Heart anatomy and developmental biology

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Summary. The subject of heart development has attracted the interest of many embryologists over the last two centuries. As a result, the main morphologic features of the developmental anatomy of the heart are already well established. Although there are still some controversial points, and there is probably much descriptive work yet to be done, emphasis is currently being placed on developmental mechanisms rather than simply on descriptive facts. The availability of new techniques and the overall advances in biological research are placing heart embryology in a new perspective. Today, we do not simply ask whether one or another embryonic structure arises further right or further left; instead, we are studying how cells, tissues, and their microenvironment interrelate at the several levels of biological organization (from the gene upwards) so as to give rise to a mature organ with a distinct shape and well-established functions.

This paper attempts to review some of the basic aspects of the developmental anatomy of the heart. Descriptive embryology is used here as a tool. Emphasis is placed on developmental mechanisms, and on the present knowledge of how these mechanisms are related to the structural development of the heart.

Key words. Heart embryology; developmental biology; differentiation; morphogenesis; gene expression.

The developmental biology of the early heart

The heart of all vertebrates arises from a paired area of the lateral mesoderm called the cardiogenic plate. The first identifiable heart primordium appears at the stage of 3–4 somites as two crescents of cardiogenic material located on opposite sides of the embryonic midline. Each cardiogenic crescent is made up of mesodermal cells, preendocardial cells, and associated extracellular material. These crescents migrate toward the midline axis where they meet each other and fuse (fig. 1). Fusion of the bilateral primordium results in the formation of a single heart tube which is located at the embryonic midline.

The movements of the precardiac areas apparently are not produced solely by the morphogenetic movements which result in closure of the endoderm. The precardiac mesoderm forms a cohesive cell sheet, epithelial in nature[50], which appears to migrate actively over the subjacent endoderm[86]. It is still unclear whether the endoderm provides the precardiac areas with any directional information. In cultures, precardiac mesoderms migrate upon a number of epithelial cell sheets to form vesicular structures of beating cardiac tissue[45].

The primitive heart tube that has formed at the embryonic midline is relatively straight. Soon, this tubular heart bends and rotates toward the right side of the embryo, being shaped into a loop (fig. 2). Concomitantly with the formation of the heart tube and the initiation of looping the heart begins to beat and cardiac function is established. The beginning of heart function is related temporally to myocardial differentiation.

In order to differentiate, cells must synthesize specific gene products. In the heart, there are a number of structural muscle proteins which are expressed at the time of fusion of the paired primordia. For example, premyocardial cells undergo a sharp increase in the synthesis of α-actin at this time[98, 102]. Immunofluorescence studies with a polyclonal antimyosin antibody[16] demonstrated the presence of myosin in the cells of the precardiac mesoderm. However, recent studies using a more specific antibody[41] did not detect myosin until the time of fusion of the heart anlage. The same pattern of staining has been demonstrated for troponin[81], another myofibrillar protein. Also at this time, glycogen starts to accumulate[50] and the first transmembrane electrical potentials can be recorded[94]. The synthesis of several muscle proteins[48] correlates structurally with the first appearance of myofilaments and their assembly into discrete myofibrils. It should be emphasized that the structural changes cited above occur quite abruptly. While the cells of the precardiac mesoderm are organized as an epithelium and do not show any of the morphologic characteristics of striated muscle, myocardial cells in the tubular heart progressively show all the characteristics of the differentiated tissue[51].

The expression of overt heart differentiation does not necessarily coincide with actual gene activation. Cells with heart-forming capacity can be demonstrated through the blastula and gastrula stages by means of fate-mapping techniques[14]. This, and the failure of BrdU to block cardiac differentiation after stage 7 of development[7], suggests that the gene(s) responsible for cardiac differentiation are activated well before the fusion of the heart anlage.

A major synthesis of tissue-specific mRNAs takes place in embryos by the end of the blastula stage[13]. However, some of these mRNAs appear to be stored in untranslatable form until tissue differentiation is to occur. Alternatively, transcription may be repressed or maintained at very low levels, as appears to be the case for the α-isoform of (cardiac and skeletal) actin[28], and for the heavy chain of muscle myosin[64]. If these findings can be applied to

