The Morphogenesis of Corrected Transposition and Other Anomalies of Cardiac Polarity

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A CRUCIAL event during the development of the heart is the coiling of the primitive heart tube. It is this coil that enables the heart to convert from a simple tube with its chambers in tandem into the adult form with two pairs of chambers in parallel. Indeed, topologically there is no other way in which a tube can by simply extending its walls form four interconnecting chambers except by first falling into a coil. It may be a naive view of evolution, but what a remarkable event it was when the heart first increased in length faster than did its enclosing space and, with this seemingly extravagant growth, put itself into the geometric form that made possible much more complicated types of development, including the four-chambered heart encountered in man. The complexity enabled by coiling is diagrammed in figure 1.

For an elongating cylinder to form a coil, there must be an eccentric distribution of different growth rates within the tube. It is the thesis of the present report that disturbances in the distribution of this difference in growth rate may account for a special group of cardiac anomalies. These are the anomalies in which the components of the heart have abnormal spatial relationships with each other or with body axes but may themselves be normally or nearly normally developed. They are disturbances in cardiac organization as contrasted with disturbances of cardiac differentiation, and go by many different names: corrected transposition, ventricular inversion, various levocardias and dextrocardias, certain types of single ventricle, etc.

As a group, these anomalies may be called disturbances in cardiac polarity, emphasizing the geometric basis of the abnormality. While in other organs the most important developmental events are often cytologic or histochecmical, in the heart they are changes in shape or geometry. Indeed, it can be said that for any theory of cardiac development to be sound embryologically, it must be consistent with the principle that all cardiac growth, both normal and abnormal, is essentially the progressive deformation of the walls of a cylinder.

The Problem

The architecture of the normal and abnormal heart can be represented by points on a three-dimensional reference figure. Therefore, for conceptual purposes the heart can be treated as having three architectural axes, each with a particular polarity with reference to the three body axes. The abnormalities of the heart in polarity disturbances are, in their classic forms, reversals of the architecture of the heart in all details on two of its three axes, either the right-to-left axis, or the anterior-posterior axis, or both.* For example, situs inversus dextrocardia is a complete reversal of cardiac architecture on the right-to-left axis, the architecture on the other axes remaining normal. On the other hand, in ventricular inversion with a left-lying heart, there is complete reversal of ventricular architecture on the anterior-posterior axis, while right-to-left and superior-inferior architecture of the ventricles remains essentially normal. In dextroversion in its simplest form there is reversal of the ventricular architecture on the anterior-posterior as

* The term “mirror image” is a geometric term for describing reversal on only one axis of a three-dimensional architectural system, the “mirror” held perpendicular to the reversed axis. It is a descriptive term and not at all a morphogenetic mechanism.
well as the right-to-left axis. This type of analysis is important because abnormal "rotation" of the cardiac tube is sometimes suggested as the cause of polarity disturbances. But a moment's reflection will disclose that rotation will always produce a reversal on two axes. Therefore, while "rotation" may explain part of the dextroversion syndrome, it cannot by itself explain the other polarity abnormalities.

Indeed, none of the current theories for cardiac polarity disturbances appears to take into adequate account the three-dimensional aspects of the problem. One widely held theory suggests that these abnormalities are due to the normally left-lying cardiac coil being caused to develop rightward.1,2 While this would explain reversals on the right-to-left axis, it cannot, without additional postulates, explain anterior-posterior abnormalities, and these are the more common ones.

In addition, in polarity disturbances there is a high incidence of special additional structural abnormalities of the heart that are not often seen with other major groups of cardiac malformations.3,4 For example, the aorta and pulmonary artery have an abnormal lie with reference to each other (called "corrected transposition," "inverted complete transposition," etc.), which rarely accompanies other types of cardiac anomalies. Also, deformity or even absence of the inflow portion of the ventricular septum and deformity of right ventricular architecture such as a rudimentary outflow tract (so-called "third ventricle"), double-inlet left ventricle, etc., occur mainly with polarity disturbances and are infrequent in association with other types of congenital heart disease. Any theory of the morphogenesis or polarity disturbances must be able to explain these associated abnormalities.

**Methods**

The histologic details of human cardiac development are, of course, best studied from human material. But the spatial relationships and general morphologic features of heart development are extremely difficult to study from human material because they exist only in the form of histologic sections. To obtain a three-dimensional view of the heart from such sections it is necessary to make scale reproductions in wax. This is so laborious and time-consuming that few em-
bryology departments have more than a single model for any given stage of development.

