube as composed of atrial, ventricular, bulbar, and truncal segments (Anderson and Ashley, 1974).

Results

A: Embryological observations in normal heart

i) **Horizon XV (Embryos H7, H10, H1917)** By this stage of growth the bulboventricular loop is fully formed but is unseptated. Though Goor *et al.* (1972) reported that atrioventricular canal migration had occurred by this stage, in our specimens which otherwise corresponded to their Horizon XV, the atrioventricular canal opened only into the primitive ventricle, and was only partially septated by the atrioventricular endocardial cushions (Fig. 1). The ventricle therefore communicates with the bulbus entirely through the bulboventricular foramen. The boundaries of this foramen are inferiorly the bulboventricular septum, and to right and left the corresponding bulboventricular ridges (Fig. 1). The superior margin is formed by the inner curvature of the heart tube which is directly continuous with the atrial wall. It can therefore be termed the bulboatrioventricular ledge (Lubkiewicz, 1969; Anderson and Ashley, 1974) and is synonymous with the conoventricular flange. The lower margin of the truncus is continuous with the distal bulbus, and at this stage it entirely overlies the bulbar cavity. The distinguishing feature of the distal bulbus and truncus is the presence within the lumen of paired, opposing but unfused endocardial swellings, the bulbar ridges (Fig. 2 a and c). Within the distal bulbus the ridges are attached sinistroposteriorly, fusing with the right margin of the left bulboventricular ridge, and dextro-posteriorly, lying beneath the right margin of the bulboatrio-

TABLE Details of embryos studied

Horizon (Streeter)	Source	Catalogue No.	Length (C/R mm)
XV	Anatomy Dept. Univ. of Manchester	H7	7 mm
	Inst. of Child Health, Univ. of Liverpool	H1917	8.5 mm
	Anatomy Dept. Univ. of Manchester	H10	10 mm
XVI	Anatomy Dept. Univ. of Manchester	H9	9 mm
	" " " " "	H11.5	11.5 mm
	" " " " "	H14	14 mm
	" " " " "	H15	15 mm
XVII	Anatomy Dept. Univ. of Manchester	H15A	15 mm
	Inst. of Child Health, Univ. of Liverpool	H1847	16 mm
	" " " " "	H1923	16 mm
XVIII	Inst. of Child Health, Univ. of Liverpool	H1901	18 mm
XIX	Inst. of Child Health, Univ. of Liverpool	H376	18 mm
	Inst. of Child Health, Univ. of Liverpool	H419	22 mm
XX-XXII	" " " " "	H1624	
	Anatomy Dept. Univ. of Manchester	H25A	25 mm
	Anatomy Dept. Univ. of Manchester	H25B	25 mm
	Inst. of Child Health, Univ. of Liverpool	H1848	28 mm

FIG. 1 *A*) Diagrammatic realization of the heart tube in Horizon XV, drawn from study of embryos H7, H10, and H1917. The atrium at this stage drains entirely to the primitive ventricle, while the truncus arises completely from the bulbus. Bulbus and ventricle communicate through the bulboventricular (BV) foramen. The bulbotruncal ridges spiral as they ascend the distal heart tube, the right hand ridge in the bulbus running anteriorly to become the left hand truncal ridge.

B) and *C*) are transverse sections of the heart tube at the levels b-b and c-c indicated in 1*A*). They show the relations of the endocardial cushion tissues to the myoblastic heart tube wall.

ventricular ledge (Fig. 1 and 2). When traced distally the ridges trace an helicoidal pattern within the truncus, the dextroposterior ridge running anteriorly to reach the left truncal wall, and the sinistro-anterior ridge passing posteriorly to the right wall (Fig. 2c).