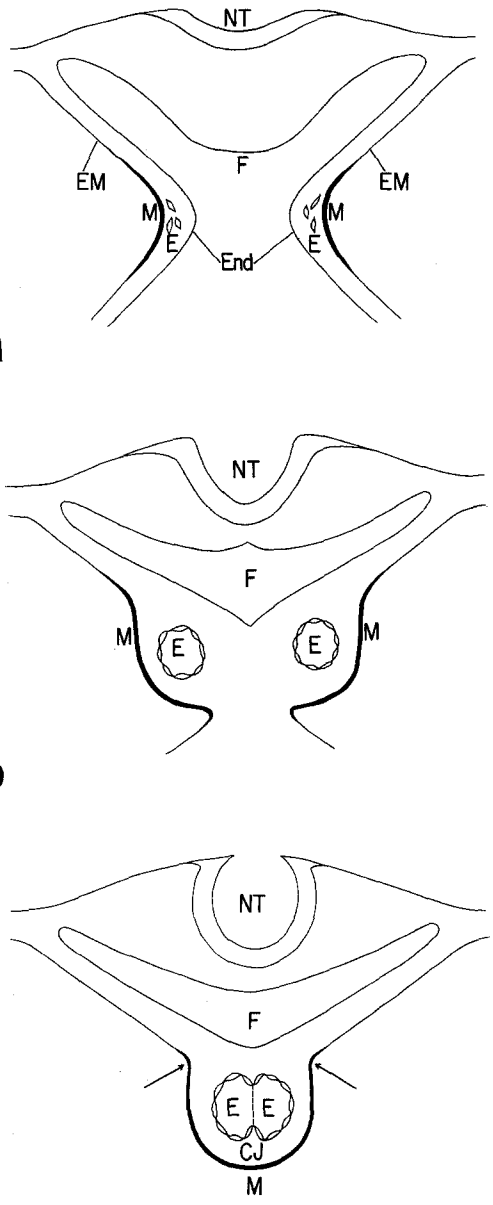

Figure 1. Diagram showing the mergence and fusion of the cardiac primordia. *a* The prospective myocardium (M) appears as a bilateral thickening of the splanchnic mesoderm (EM). The primitive endocardial cells (E) are first seen between the prospective myocardium and the endodermal (End) layer. *b* The paired heart anlage is moving toward the embryonic midline. The myocardium is enwrapping the primitive endocardial tubes (E). The endodermal foregut (F) is closed. *c* The paired heart anlage has fused below the developing foregut. The space between the developing endocardium and the myocardium is occupied by a layer of extracellular material named cardiac jelly (CJ). Dorsal to the developing endocardium the right and left mesodermal layers are still unfused; they form the dorsal mesocardium (arrows). (NT), neural tube. (From Icardo[31]).

the heart, then there could be a developmental point when transcription and/or translation of the mRNAs are activated, and meaningful synthesis of specific proteins occurs. This developmental stimulus does not correspond to fusion of the paired primordia. Unpaired fusion of the heart anlage[14,24] results in the formation of two independent hearts that are able to differentiate and beat. Furthermore, heart contractions start in higher vertebrates before the first fusion of the lateral primordia is completed[25]. What then causes overt heart cytodifferentiation?

It has been postulated that contact with the endoderm is necessary for the mesoderm to differentiate into cardiac tissue[3,73]. However, when mesoderm from heart-forming regions is cultured alone, some degree of self-differentiation occurs[11,45]. Thus, the evidence for endodermal induction still appears unsatisfactory.

It must be stressed that tissue competence is not equal to tissue fate. Even if the developmental competence of an embryonic tissue is high, it still may need some kind of stimulus to support the process of differentiation that is already underway[70]. Furthermore, this stimulus does not need to be very specific. It has recently been reported that when the precardiac mesoderm is cultured in the presence of inhibitors of collagen synthesis, it fails to differentiate into myocardial tissue[99]. This does not necessarily mean that collagen is directly responsible for the differentiative event. Rather, the presence of collagen may modify the physico-chemical characteristics of the extracellular matrix, providing the precardiac areas with the stimulus necessary to proceed along the path of differentiation.

The process of cardiac differentiation is not completed with the first appearance of myofibrils and the establishment of heart function. Muscle proteins exist in several molecular variants, generally called isozymes or isoforms. As for myosin, variations in isomyosin composition have been shown to occur between embryonic, neonatal, and adult hearts. Different isomyosins also occur in the atria, ventricles and conduction system; differences also occur between neighboring myocytes and in gradients across the heart wall[12,22,23,49,89,92,97]. The molecular characteristics of the variant forms of myosin confer cardiac cells with different contractile and electrophysiologic properties[79,80]. Although the full range of the myosins expressed during embryonic development is unknown as yet, the coordinated expression of the several isomyosins appears to be necessary for normal myocardial differentiation. The isoforms of actin, tropomyosin and troponin expressed in cardiac muscles are different from those expressed in skeletal muscles; however, no differences have been observed between the forms expressed in heart tissues[20,100]. The mechanisms which regulate the expression of the different molecular variants are also unknown. The study of these mechanisms during embryonic development is more complicated due to the possible regulating influence of humoral and functional factors. For example, changes in myosin expression can be induced experimentally by hormonal action and by changing the heart workload[8,63].