The chick embryo has many advantages over human material for such studies. In the first place, the morphologic changes that take place during the development of the chick heart are essentially the same as in man. Within a week of fertilization, the chick heart evolves from a simple tube to a complex four-chambered organ that is virtually identical with that of man in shape and proportion. In addition, the chick heart is easily dissected from the embryo at any stage and can be further dissected to study three-dimension architectural relationships in detail without resorting to microscopic sections or fear of wasting or destroying valuable specimens. Finally, since the chick embryo lies immediately beneath the air sac, it can be studied under the dissecting microscope while still functioning at every stage of development. One can observe the movements of the various parts of the heart, the location of turbulent and laminar flow, and many other features that shed light on the developmental changes which take place.

My efforts to explant the chick heart and have it continue to differentiate have so far been unsuccessful. The heart remains viable, it continues to grow and to contract rhythmically for several days, but early it loses its morphology and differentiation ceases. Finding a method for the organ culture of the heart to sustain differentiation will be an extremely important advance in cardiac embryology and teratology, for it will provide the definitive tool for studying mechanisms and testing etiologies of abnormal cardiac development.

**Embryogenesis of the Heart Coil**

How is the coiling of the heart tube brought about? If the increase in the rate of cellular multiplication were generalized throughout the heart tube and random in direction, the tube would increase in diameter and little in length: it would balloon out. For it to elongate more rapidly than it widens, the increased cellular multiplication must be oriented in the direction of the long axis of the tube. If, with this orientation, the increased rate were symmetrical around the tube, the tube would elongate and fold on itself (since the thoracic length does not increase as rapidly), but it would not necessarily fall into a coil. To form a coil the region of highest rate of cellular multiplication must have, in effect, a winding or helical course around the tube. This is best appreciated by studying the torsions that take place in a piece of pliant rubber tube when its two ends are brought toward each other along the axis of the tube (fig. 2). At first the tube folds upon itself. Then, at the instant it falls into a coil, a sudden torsion or torque is felt at both ends. The torque is due to the unequal distribution of tension within the wall of the tube produced by the geometry of a coil. To make the tube form a coil as the two ends are brought together one must first introduce a torque into the tube. If the coil is

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* At early stages the chick heart is transparent, making study of details in the explanted heart difficult. Following the suggestion of Dr. W. A. Voogd van der Straaten of the Laboratory of Cytology in Leiden, it was found that dipping the specimen briefly in a dilute solution of chlorozol black greatly improved its visibility without altering its transparency. For purposes of photography, the specimen can be cleared in methyl salicylate, after dehydrating it in increasing concentrations of alcohol, without significantly altering its morphology.

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**Figure 2**

Mechanics of coiling. In causing the tube at the left to form the coil, B, a twist in its walls will take place, indicated by the path of the solid line. The "twist" is shown in planar form in C. To show this reversely, if the coiled surface D be grasped at A and B and pulled straight, the ends held fixed, the 360-degree twist shown in E will result.
to be tight and lie in the same plane as the axis formed by the two ends of the tube, the torque or twist must be about 360 degrees. If the coil is to lie at right angles to the axis in which the tube is held (and this resembles the lie of the embryonic heart coil with reference to its truncus and sinus attachments) the torque must be about 180 degrees.

It is not suggested that such torques and torsions occur in the embryonic heart tube. Rather, it must be that the geometry of coiling is itself the way in which the heart tube "solves" the mechanical tensions produced by a particular type of asymmetrical growth within the tube. At the embryonic stage when coiling develops, the cellularity of the tube has a relatively uniform histologic appearance. Elongation appears to be mainly due to cellular multiplication at the caudal end of the tube. The asymmetrical growth results first in kink at its caudal end, and the asymmetric growth is propagated into the kink along a winding helical course of, perhaps, 180 degrees, so that the kink elongates into a coil. In other words, it seems probable that this segment of the heart tube resolves the mechanical torques of its helical growth differential by falling into a coil (fig. 3).