ii) Horizon XVI (Embryos H9, H11-5, H14, H15) Within this period, according to our observations, the opposing atrioventricular cushions (superior and inferior) fuse to septate the AV canal, and the right canal migrates to make contact with the bulbus. The exact mechanics of this process are contentious and beyond the scope of this presentation (see Goor, Edwards, and Lillehei, 1970; Anderson and Ashley, 1974). The truncal cushions also fuse within this growth period, but their fusion produces a relatively straight septum within the truncus, the helicoidal pattern described above

having disappeared. At the level of the bulbotruncal junction excavations of the cushions produce the primordia of the semilunar valves, with the aortic valve lying posteriorly to the pulmonary valve (Fig. 3 and 4). The ridges in the distal bulbus are more obvious, but are unfused and continue to occupy the positions noted in Horizon XV. Their proximal edges form an archway above the bulbar cavity, stretching from the dextroposterior wall to the sinistroanterior wall, and the ridges therefore partially septate the distal bulbus (Fig. 3 and 4). However, though AV canal migration has occurred, the aortic component of the distal bulbus overlies the bulbar cavity, and the posterior wall separates the developing aortic valve primordia from the atrioventricular cushions, i.e. at this stage of development there is no fibrous continuity between the developing aortic and mitral valves. The blood from the left AV orifice therefore continues to

FIG. 2 Sections from embryo H7 illustrating the spiral arrangement of the bulbar ridges at this stage of development. The plane of the sections is indicated by the diagram (E) and the embryonic nature of the tissues is shown in Fig. 2B and 2D, which are drawn from Fig. 2A and 2C, respectively.

FIG. 3 Representation of the heart tube in Horizon XVI, drawn from study of embryos H9, H11-5, H14, and H15. In this stage the atrioventricular canal has been brought into contact with the bulbus, but the truncus still overlies the bulbar cavity in its entirety. The truncus has also rotated in counterclockwise fashion looking downstream, so that the bulbar ridges have been 'unwound' and fuse in straight fashion. After fusion, the semilunar valve primordia are formed at the bulbotruncal junction, so that a segment of distal bulbus separates the posterior aortic valve from the fused AV cushions.

A) shows a frontal section, and a transverse section. Solid arrows indicate the course of left atrial blood through the left atrioventricular (LAV) orifice, and left ventricle (LV) to the posterior aorta. Open arrows show the course of right atrial blood beneath the BAV ledge and the lower ends of the bulbar ridges.

transverse the bulboventricular foramen, still surrounded by bulboventricular musculature, to reach the presumptive aorta. The blood from the migrated right AV orifice passes beneath the right margin of the bulboatrioventricular ledge and the dextro-posterior bulbar ridge to reach the bulbar cavity

and thence the anteriorly situated presumptive pulmonary artery (Fig. 3 and 4).

iii) **Horizon XVII (Embryos H15A, H1847, H1923)** In this developmental horizon conspicuous shortening of the distal bulbus occurs, par-

FIG. 4 Representative sections from embryo H15, cut in the plane indicated by the diagram (E). A) shows clearly that the presumptive (pres) aorta and the presumptive pulmonary artery (pres. pulm. art.) are above the bulbar cavity. C) shows the ridges fusing in straight fashion, and the developing (dev.) aortic valve separated by bulbar musculature (bulb. musc.) from the atrioventricular canal.

B and D are drawings indicating the embryonic nature of the tissues.

FIG. 5 Representation of the heart tube after absorption of the distal bulbus and reorientation of the posterior part of the bulbus occurring in Horizons XVII and XVIII. This process produces attenuation of the midportion of the bulboatriventricular ledge, and takes the aorta above the primitive ventricle (solid arrow). The primary bulboventricular foramen (BVF) is thus reorientated to form the aortic vestibule, and the secondary foramen (2° IVF) is formed between the aorta and the right ventricle (RV). The right margins of the BAV ledge and the lower edge of the bulbar septum form the crista supraventricularis (crista SV).

ticularly in its posterior wall. This is indicated by the fact that the aortic valve is brought into close apposition with the atrioventricular cushions, now differentiating into the central fibrous trigone and the septal AV valve cusps. However, though in close apposition the valve primordia are still separated by a complete rim of bulboatrioventricular ledge tissue (Fig. 5 and 6). As a result of this bulbar absorption the aortic valve is carried to the

left, a migratory process emphasized by simultaneous expansion of the right atrioventricular orifice. As the bulboatrioventricular ledge becomes much smaller the aortic orifice is also carried above the left ventricle, with associated reorientation of the bulboventricular foramen (Fig. 5). The absorption also brings the proximal edges of the bulbar ridges down into the bulbar cavity, and the left portion of the bulbar septum is incorporated into the bulbo-

FIG. 6 Sections from embryos in Horizon XVII (H1923) and Horizon XX (H25A) showing how in this period the persisting portion of bulbar musculature between the aortic valve and the AV cushions is absorbed to produce fibrous mitral-aortic valvular continuity. Plane of section is shown in the diagram (E) and B and D show the embryonic nature of the tissues.