Differentiation and morphogenesis

The acquisition of differentiated properties occurs concomitantly with the development of organ shape. How-

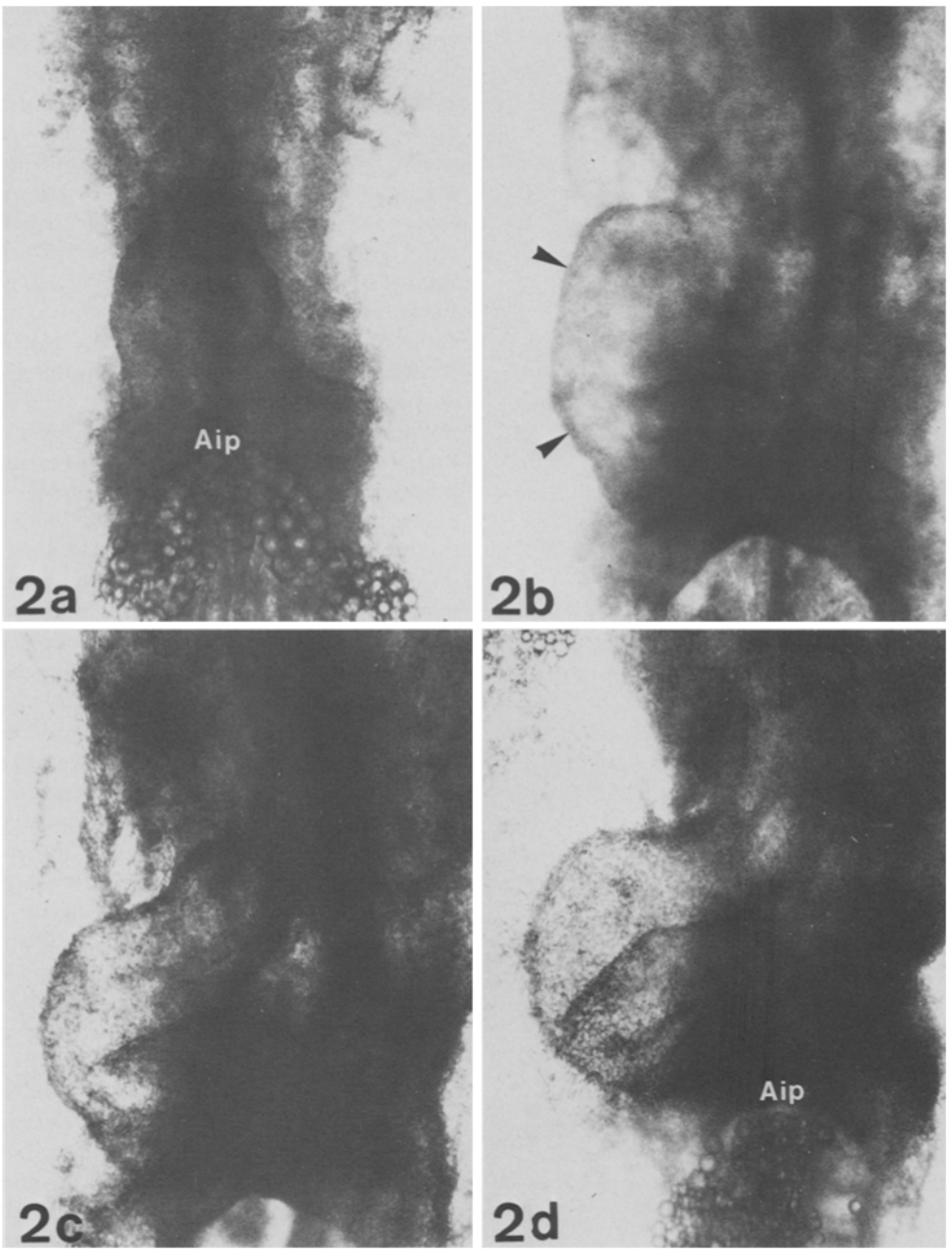

Figure 2. Light micrographs depicting a sequential study of the formation of the cardiac loop in the chick. *a* The straight heart tube formed after fusion of the paired primordia begins to bulge outwards. *b* The heart tube rotates toward the right side of the embryo, acquiring the shape of a 'C'. Arrowheads mark the convex right side of the loop. *c* The bending of the heart tube continues. At this time, the rupture of the dorsal mesocardium leaves the heart tube attached to the embryonic trunk only by its two ends. *d* After rupture of the dorsal mesocardium the heart twists upon itself and acquires a sigmoid form. (From Icardo et al.[34]).