This is, of course, only a hypothesis and an extreme simplification of a complex event. Grohmann has shown that there is indeed an asymmetry of growth rate in the heart tube

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**Figure 3**

Three stages in the development of the heart coil in the chick embryo, at 1½, 2, and 3 days. Above, the thoracic and cephalic portion of the embryo; the central thoracic wall has been dissected away to show the heart. Below, the heart has been dissected from the embryo at each of the above three stages. Note how much more rapidly the cardiac tube elongates than does the thoracic cage. The tightness of the coil below in C has been somewhat lost in dissecting the heart free from the embryo, but early evidence of surface of the truncal ridges and A-V cushions can be seen.
at this early age. And there can be no question that coiling must involve three-dimensional growth asymmetries and not just right-to-left asymmetry alone. The concept presented above is a way of formulating these asymmetries. It provides a basis for explaining certain aspects of the morphogenesis of polarity disturbances of the heart but, if it proves valid, is only a first approximation toward understanding these anomalies.

**Differentiation of the Coil**

Morphologic differentiation of the various parts of the heart tube takes place at the same time as coiling. First, enlargement appears in the region of the tube that is to become left ventricle, giving the part of the coil distal to the atrium a sickle-shape, much more striking in the functioning chick heart than in the dissected specimen. The “handle” of the sickle is the atrioventricular region, which is relatively very much larger at this stage than in the adult heart. The left ventricle forms the first part of the “blade” of the sickle, with the interventricular canal, the right ventricle, and the truncus arcing gently in tandem from it. In a study of the functioning chick heart at this age, it is apparent that the atrium and the left ventricle are the main propelling parts of the heart, the right ventricle playing little

![Figure 4](http://circ.ahajournals.org/)

**Figure 4**

Chick embryo heart during early development. A, two views of the same heart 2½ days to show the planar surfaces between truncal ridges and A-V cushions. B, C, and D, the heart at 2½, 3½, and 4½ days all at some magnification. The rapid differentiation of the left ventricle is evident. The inner concave surface of the coil becomes smaller and smaller with the rightward widening of the A-V canal. The black rods in A are drawn glass threads used to hold the specimen in position for photography. The specimens are photographed with transmitted light.
Dissections of the chick embryo heart with reflected light. A, a 3-day-old heart, the atrial and ventricular regions dissected apart at the A-V ring to show the A-V cushions (a-v cush.), truncal ridges (tr.r.), and first evidence of interventricular septum (i-v s.). The lie of the components with reference to body axes is shown in the diagrams below. B, chick heart at 3 days. The outer layer of connective tissue has been dissected away and the specimen lightly tinted with chlorazol black to bring out the directions of superficial muscle fibers. They are circumferential, perpendicular to the path of inflow from the atrium but parallel with the path of outflow into the interventricular canal, right ventricle, and truncus. C, chick heart at 5 days; the appendage of the right ventricle and partitioned truncus can be seen. The superficial connective tissue and superficial layer of musculature of the right ventricle have been removed, revealing the extremely spongy network of trabeculations immediately beneath. The trabeculations of the human right and left ventricles are equally spongy at this stage of development.

or no active part in ejection. Blood flow appears to be laminar through the right ventricle and truncus.

Between the two A-V cushions and the two truncal ridges blood flow is planar. Therefore, the angular relationships of these regions can be easily studied, making it possible to measure any “torsions” of the heart tube that may take place during subsequent development. The planar surfaces are readily seen in figure 4, and, from another view, in figure 5A. Here, the atrium was dissected from the left ventricle at the A-V ring. The two A-V cushions can be seen protruding from the orifice of the atrium (not yet partitioned into a right and left atrium); the two truncal ridges and the first evidence of the ventricular septum are also evident.

It can be seen that the plane between the two A-V cushions is relatively parallel with the frontal plane of the body, and this lie is more or less maintained throughout their subsequent differentiation. Likewise, the twisting plane between the two truncal ridges has a path with reference to body axes that is the same as the plane that describes the path of the pulmonary artery and aorta in the adult heart. These observations indicate that, in the chick heart at least, there is little torsion or rotation of the truncus of A-V regions of the heart tube after coiling is established. This is a point about which there has been much speculation in the past, leading to quite complex torsion-detorsion theories to explain cardiac development.

When the heart is a coiled tube, the left and right ventricle are in tandem, joined by the interventricular canal. They lie in the frontal plane of the body, with the left ventricle to the left of the right ventricle, and the first evidence of the interventricular septum relatively perpendicular to the frontal plane of...
the body. But in the adult heart, the right ventricle is mainly anterior to the left ventricle, and the ventricular septum parallel with the frontal plane of the body. How is this change in relative positions of the two ventricles brought about?