E.

FIG. 7 Sections from embryo H1923 (Horizon XVII) showing A) the relations of the newly formed secondary interventricular foramen and B) the reorientation of the primary foramen to form the aortic vestibule. The sections also show how the crista supraventricularis is composed of both the right margin of the BAV ledge, and the lower edge of the bulbar ridges.

The diagram (E) indicates the plane of the sections, and the embryonic nature of the tissues is shown in B and D, drawn from A and C.

ventricular (interventricular) septum as the aorta moves posteriorly and to the left. The pulmonary artery is thus separated from the left ventricle and the aortic outflow tract. However, a communication persists between the newly formed aortic outflow tract (bulboventricular foramen) and the right ventricle (Fig. 7). This communication is the secondary interventricular foramen, and is bounded by the bulboventricular septum inferiorly, the bulbar septum anteriorly, and the atrioventricular endocardial cushions superiorly and posteriorly. Since the bulbar septum is still oriented from sinistroanterior to dextroposterior, it follows that though its left segment has been incorporated into the ventricular septum, the right segment together with the persisting right margin of the bulboatrioventricular ledge span the right ventricular cavity and form a spur of tissue between the developing tricuspid and pulmonary valves (Fig. 7).

iv) Horizons XVIII–XXII (Embryos G1901, H376, H419, H1624, H1848, H25A, H258B) In the growth periods after the rapid absorption of the distal bulbus described above, the alignment of the aorta with the left ventricle is completed. In-

cluded in this process is the attenuation of the middle portion of the bulboatrioventricular ledge so that the aortic valve is brought into fibrous continuity with the newly developed mitral valve (Fig. 6c). The atrioventricular cushions themselves are incorporated into the right wall of the aorta as the atrial portion of the membranous septum (Fig. 7), while the remaining portion of the secondary interventricular foramen is closed by growth from the inferior atrioventricular cushion (Fig. 7). The inflow tract of the right ventricle is at this stage lined by endocardial cushion tissue. It is difficult to be sure of the origin of the lateral cushion, but the medial cushion is derived from the inferior atrioventricular cushion. This tissue extends a considerable distance towards the apex of the right ventricle. Anteriorly it overlies the conducting elements of the right bundle-branch, and becomes muscularized to form a structure approximating to the trabeculum septo-marginalis.

B: Morphological observations in normal heart

i) Morphology of normal ventricular outflow tracts

The left ventricular outflow tract is formed

FIG. 8 Diagram in transverse section of the completed ventricular outflow tracts showing the embryonic nature of their constituent parts.

by the reorientated bulboventricular foramen; consequently its superior margin is considerably posterior to its inferior margin (Fig. 9). The boundaries of the tract are as follows: antero-sinistrally is the left bulboventricular ridge; antero-dextrally is the left margin of the bulbar septum which fuses with the left bulboventricular ridge; postero-sinistrally is the region of mitral-aortic fibrous continuity and the central fibrous trigone and postero-dextrally is the membranous septum. The latter itself is in two parts, a larger aorto-right atrial segment and a smaller aorto-right ventricular segment (Fig. 8 and 9).

The right ventricular outflow tract is completed when the proximal bulbar septum fuses with the ventricular septum. Its boundaries are: anteriorly is the free wall of the infundibulum; postero-sinistrally is the left bulboventricular ridge; and postero-dextrally are the fused bulbar ridges and the right margin of the bulboatrioventricular ledge (Fig. 8 and 9).

Thus, in the definitive heart the pulmonary outflow tract is a purely muscular structure while the aortic outflow tract is in part muscular and in part fibrous tissue.

ii) Morphology of normal crista supraventricularis The basic morphology of this structure is similar in all hearts studied. Its major part is formed by the external wall of the right ventricle beneath the right auricle. On its inner aspect this represents a broad strip of myocardium, with the anterior cusp of the tricuspid valve arising from its posterior aspect. A thickened bar of myocardium is present in the middle portion of this structure, which becomes wider at its septal extent (Fig. 9). The magnitude of this myocardial bar varies in different hearts, but in all cases a trabeculated crevice is present between the bar and the anterior tricuspid valve cusp. The parietal extension of the bar extends downwards towards the ventricular apex where it becomes continuous with the moderator band. The septal extension of the bar becomes incorporated into the ventricular septum as its bulbar portion. However, on gross dissection it is also continuous on the septal surface with the trabecula septo-marginalis.