ever, it is the adequate temporal and spatial integration of the different components of the developing organ that ultimately results in shape. For example, if isolated precardiac mesoderm is cultured, only simple masses of beating tissue can be obtained; however, if neighboring tissues are also included in the explant, tissue vesicles displaying a heart-like organization are obtained[11,45]. Thus, the changes in shape that the heart tube undergoes during looping may not result directly from the acquisition of the differentiated state (including biochemical and electrical maturation).

Throughout loop formation (fig. 2) the heart is a 'tube within a tube' structure, which is organized into layers. There is an outer layer or myocardium and an inner layer or endocardium. The cardiac jelly, the extracellular matrix of the developing heart, occupies a middle position

between the two tissue layers. If looping results from the coordinated integration of the different components of the heart tube, then, one, two, or all three heart layers should be the driving force responsible for looping. The endocardium does not appear to have the structural entity required to support looping. The myocardium could be well suited for this role; however, none of the myocardial cellular activities (including those of the prospective myocardium) which have been explored, appears to provide an explanation for heart deformation. Thus, asymmetric contribution from the right and left cardiac areas[86], asymmetries in the process of differentiation[41], differential mitotic rates[82,87], DNA synthesis[41], cytokinesis[33], and the molding effects of blood flow[54], have been considered as non-substantial to loop formation.

The cardiac jelly is a wide band of extracellular material, heterogeneous in composition and structure, which presents a number of important biochemical and physiological properties[30,52,55,56,60]. The cardiac jelly also has well-defined physical characteristics; it is able to maintain its shape in the absence of myocardium, and to swell and shrink in response to osmotic changes in the surrounding medium[65]. These physical properties of the cardiac jelly appear to depend upon its glycosaminoglycan (GAG) composition[66]. Extracellular matrices enriched in GAGs produce a hydrostatic pressure that is able to induce deformation in the surrounding epithelia. However, the internal tissue pressure [amounting to about 0.5 mm H_2O in the cardiac jelly[55]] is not sufficient to produce the complex deformation that results in looping. In the first place, the epithelium has to be deformable. A uniform tissue pressure could only deform the epithelium that surrounds it asymmetrically if the epithelium presents regional differences in compliance. It is intuitively obvious that in the absence of regional differences in compliance the epithelium will only expand (inflate) and, if the pressure exceeds the resistance of the epithelium, it will burst. If we admit that the myocardium presents regions of different compliance[58], i.e., the capability to be differentially deformed, then there must be an additional factor to control the quality and the extent of the deformation.

Control of bending in hydrostatically-supported organisms is effected by extracellular systems of fibers which adopt helical winding patterns[96]. In the heart, such a system cannot be found in the extracellular milieu; however, it could reside in the myocardium. Earlier experimental evidence suggested that assembly of muscle proteins into myofibrils is required for the heart to undergo looping[53]. Examination of the whole early heart under the polarizing microscope shows that myofibrils arrange in a predominantly circumferential fashion[67]. In situ observation of the myofibrils with the scanning electron microscope[57] revealed a greater complexity of the myofibrillar system, as well as regional and age changes in the density and disposition of the myofibrils. It was suggested that such a structural disposition could be consistent with a helical pattern and, therefore, the myocardium could regulate the deforming pressure exerted by the cardiac jelly[55,56,58].

The above model of looping relates cytodifferentiation, phenotypic expression, biochemical, and subcellular and cellular events to heart shape and heart shape changes. Some of the proposals of this model have not been demonstrated unequivocally. The model does not take into account the possible participation of extracardiac factors in looping, nor does it explain why the heart always loops to the right. However, it is a testable hypothesis where some of the parameters are falsifiable and can be studied experientally. The existence of a strain of mice (iv/iv) where the heart of half of the specimens loops to the left[44] and develops diverse types of situs[43], provides us with an animal model to test some of the intra- and extracellular factors involved in the regulation of looping.

Heart septation and developmental maturation

Whereas looping appears to be mostly related to deformation of epithelial sheets, heart morphogenesis after looping is dominated by processes of differential tissue growth and tissue remodeling. During this period the heart increases several times in size and mass, develops a system of septa and a valve apparatus, and progressively acquires the adult configuration (fig. 3).