The explanation lies in the different pattern of growth of the left ventricle as compared with the right ventricle. The left ventricle increases in size by symmetrical growth along its long axis, extending leftward and inferiorly like an expanding cone. On the other hand, the right ventricle increases in size asymetrically, its anterior and leftward regions growing much more than its rightward and posterior regions. The leftward extension of the right ventricle causes it to grow over the anterior wall of the left ventricle, and the overlapped region becomes, of course, the ventricular septum. This sequence of events is illustrated diagrammatically in figure 6.

The evidence for this explanation comes from studying the internal appearance of the heart at each stage of development. On dissecting the cardiac coil at the stage when the left ventricle is first clearly differentiated, one can see that already the left ventricle has certain of the same internal morphologic characteristics as the adult left ventricle. The anterior inner surface is smooth and nontrabeculated, resembling the smooth, nontrabeculated anterior outflow wall of the adult left ventricle. And the posterior surface already shows the rather fine, systematic trabeculation that characterizes the posterior inflow wall of the adult left ventricle. In the adult heart the smooth anterior wall is also the septal surface of the left ventricle. In the embryonic heart the smooth anterior wall is not yet the septal surface because the right ventricular trabeculations have not yet overgrown it. By

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* In man (and only to a slightly lesser extent in the chick) it would be much more appropriate to call the two ventricles an "anterior" and a "posterior" ventricle than a "right" and "left" ventricle, as can be seen in the angiocardioogram of any normal subject.

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**Figure 6**

External and internal views of the developing chick heart demonstrating the conversion from the tandem arrangement of the chambers in the embryonic heart to the parallel arrangement in the adult heart. Approximate ages are 2, 3, 5, and 8 days, but the scale is different for each age and not shown in the diagrams. At lower left are shown the regions of the coiled tube that will differentiate into truncus (TR), right ventricle (RV), left ventricle (LV), left atrium (LA), and right atrium (RA). The developing interventricular septum (i-v s.), interatrial septum (a.s.), and A-V cushions (a-v c.) are indicated by shaded areas. The two arrows in the lower right figure correspond to the arrows shown in figure 1.
making such dissections at each stage of cardiac development one can observe the gradual extension of right ventricular trabeculation over this anterior, smooth-walled region of the left ventricle, creating the ventricular septum.

The difference in pattern of growth explains why the two ventricles are so different architecturally in the adult heart. In the fully developed heart, the right ventricle is pyramidal in shape, embracing the base of the conically shaped left ventricle. The septum is not a flat partition between the two ventricles, as often depicted in diagrams, but, being the segment of the left ventricle to which the right ventricle attaches, it is curved, conforming with the shape of the left ventricle. In man, the septum forms an arc of nearly 90 degrees of the left ventricle. Part of it is perpendicular to the frontal plane (the region of the membranaceous septum) and part parallel with the frontal plane (the region of the apices of the two ventricles). The most primitive part of the septum, the first to form, is perpendicular to the frontal plane (fig. 5A). It is the part in the embryonic heart ridging the interventricular canal that will be later obliterated by the development of the membranaceous septum. The last part to develop is parallel with the frontal plane; it is the region of anterior wall of the left ventricle converted into septum by the overlapping growth of the right ventricle.

Incidentally, this difference in ventricular growth may perhaps also account for the difference in the pattern of distribution of the right and left ventricular conduction networks. It will be recalled that the left bundle crosses the septum adjacent to its membranaceous region and nearly immediately divides into its various branches. On the other hand, the right bundle traverses the septal surface of the right ventricle all the way to the moderator band before it divides significantly. This is the direction in which the right ventricle grows in overlapping the anterior wall of the left ventricle. It seems possible that the right bundle is, in effect, drawn and extended leftward by the asymmetric growth of the right ventricle.

When the heart tube of the chick is still in the form of a coil, the superficial fibers of the left ventricle begin to fall into circumferential syncytial sheets or bundles (fig. 5B). The epicardial connective tissue of this specimen has been gently dissected away and the specimen tinted with chlorazol black to bring out the directions of the fibers. No such alignment of superficial fibers can be made out on the surface of the right ventricle at this time. Nor are obliquely or axially directed bundles, such as are found in inner layers of the adult left ventricle, yet present. Immediately beneath the circumferential fibers is a dense, spongy network of trabeculations, similar to that shown for the right ventricle in figure 5C, and the same sponginess is found also in the human heart at a comparable age.