Discussion

The conclusions drawn from our investigation are, for the most part, endorsements of the concept of cardiac ontogenesis expressed in the recent publication of Goor *et al.* (1972). Since these workers themselves indicated that they were substantiating work previously reported in the German literature,

our conclusions can in no way be claimed as original. However, we consider them important since they focus attention on Goor's concept that the distal bulbus is a vital centre in disordered ontogenesis. We shall show in the second part of our study how all bulboventricular malformations, including transposition of the great vessels, stem from disordered growth in the distal bulbus, but first we shall consider the relevant features of normal growth presently reported.

As Goor *et al.* (1972) have reported, the vital features of normal growth are absorption and inversion of the distal bulbus. We have already indicated that their usage of the term 'conus' excited some controversy (Lev, 1972), and we have purposely avoided this term, but our 'distal bulbus' is equivalent to their 'conus'. They showed quite clearly in their presentation that the bulbar ridges, though formed in helicoidal fashion, fused together to form a straight bulbar and truncal septum. This fact was in fact previously reported by Los (1968) and is confirmed in this investigation. This process in itself has several important implications. First, the proximal ends of the bulbar ridges retain their original position throughout ontogenesis. Thus the right-sided ridge, termed dextro-posterior presently, dextro-dorsal by Van Mierop *et al.* (1963), parietal by Los (1968), and conus ridge 3 by Goor *et al.* (1972), is always related to the right hand margin of the bulboatrioventricular ledge (conoventricular flange). The left hand ridge, termed sinistro-anterior presently, sinistro-ventral by Van Mierop *et al.* (1963), septal by Los (1968), and conus ridge 1 by Goor *et al.* (1972), is always related to the anterior margin of the bulboventricular foramen. Therefore the presumptive pulmonary outflow tract is always anterior and to the right of the presumptive aortic tract. However, the orientation of the semilunar valves changes during ontogenesis. Before fusion of the ridges, the presumptive primordia are so arranged that the pulmonary primordium is to the left of the aortic primordium. At the stage at which valvular cusps are first recognized, after fusion in the truncus but before bulbar absorption, the aortic valve is posterior to the pulmonary valve. Thus, as Goor *et al.* (1972) have stated, and as the reconstructions of Los (1968) show, considerable torsion and rotation of the truncus in a counterclockwise fashion looking downstream occurs before bulbar absorption. This is a vital feature of ontogenesis, and is necessary to 'undo' the twisting of the distal bulbus and truncus produced during looping. It can be shown quite easily on rubber tubing that the process of looping as in the heart tube produces helicoidal ridges in the area of tube corresponding to the distal bulbus and truncus. The truncal rota-

tion brings the semilunar primordia into concordance with the presumptive outflow tracts. Since the rotation occurs after junction of the aortico-pulmonary and truncal septa, the torsion is transferred to the great vessels, as both Los (1968) and Goor *et al.* (1972) have proved.