Septation of the heart takes place by formation of several independent septa that become united later to transform the tubular heart into a four-chambered organ. The septation of the atrium is carried out by the formation of a double septum that ensures communication between the two atria until the establishment of pulmonary circulation. The development of the interventricular septum appears to be related to the process of ventricular trabeculation; coalescence of the primitive trabeculae near the apex of the primitive ventricle appears to be the origin of the muscular part of the interventricular septum. The division of the atrioventricular canal and that of the bulbus cordis takes place by formation of opposite masses of tissue, the endocardial cushions, that grow toward each other and fuse. The endocardial cushions are masses of acellular cardiac jelly that soon become invaded by cells of endocardial origin and are progressively transformed into mesenchymatous structures. The contribution of neural crest cells to the truncal cushion tissue has also been described[37]. Fusion of opposite cushions divides the single lumen into separate communications. All of these septa meet on top of the interventricular septum in such a way that the ventricles attain independent circulatory connections[31,56,74,88,95]. The septation of the most distal part of the heart and its transformation into the proximal part of the aorta and the pulmonary artery is still the subject of some controversy[32,40,91].

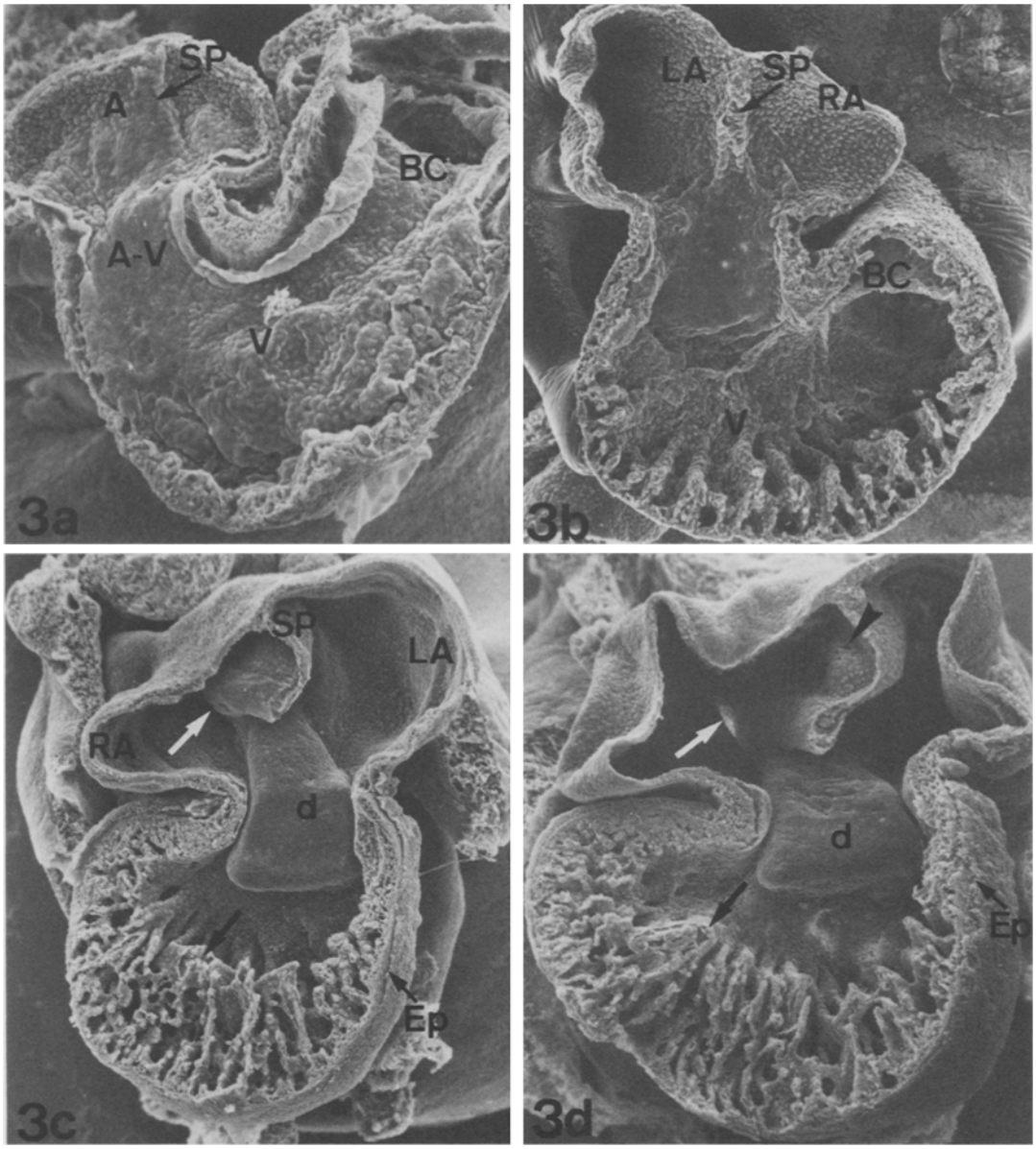

Figure 3. Scanning electron micrographs of chick embryo hearts depicting some of the progressive changes that take place in the inner surface of the heart. The hearts have been dissected frontally. *a* Third day of incubation; ventral half of the specimen. *b* End of the third day of incubation; ventral half of the specimen. *c* Four and a half days of incubation; dorsal half of the specimen. *d* Fifth day of incubation; dorsal half of the specimen.
The primitve atrium (A) appears, separated from the ventricle (V) by the atrioventricular canal (A–V). The development of the septum primum (SP) divides the primitive atrium into right (RA) and left (LA) atrial chambers. The septum primum grows caudally towards the cushions of the atrioventricular canal. The foraminae that open in the septum primum are indicated by the arrowhead in *d*. The lumen of the atrioventricular canal is progressively occupied by the growing dorsal (d) and ventral (v) endocardial cushions. The bulbus cordis (BC) constitutes the prospective outflow tract region of the heart. The inner surface of the primitive ventricle (V) is modified by the development of the trabeculae. The single ventricle is divided into two chambers by the interventricular septum (large black arrow in *c* and *d*). The interventricular septum appears to develop by coalescence of the primitive trabeculae near the ventricular apex. The sinus venosus (the prospective coronary sinus) opens (white arrow, *c* and *d*) into the dorsal wall of the right atrium. The epicardium (the prospective visceral pericardium) (EP) appears in *c* and *d*. (From Manasek[56] et al.).

