In this series of lectures I artificially made a division into topics, whereas in reality many processes occur at the same time and are intimately associated to one another. Lectures will be highly interactive. Consequently the program may change during the course.

1. **Early embryonic development**  
   Depending of the background of the students the subject of this lecture will be early embryonic development, formation of the germ layers and the embryonic axes. Then the folding of the embryo, when concomitantly the heart forms. In particular determination of the left-right axis is important with respect to the formation of the correct connections within the heart.  
   **Clinical significance:** understanding the etiology of isomeric and discordant hearts.

2. **The organization of cardiac growth**  
   How does the heart tube forms from a flat embryonic disc? How does it grow, without cell division and without hypertrophy? This is the subject of this lecture.  
   **Clinical significance:** understanding the etiology of left and right ventricular hypoplasias.

3. **Cardiac chamber formation and the development of a coordinated activation pattern (ECG)**  
   Cardiac myocytes share a number of characteristic features that distinguish them from other cells. All cardiac myocytes have sarcomeres and a sarcoplasmic reticulum and, in principle, share the capacity of producing an intrinsic cycle of electrical activity resulting in contraction. This phenomenon is called automaticity, or pacemaker activity. Varying degrees of differentiation are seen in early populations of cardiac myocytes, which can be categorized as forming working, nodal, conducting and primary myocardium. Cells of the atrial and ventricular working myocardium display virtually no automaticity, but are well coupled and have well developed sarcomeres and sarcoplasmic reticular structures. The development of the synchronously (fast) contracting working myocardium requires fast conduction of the depolarizing impulse, and so the cells possess well-developed gap junctions. In marked contrast, the cells forming the nodes of the cardiac conduction system have the opposite phenotype, and resemble the myocytes which are found initially in the primary heart tube. The cells of the putative atrioventricular and peripheral ventricular conduction system have an ambiguous phenotype: the cells are well-coupled, thus allowing fast conduction of the depolarizing impulse, but otherwise retain an embryonic phenotype. The division does not imply that the cells belonging to one group are identical, but rather that they share distinguishing features developed to variable degrees.  
   **Lecture topics:** Chamber myocardium develops regionally and remains flanked by primary myocardium. This design explains how the embryonic heart can function without valves and a distinct conduction system. In later stages this myocardium develops into the different components of the conduction system.
4. Development of the sinus node

During development dominant pacemaker activity always is at the intake of the heart, whereas the heart grows by addition of cells from the dorsal pericardial wall, or second heart field. How is this being achieved? And why is the sinus node at the right side?

Clinical significance: remnants of sinus myocardium may underlie the development of tachycardia's originating in the right atrium around the venous orifices. Mutations in the left/right pathway may cause underdevelopment of the sinus node, or bilateral development of the sinus node.

5. Development of the atrioventricular conduction axis

Without fibrous insulation and without an atrioventricular node mammalian embryos and adult lower vertebrates have a proper AV delay, owing to the slow-conducting properties of the atrioventricular myocardium. Only in mammals, including man, a distinct AV node develops along with a fibrous insulating layer in between the atria and ventricles, albeit the lower rim of the atria still has slow-conducting properties.

Clinical significance: Failure of proper development of the fibrous insulation may cause pre-excitation of the ventricles, provided the original AV myocardium, or in the adult the lower atrial rim, no-longer has maintained its slow-conducting properties, which guarantees in lower vertebrates and mammalian embryos a proper AV delay.

6. Cardiac septation and development of the valves

The process of septation can be divided into septation of the ventricle by formation of the muscular ventricular septum, septation of the atria by formation of the primary and secondary septum and septation of the primary heart tube by the cardiac cushions and alignment with atrial and ventricular septa. Also the valves develop from the cardiac cushions. Lineage studies have shown that most of the cushion mesenchyme forming the valves is derived from the endocardium, albeit epicardium-derived mesenchyme populating the lateral cushions also contributes. Neural crest-derived mesenchyme plays a crucial regulatory role in the formation of the arterial valves.

Clinical significance: Septal defects and valve malformations are among the most frequent cardiac congenital malformations. Insight into the development of these structures is crucial for the understanding of their origin.

7. Development of the atria, the venous pole and venous system

The development of the atria betrays its complex evolutionary history. The atrial chambers start to form at the dorsal and caudal part of the heart tube and will eventually develop into the atrial appendages. The lower rim of the atria is derived from atrioventricular canal myocardium, whereas the smooth-walled right atrial wall originates from the sinus venosus and the smooth-walled left atrial wall takes origin from the mediastinal, or pulmonary myocardium. All these different components have a distinct molecular signature.

Clinical significance: Biopsies of atrial tissue generally are taken from the appendages, which have a significantly different molecular composition than the other atrial components. The origin of the pulmonary myocardium is fundamentally different from that of the sinus node. Therefore, tachycardia's originating from the pulmonary myocardium cannot simply be explained by the erroneous assumption that it is all sinus muscle.
8. Development of the outflow tract and great arteries
The development of the outflow tract is intimately associated with the development of the pharyngeal region, witness many shared congenital syndromes, such as diGeorge. The aortic and pulmonary channels are separated by fusion of the outflow tract cushions with one another and with a protrusion of neural crest derived mesenchyme at the distal outflow tract. This process is preceded by extensive remodeling of the aortic sac and pharyngeal arch arteries forming the arterial pole. A number of malformations will be discussed.

Clinical significance: The cardiac outflow tract is highly prone to malformations. Understanding its development is crucial to get a grasp of the ontogenesis of these congenital malformations.

9. Cardiac evolution
During evolution the serial heart as seen in fishes developed into a parallel heart providing the pulmonary and systemic circulation. Whereas the reptilian heart, having a single ventricle only, can regulate blood flow in both circulations independently, the mammalian heart can't change volumes, but can maintain distinct blood pressures in both circulations. Despite huge differences, a remarkable similar ECG can be derived from all vertebrate hearts, indicating a similar building plan. In contrast to the low-pressure hearts of the cold-blooded vertebrates, birds and mammals have developed a high pressure heart. The spongy trabeculated ventricle of the lower vertebrate heart has evolved into ventricles with a compact wall and a ventricular conduction system, permitting high heart rates and high blood pressures to meet the high metabolic demands of the warm-blooded birds and mammals.

Clinical significance: Knowing the differences and similarities of the hearts of different widely used experimental animals, like zebrafish, Xenopus and mouse, is essential for the proper interpretation of experiments. Septal defects and cardiac non-compaction are among the most frequent cardiac congenital malformations, but their origin is still poorly understood. Comparison of the regulation of the development of these structures in the different vertebrate classes will shed light into the underlying processes. Recent findings will be presented that have demonstrated the molecular difference between the trabeculated myocardium of lower vertebrates and the compact myocardium of mammals on the one hand, and the similarities between the trabeculated myocardium of lower vertebrates and the trabeculated myocardium of the embryos of birds and mammals on the other hand. Most importantly the similarities of the trabeculated myocardium of lower vertebrates and the conduction system in mammals is striking and will be discussed in detail.

10. Cardiac sequential segmental analysis
Prior to the Anderson-Becker era, controversies were raging in the field regarding the description of cardiac malformed hearts. Since then a system has been introduced seemingly unbiased by ideas about the development of the heart. Albeit weaknesses of their approach can be put forward, the great strength was their sincere attempt to describe malformed hearts solely based on their anatomy, rather than on preconceived ideas on how cardiac malformations could have been arisen. Albeit their system has simplified the field, it has enormously helped the field of cardiac embryology, because the system structured cardiac anomalies, for which the field has to find explanations, which is the clinical significance.