Up to this stage of development, the four chambers of the heart are in series. Another group of growth differentials now changes them into the parallel arrangement seen in the adult heart. Elongation of the tube ceases and now the directions of growth are those that rapidly increase the diameters of the coil, especially in the atrioventricular regions. As a result, the inner concave surface of the coil becomes relatively and absolutely smaller and smaller, while the outer convex surface becomes vastly greater. Indeed, the inner concave region undergoes relatively little further expansive growth during the remainder of cardiac development. The root of the truncus becomes incorporated into the greatly increased ventricular mass, and the A-V ring widens behind the truncus so that the common atrium and the A-V cushions come to communicate with both ventricles (fig. 6). The aortic part of the truncus is now in a position to become outlet for the left ventricle, and the right atrium comes to communicate with the right ventricle. The two arrows showing this in the last drawing of figure 6 correspond to the two arrows shown in the diagram of figure 1.

A Theory of the Morphogenesis of Polarity Disturbances

The heart tube forms a coil on elongating because there is an asymmetry in cellular multiplication at its caudal end. It is probable
that the growth differential has a helical or winding course, either in time or space or both, within the portion of the tube which becomes the coil. We shall now study the extent to which polarity anomalies may be due to disturbances in the timing or distribution of this growth differential during the development of the coil.

It is intrinsic in the mechanics of coiling that for the heart coil to be left-lying with its caudal limb posterior to its cephalic limb, the torque or "twist" effected in the tube must be counterclockwise as viewed from its caudal end. It so happens that this is exactly the same direction of "twist" that the pulmonary artery and aorta make with respect to each other in the adult heart. There are no doubt many factors in the twisting course that partitioning of the truncus arteriosus follows, but it is possible that the torque of coiling is one. In any case it is a most remarkable fact that if this 180-degree reversal were to take place not in the truncal region but in the region where the ventricles will develop, all morphological features are produced of what is called "corrected transposition": the heart is left-lying, the left ventricle is anterior to the right ventricle, and the aorta and pulmonary artery no longer coil but are parallel, with the aorta to the left of the pulmonary artery (fig. 7).

"Corrected transposition" is perhaps the commonest polarity disturbance encountered clinically. Its name is an unfortunate one for, as generally used, it really describes only a physiologic situation. It says merely that, by virtue of an abnormal lie of the great vessels, blood passing through a "wrong" chamber is finally delivered into the "right" great vessel for survival. The term does not specify the anatomic abnormalities; and atrial inversion, ventricular inversion, or simply an especially large ventricular septal defect may be responsible for the "abnormal" flow that is "normalized" by one or another abnormal lie of the great vessels. Anatomic definition is lost in such a term and morphogenetic analysis is impossible.

Furthermore, the term "transposition" is already widely used for another altogether unrelated anomaly. This is so-called "complete transposition" (and "incomplete transposition," although I know of no quantitative evidence that such an anomaly exists; it has been shown quite conclusively that in so-called "dextroposition" and "over-riding" of the aorta in tetralogy of Fallot there is no abnormality in the lie of the great vessels). The anatomic difference between the two types of "transposition" is well known to radiologist and clinician. In corrected transposition the aorta and pulmonary artery are parallel with each other in the frontal plane, the aorta to the left of the pulmonary artery. In complete transposition, on the other hand, the aorta is anterior to the pulmonary artery and often slightly to its right. This has been confirmed by careful anatomic study: in complete trans-
position the aortic and pulmonic rings are rotated about 90 degrees from their normal lie with reference to the fibrous ventricular skeleton, while in corrected transposition the rotation is in the neighborhood of 180 degrees. That the anatomic difference is due to a morphogenetic difference is suggested by the fact that in most cases of complete transposition the membranous septum is abnormal in size and its translucency is partially or completely obliterated by ventricular musculature; there often are other abnormalities of the insertion of ventricular muscle on the ventricular fibrous skeleton. On the other hand, in three hearts with corrected transposition and intact ventricular septa that I have had the opportunity to study, the membranous septum transilluminated normally and no abnormalities of insertion of ventricular musculature were evident. It has been suggested from this and other evidence that the embryologic defect responsible for complete transposition may be related to a disturbance in the formation of the ventricular fibrous skeleton. This takes place long after the cardiac coil is formed, and there is no reason to consider complete transposition an abnormality of the coiling process.