The emphasis classically placed on gross morphologic changes has obscured the fact that, at the cellular and subcellular levels, differentiation has not been completed and that, in many respects, the heart is still an immature organ. Thus, there are a number of histological, physiological and biochemical events that are still well underway. For example, the developing myocytes continue to accumulate myofibrils which progressively appear orientated along the longitudinal cell axis. Furthermore, myofibrillogenesis continues through the early postnatal period[47]. Concomitant with the progressive accumulation of myofibrils, biosynthetic changes in the expression of isomyosins occur (see above). Early myocardial cells are joined by apical junction complexes[51]. These primitive

junctions soon give rise to intercalated discs. The intercalated discs are complex regions of the cell membrane that participate in the structural and electrical connection between the cardiomyocytes, and to which several cytoplasmic components, such as myofibrils and intermediate filaments, become attached in the course of development[18]. The extracellular matrix also undergoes a process of maturation which is basically characterized by an increase in the amount of highly-sulfated glycosaminoglycans, the formation of proteoglycan complexes, the appearance of several types of collagen (other than type I), and the perinatal development of a complex network of matrical fibers (see above for references).

Developmental changes also occur in the electrical properties of the myocyte membranes. Synchronized heart beating starts very early in development, when a specialized conduction system is yet to be developed. Myocardial cells are electrically coupled by low-resistance pathways that appear to be located at the level of the gap junctions. Gap junctions permit action potentials to be conducted along coupled cells, also providing for metabolic coupling[6, 21, 83]. During looping, a decrease in electrical resistance occurs concomitantly with a sharp increase in gap junctional area[26]. At this time, the electrical potentials of the membrane are low and rise slowly. These action potentials are generated by the presence of slow-Na^+ channels which are insensitive to tetrodotoxine but are blocked by verapamil. At later stages, however, the action potentials are higher and show a fast-rising peak and a plateau. The potentials are due to the appearance of fast-Na^+, and slow-Na^+ and Ca^{2+}-Na^+ channels which are insensitive to verapamil but are blocked by tetrodotoxine[15, 38, 46]. Also, a positive response to catecholamines develops at this time[84]. These changes in action potentials are accompanied by a decrease in cell automaticity, and appear to result from a process of maturation at the level of the cell membrane. It has been suggested that the number of the sialic acid residues at the cell periphery increases with age, playing an important role in the regulation of the flux of ions through the cell membranes[69].

The cardiac sarcolemma is also involved in the generation of the transverse tubule system. The T system appears to ensure the synchronous contraction of all the myofibrils within a cell, avoiding possible delays between excitation and contraction[19, 68]. However, despite its physiologic importance, the T system does not develop until after birth, and it apparently occurs only in mammals.