The second vital feature of normal ontogenesis, after truncal rotation, is absorption of the posterior segment of the distal bulbus. Goor *et al.* (1972) suggest that this absorption occurs after the bulbar migration which carried the aorta above the left ventricle. Our findings suggest that the migratory process itself is one of the consequences of bulbar absorption, together with production of mitral aortic continuity and reorientation of the bulbo-ventricular foramen. This absorption of the bulbo-atrioventricular ledge is a well-known feature of cardiac growth, but doubt has been expressed as to whether absorption is real or apparent. The measurements of Goor *et al.* (1972), together with the photomicrographs presently illustrated, show conclusively that originally the mitral and aortic valves are separated by an extensive segment of bulbar musculature. By Horizon XXII the two valves are in fibrous continuity. The reorientation of the bulboventricular foramen has also been clearly described previously, in particular by Van Mierop and his associates (1963). They show how the foramen becomes oblique and forms the aortic outflow tract, and at the same time how the secondary, or interventricular foramen is produced. This secondary foramen connects the newly formed aortic vestibule to the right atrium and right ventricle. Our results are in complete agreement with this concept, and it seems unnecessary to us for Goor *et al.* (1972) to extend the same process to embrace three interventricular foramina. Another feature relative to bulbar absorption where our results do substantiate those of Goor and his associates (1972) is regarding formation of the bulbar septum. We have already described the position of the bulbar ridges. At the time of fusion of the truncus septum, the proximal edges of these ridges form a high arch above the right ventricle. As bulbar absorption occurs the proximal edges are drawn into the right ventricle, and as the bulboventricular foramen is reoriented the left margin of the ridges is incorporated into the anterior bulboventricular septum as the bulbar or conus septum, and forms the anterior margin of the newly formed secondary interventricular foramen. After this incorporation the conus septum is in line with the infundibulo-left ventricular part of the interventricular septum, but makes a considerable angle with the posterior ventricular septum. Thus the process of bulbar absorption is also responsible for completing the

separation of the pulmonary artery from the left ventricle. Regarding closure of the secondary interventricular foramen, our results endorse the view of Los (1968). He showed that the fused atrioventricular cushions form the aorto-right atrial segment of the membranous septum, while the aorto-right ventricular segment is closed by growth from the inferior atrioventricular cushion.

It will be appreciated that in the differential conal absorption theory espoused by Goor *et al.* (1972), and endorsed by this investigation, an essential part is rotation of the distal bulbus. As Harris and Farber (1939) pointed out, the previous conal absorption hypothesis of Keith (1909) was discarded because the pulmonary valve could not be shown to lie to the left of the aortic valve. This latter point was the vital premise in both Keith's hypothesis, and also the differential conal growth hypothesis of Van Praagh and Van Praagh (1966). Though Van Praagh (1973) has subsequently shifted emphasis to a conal absorption theory, it is important to appreciate that the pulmonary valve is to the left of the aortic valve only in a very early stage of development, and is subsequently moved by the normal counterclockwise truncal rotation. Therefore in propounding any hypothesis to account for malformations with a left-sided pulmonary artery, it is not sufficient to simply propose conal absorption, it is also necessary to specify absence of normal distal bulbar inversion. Thus Fig. 5A of Goor *et al.* (1972) is the starting point of several bulboventricular malformations. Goor himself has briefly developed this theme in association with Edwards (Goor and Edwards, 1972). As will be shown in the second part of this study, we have reached independent but identical conclusions.

Bulbar absorption is also of relevance to the formation of the normal crista supraventricularis. Van Praagh (1967) and Goor *et al.* (1970) have previously expressed dissatisfaction with the definition of the crista as possessing septal and parietal bands. This concept was initially introduced by Keith (1909), but, as Walmsley (1929) has stated, the original crista was described as the supraventricular mass separating the tricuspid and pulmonary valves. Quite obviously, this definition cannot include the septal band or trabecula septo-marginalis. Both Van Praagh (1967) and Goor *et al.* (1970) therefore plead for redefinition of the crista as parietal band, or conus septum alone. While we support this contention, we also believe that the conus, or bulbar septum, is only part of the crista. It is an easy matter to dissect away the muscular trabecula which we believe represents the extension of the dextro-dorsal ridge, and still leave a substantial muscular 'crista' above the right ventricle. Goor

et al. (1970) suggest that the ridge becomes exteriorized. Our results do not support this theory, but instead show that the bulbar ridge lies inside the right margin of the bulboatrioventricular ledge, and is muscularized from this ledge. We believe, therefore, that the crista is indeed a supraventricular structure, but is composed in part of the conus septum and in part of the bulboatrioventricular ledge. In that R. Van Praagh (1973, personal communication) considers the bulboatrioventricular ledge as conal free wall, he does not disagree with this. Additional evidence to support this theory of duality, originally expressed by Lubkiewicz (1969), will be presented in the second part of this study, when it will be shown that each component can have a separate existence in malformed hearts.

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Requests for reprints to Dr. R. H. Anderson, Department of Anatomy and Embryology, Institute of Child Health, Alder Hey Children's Hospital, Eaton Road, Liverpool L12 2AP.