There is another important difference between the two types of transposition from the clinical point of view: they each tend to be associated with quite different types of additional intracardiac anomalies. For example, complete transposition is in most instances associated with ventricular septal defects confined to the bulbar region of the septum, while in most cases of corrected transposition the bulbar septal musculature can be identified and is quite complete; when septal defects are present, they usually involve the inflow portion of the septal musculature. Similarly, complete transposition is frequently accompanied by various types of outflow tract atresias, stenoses, etc., while these are uncommon in corrected transposition, where anomalies of the A-V rings and inflow tracts predominate.

In short, the great vessel anomaly called corrected transposition is anatomically, embryologically, and clinically a different great vessel anomaly from complete transposition. If the term “transposition of the great vessels” is used for the 90-degree rotation, perhaps the term “inversion of the great vessels” would be appropriate for the 180-degree rotation abnormality. Such terminology would have the additional advantage of requiring accurate anatomic definition of the polarity disturbance of the ventricles or atria that the great vessel inversion is “correcting.”

Indirect evidence to support this theory of the morphogenesis of polarity disturbances is found on studying the pathologic details of hearts with these abnormalities. In general the evidence is of two types: (1) the presence of torsional abnormalities in the internal architecture of the ventricles, and (2) the presence of associated deformities of the chambers of the heart ascribable to the coiling stage of development.*

In the first place, in every heart with corrected transposition and ventricular inversion the internal architecture of the left ventricle was “rotated” to a different degree than in the normal left ventricle. For example, the two papillary muscles of the left ventricle were displaced with reference to the lie of the septum. Normally, one papillary muscle arises adjacent to the septum and the other from the free wall (hence their anatomic names, “septal” and “lateral” papillary muscles) and both about the same distance from the apex. In all cases of ventricular inversion studied, both papillary muscles arose from the free-wall portion of the left ventricle far removed from the septum, and the “lateral” papillary muscle much nearer the mitral ring than the

* I am greatly indebted to Professor Dankmeier and his staff in the Department of Embryology and Anatomy of the University of Leiden for permitting me to study the human pathologic material in his collection, among which are seven instances of what is called “corrected transposition,” three other types of polarity disturbances, and five dextroversions. It is neither my purpose nor my prerogative to describe the material in this superb collection in detail, for this is currently being done by Dr. Dekker and Dr. van Ingen. I wish particularly to thank Dr. van Ingen for her constant interest and invaluable help in studying the pathologic material.

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“septal.” In the second place, while the term “inversion” implies a 180-degree reversal of location of the ventricles with reference to the body axes, on careful study of these hearts (the diaphragm and the lungs were in most instances still attached to the specimen) the reversal varied markedly from 90 to 180 degrees with reference to body axes. In other words, while in the normal heart the inflow part of the ventricular septum is parallel with the frontal plane of the body, in hearts with ventricular inversion the septum varied between perpendicular to parallel with the frontal plane. Furthermore, while in the normal heart and in most instances of ventricular inversion the smooth internal wall of the left ventricle coincides with the septal wall of the left ventricle, there was one heart in the Leiden collection with ventricular inversion (no. 2918) in which the smooth wall was only partially the septal wall. Here, presumably, the overlapping of left ventricle by right ventricle during embryogenesis was misaligned by the torsional abnormality responsible for the ventricular inversion.

Finally, while in the normal heart the ventricular and atrial septa are parallel and topologically continuous with each other, this was often not the case in the hearts with ventricular inversion. In one heart (no. 535), the mitral orifice of the left atrium “overrode” the defect of the ventricular septum to such a degree that the chordae tendineae of the posterior mitral cusp inserted on the margin of the ventricular defect and both A-V orifices opened principally into the right ventricle.

While in ventricular inversion there is reasonably accurate mirror-imaging of internal structure of the right and left ventricles (the mirror held parallel with the frontal plane, i.e., reversal on the anterior-posterior axis alone), this did not in any case apply to the course of the external myocardial fibers of the heart. The external fibers followed the same clockwise course (as viewed from the apex) as seen in the normal heart, and this was also true of the hearts with meso- and dextroversion. That there is no “mirror-imaging” of the external fibers of the myocardium in spite of inversion of the chamber architecture is additional proof that the defect has to do with the torsional events in cardiac development and not with some disturbance in body laterality, a primordial inversion of the body’s sense of “right” versus “left,” or “anterior” versus “posterior.”