Most of the developmental changes cited above appear to be genetically programmed. However, each separate morphogenetic event probably depends upon independent, although interacting, morphogenetic mechanisms. The sequential appearance of non-muscle cells in the myocardium complicates the developmental picture even more. The complexity of the system has impeded the elaboration of comprehensive models accounting for late heart development. Thus, the relationship between the expression of the genetic information and the acquisition of heart shape still remains elusive.

Growth and growth control

Organ morphogenesis is regulated by both intrinsic and extrinsic (epigenetic) factors[105]. While early heart development appears to be regulated basically by intrinsic factors, late heart development seems to be highly influenced by several epigenetic factors. Epigenetic factors act as modifiers of the intrinsic developmental programs, modulating the expression of the genetic information; in turn, they are influenced by the gene activity. For example, the effects of several hormones, such as thyroxine, growth hormone, and adrenalcorticoids, on heart growth is well documented[105]. However, what has attracted the greatest interest is the relationship between heart function and growth.

The heart grows in response to increasing circulatory demands by adjusting its mass to the hemodynamic load. This is clearly shown by the rapid enlargement of the left ventricle which takes place postnatally after closure of the foramen ovale. An increase in load, whether it is due to physiological activity or to pathologic states, results in heart growth[1, 90, 104]. The heart stops growing when the enlargement matches the load increase. Furthermore, reduction of load results in atrophy (or regression of hypertrophy)[85, 93]. An increase in growth involves an increase in both cell size and the rate of division, and affects both muscle cells and non-muscle cells[17].

Most of these studies have been carried out in the postnatal or mature heart, and many of them relate to hypertrophic rather than to physiologic growth. It is true that there are some differences, especially at the cell and tissue level, between growth under normal and abnormal hemodynamic conditions[2, 59]. However, there is experimental evidence suggesting that the growth of the heart during the embryonic period is also influenced by the increase in circulatory demands; if the heart workload is increased, the growth of the embryonic ventricles is accelerated[9].

Up to here, the effects of the hemodynamic load upon heart growth have been considered taking growth as the sum of hypertrophy and hyperplasia. A different but related question is whether hemodynamic forces modulate heart shape changes. Although the answer to this question is most probably affirmative, there are some considerations to be made.

The development of heart malformations after diverse manipulations assumed to alter blood flow appears to suggest an important role of hemodynamics in heart shaping and development. However, from a biological viewpoint, the classic concept of flow molding is outmoded since it proposes neither a real explanation nor mechanisms for the molding. Mechanical and pharmacological agents may affect other factors in addition to blood

flow. For example, the migration into the heart of cells derived from the neural crest[37] may be stopped after ligation of the truncus; this maneuver in itself may produce heart malformations. The induction of heart malformations by the administration of a number of drugs, such as isoproterenol[10] and epinephrine[77], appears to be secondary to modifications of the hemodynamic load. Interestingly enough, a number of events classically attributed to the molding effects of the blood flow, such as looping, trabeculation, and the opening of the foramen secundum, appear to be unrelated to flow. On the other hand, heart shape and function develop simultaneously, and it is very difficult to separate the effects of turbulent flow from those derived from the altered hemodynamic load.

More interesting is the question of how heart tissues respond to modifications of hemodynamic forces. For example, the response of cardiac myocytes to modifications in the workload is not restricted to changes in cell size and number. The electrical properties of the sarcolemma, the expression of contractile proteins, the muscle efficiency and the speed of contraction also undergo changes[36]. The endocardium, located at the interface between the blood and the rest of the heart wall, is also influenced by hemodynamics; the orientation of endocardial cells can be modified by changing the normal pattern of flow[56]. Clipping of the aortic arches results in changes in the intensity and location of the areas of cell death in the heart mesenchyme[75]. On the other hand, it is not wildly speculative to suggest that the synthesis and deposition of the extracellular materials may also be modified. For example, the space occupied by extracellular material increases in hearts subjected to hemodynamic overload[59].

The simple force of contraction appears to be a direct stimulus for myosin synthesis in both skeletal[101] and cardiac[62] muscles. Synthesis of new proteins can be elicited in the hearts of rats exposed to diverse forms of stress, such as hyperthermia and banding of the ascending aorta[29,42]. These biosynthetic changes appear to be controlled at the transcriptional level. Although some other examples of epigenetically controlled gene expression could be cited, the regulatory mechanisms which translate the physical stimuli into modifications of the biosynthetic pattern remain unidentified as yet. There is some evidence, however, suggesting that the cell membrane and its associated cytoskeleton may act as transducers of external signals[35], and that changes in the cell cytoplasm may readily influence the kind of genes expressed by the cell nucleus[27]. The analysis of organ development at the genetic level is just beginning. The development of specific probes for the genes and their products, and the analysis of the levels at which gene expression is regulated, appear to be basic prerequisites for understanding how cells differentiate and how the organs acquire and maintain their distinct morphological and physiological characteristics.