One would expect that if there were anomalies due to abnormalities in the coiling process, they would often be associated with abnormalities in the absolute lie of the coil in the thoracic cavity. This proved to be the case, and among hearts with essentially the same type of ventricular and great vessel inversion there was a continuum from the left-lying position through various degrees to meso-position, to a frankly right-lying heart. The latter were instances of what is called dextroversion. This continuum is illustrated in figure 8. Here, then, is additional evidence that dextroversion is a polarity disturbance due to abnormal coiling, and that it is embryogenetically different from situs inversus dextrocardia.

To understand how abnormalities in coiling might result in the special additional anomalies often found with ventricular inversion, one must remember that, while the left atrium and left ventricle are in direct communication from the earliest stages of heart tube development, the communication between the right atrium and right ventricle depends upon widening of the A-V canal portion of the heart tube after coiling is completed. It would then be expected that abnormalities in the coiling mechanism might often be accompanied by serious disturbances of the inflow region of the right ventricle. Several different manifestations of this were to be found in the Leiden collection and have also been reported by others: 2-4 (1) absence of an inflow portion of the right ventricle, with a small, rudimentary bulbar chamber communicating with the left ventricle through a septal defect; (2) both A-V orifices well-developed but both opening into the left ventricle; (3) single ventricle (that is, entire absence of inflow portion of the septum; in an admittedly limited experience, bulbar septal musculature can be identified in most cases of “single ventricle†).
In regard to the mechanism of these defects, it can be hazarded that, if the widening of the A-V region of the coil fails to take place, no inflow portion of the right ventricle can develop, and the result is the rudimentary bulbar outlet chamber, with or without double inlet left ventricle. On the other hand, if the widening of the A-V portion occurs, but the overlapping growth of right ventricle over the smooth-walled part of the left ventricle is impaired because of the torsional defect, the inflow portion of the ventricular septum will not develop, resulting in what is called "single ventricle."

While these defects can no doubt occur without evidence of polarity disturbance elsewhere in the heart, they are especially common in ventricular inversions, dextroversions, etc. Furthermore, they are all defects that depend upon abnormalities at the time of elaboration of the cardiac coil, unlike such anomalies as bulbar septal defect, complete transposition, tetralogy of Fallot, Eisenmenger, and double outlet right ventricle, all of which are due to later developmental defects.

But one must be exceedingly cautious in using pathologic material for the support of any theory of the morphogenesis of cardiac anomalies. Nearly all important congenital cardiac anomalies are acquired during the first month of fetal life. Only those in which the anomaly is structurally compatible with survival for the succeeding eight months of intra-uterine life come to the attention of the clinician or the pathologist.

Intra-uterine survival is therefore an ex-
ceedingly important "selecting" mechanism in pathologic material. For example, while in the present theory it is postulated that the great vessel inversion and the ventricular inversion of corrected transposition are both related to a single defect in heart coiling, one must not overlook the fact that most instances of ventricular inversion could not have survived the intra-uterine months unless there were some additional ameliorating defect such as a great vessel inversion or huge ventricular septal defect to "correct" the abnormal flow. In other words, the fact that a particular great vessel anomaly occurs in most cases of ventricular inversion cannot be considered in itself evidence that the two are morphogenetically related. This is true, of course, of many other "syndromes" among congenital heart disease. Until methods for the reliable experimental production of particular cardiac anomalies are developed, morphogenetic theories based upon human pathologic material must be considered only conjectures.

Summary and Conclusions

The coiling of the primary heart tube is one of the most critical events to occur during heart development. The mechanics of coiling are such that it must be the result of a helical or winding distribution of growth differential in the heart tube. The events during coiling of the heart tube are described in detail, from studies of the chick heart embryo. It is postulated that abnormalities in the timing or distribution of this growth differential could produce cardiac anomalies wherein the lie of the cardiac components is abnormal with reference to body axes, but the components themselves might be normally developed. They are therefore called "polarity disturbances" and include such syndromes as corrected transposition, ventricular inversion, dextroversion, and levoversion.

In the case of "corrected transposition" it is suggested that the torque of coiling is expressed in the ventricular region of the coil instead of in the truncal region. Indirect evidence to support this theory is presented, obtained from the study of human specimens in the collection of the University of Leiden. This evidence is of two types: (1) there is a high incidence of other torsional alterations of cardiac architecture in these hearts, and (2) the additional severe structural abnormalities often associated with polarity disturbances are those that would be produced at the time of coiling.

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