Morphogenesis and teratogenesis

To explain the development of congenital heart disease (CHD) researchers have usually referred to descriptive embryology, looking for similarities between embryonic and adult structures. However, it is now clear that embryonic hearts are not small adult hearts. In the same way, there is not a linear relationship between the existence of a developmental defect and the production of the CHD[4]. Cardiac structures are continuously being reshaped, and a defect in the developmental chain may be self-corrected; it may be of no importance to the life of the individual; or, it may result in a gross malformation. A number of possible developmental mechanisms have been reviewed in this paper, and the same factors operate whether development is defective or not. So, what is the difference between normal and abnormal development? From a mechanistic point of view, the difference may be minimal; it is the end result that may be grossly different. The form and function of organs emerge as a result of the behavior of cells. That is, provided that adequate developmental competence is acquired, and that the specific developmental programs are switched on. Cells, either singly or as groups, present only a limited repertoire of behavior; they divide, secrete extracellular materials, interact with other cells and with the environment, and die. Qualitative and quantitative differences in the coordinated expression of this repertoire make each organ unique[5]. Deviations from the normal patterns of cellular activity during the organ's ontogeny may result in congenital disease. These deviations may be due to intrinsic defects or to the action of teratogens.

Differential mitotic rates originate morphologic changes, and abnormal patterns of cell proliferation may be at the origin of heart anomalies. Both the increase[76] and the decrease[72] in the intensity of cell death have been related to the production of cardiac malformations. Metabolic alterations appear to be the cause of the teratogenic effects of several chemicals[61,78]. Defects in the capability of cells to interact with their environment may also produce heart malformations. For example, heart fibroblasts in infants with Down's syndrome present increased adhesiveness when compared to controls[103]. If the endocardial cushions are populated by a small number of mesenchymal cells, cushions may be hypoplasic[39]. Hypoplasia of the cushions leads to a wide spectrum of cardiac anomalies.

The concept that heart malformations are the result of defective cell behavior is an appealing one. It must be stressed, however, that the production of CHD is inherited multifactorially[71]. Cellular behavior depends upon both the expression of specific genes and the influence of the environment. Even in those cases where developmental anomalies can be attributed to a definite cause, such as a chromosomal defect or a teratogenic agent, heart malformations do not develop in every case. If searching for the mechanisms which regulate single gene

expression is not an easy task, the understanding of the influence of the expression of polygenic traits on heart shape is even more difficult. It is hoped that the study of mutant animal strains will yield clues which allow us to advance towards an understanding of the developmental mechanisms which regulate heart shape and function.

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Cardiac design in lower vertebrates: what can phylogeny reveal about ontogeny?

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Summary. In very few instances can the cardiovascular systems of adult 'lower' vertebrates serve as *direct* models for development in 'higher' vertebrates, primarily because numerous evolutionary specializations for preferential distribution of cardiac output between systemic tissues and gas exchange organs occur in the highly derived circulation of most extant lower vertebrates. Yet, the extensive literature on the cardiovascular anatomy and physiology of aquatic and air breathing fishes, amphibians and reptiles offers important conceptual insights into both patterns and mechanisms of development in birds and mammals. The primary contribution of such studies to the student of developing bird and mammal circulations is the clear demonstration that surprisingly complex hemodynamic function can develop from supposedly 'simple' cardiovascular systems typified by incompletely divided heart chambers. Thus, the hemodynamics of embryonic bird and mammal circulations should be determined by measurement, rather than inferred from structure.
Key words. Heart; circulation; blood; lower vertebrate; embryology; evolution.

What can developmental biologists gain from studying lower vertebrates?

During the course of development, the heart of embryonic birds and mammals progresses through a series of complex and critical stages involving both morphological and physiological changes. While some of these developmental stages clearly resemble the cardiovascular systems of adults of various lower vertebrates, the classic notion of 'ontogeny recapitulates phylogeny' long ago fell out of favor due to excessively literal interpretations. It is certainly not the intent of this article to attempt to revive it on even a limited basis, nor to suggest as a corollary that phylogeny recapitulates ontogeny! Rather, it is important to emphasize that understanding cardiovascular form and function in lower vertebrates – and in particular recognizing how surprisingly complex hemodynamics can arise from anatomically undivided hearts – can facilitate our understanding of developing hearts in embryonic birds and mammals. This facilitation can occur on two levels.