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The Periods of Determination of Cardiac Malformations

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Summary. The timing and sequence of the critical events in cardiogenesis are presented in tabular form according to Streeter's horizons, C. R.-Length, somites number and ovulation age. The results are based on previous reports and personal series of seven human embryos [XV; XVIII; XIX; XX(2); XXII, and XXIII horizon according to Streeter].

The principal events of cardiogenesis are discussed succinctly in a general part.

The periods of determination for the different malformations are analysed in a special part.

Zusammenfassung. Die kritischen Entwicklungsphasen der Cardiogenese werden zeitlich geordnet und unter Berücksichtigung der Alterseinteilung (Horizons) nach Streeter, der S.S.-Länge, der Ursegmentanzahl und des Ovulationsalters tabellarisch dargestellt. Die Untersuchung erfolgte anhand der einschlägigen Literatur und eigener Schnittserien menschlicher Embryonen [XV; XVIII; XIX; XX (2); XXII und XXIII Stadium nach Streeter]. Die wichtigsten Vorgänge der Herzentwicklung werden in einem allgemeinen Teil zusammenfassend erörtert.

In einem speziellen Teil wird auf die Determinationsperioden der einzelnen Herzmißbildungen eingegangen.

The possibility of defining those time periods during which cardiac malformations arise rests essentially upon an exact knowledge of cardiogenesis. Those periods, in which the individual developmental events occur, have proven to be the critical developmental phases in this regard. Sissman (1971) and shortly thereafter O'Rahilly (1971) have compiled the most important data about normal cardiac development from the Anglo-American literature. Dankmeijer (1957, 1964), Los (1968), Goerttler (1958, 1963b, 1968a, b, 1971) and Doerr (1970) have presented the critical periods for determination of the most important cardiac malformations. Since the previous work in this field consists chiefly of single reports, we would like to present a comprehensive survey according to Streeter's age divisions (1942, 1945, 1948, 1951).

Materials and Methods

The present investigation is based upon the work of de Vries and Saunders (1962, IX. through XV. horizons) and Asami (1969, 1972, XV. through XX horizons), as well as original material comprising 7 human embryos:

1 embryo from the XV. horizon (8 mm C.R. length);
1 embryo from the XVIII. horizon (15 mm C.R. length);
1 embryo from the XIX. horizon (18 mm C.R. length);
2 embryos from the XX. horizon (19 mm and 19.5 mm C.R. length);
1 embryo from the XXII. horizon (25 mm C.R. length);
1 embryo from the XXIII. horizon (28 mm C.R. length).

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Table 1. Critical periods of human cardiogenesis

Horizon	IX	X	XI	XII	XIII	XIV	XV	XVI	XVII	XVIII	XIX	XX	XXI	XXII	XXIII
somite number	1–3	4–12	13–20	21–29	30–38										
Cardiogenic plate	*														
Ct fusion		*													
Heart loop		—	—												
AC migration			—	—	—	—	—	—							
AC-MA alignment								*							
MA expansion					—	—	—	—	—						
Sinoatrial orifice			—	—	—										
E. cushions					—	—	—	—	—						
S. primum					—	—	—	—	—						
O. secundum							*								
S. secundum									—	—	—	—	—	—	—
Ventricular septum						—	—	—	—						
B. displacement					—	—	—	—	—	—	—				
B. backtorsion							—	—							
Truncus torsion							—	—	—	—	—	—			
Truncus septum							—	—	—						
Bulbus septum									—	—	—				
IVF closure										—	—	—			
AVO expansion								—	—	—	—	—			
Coronary arteries									*						
Pulmonary veins					—	—	—								
Aortic system															
I. Stage		—	—	—	—	—	—	—	—						
II. Stage									—	—	—	—			
Venous system															
I. Stage					—	—	—	—	—						
Transitional stage									—	—					
II. Stage										—	—				
Definitive stage											—	—	—	—	—
C–R length (mm)	1,5	2	2–3	3,5	4–5	6–7	7–8	9–10	11–14	14–16	17–20	21–23	22–24	25–27	28–30
Ovulation age	18	22	24	26	28	29	31	33	35	37	39	41	43	45	47

Abbreviations. Ct = Cardiac tubes, AC = Auricular canal, MA = Metampulla, E = dorsal and ventral endocardial, S = Septum, O = Ostium, B = Bulbus, IVF = Interventricular foramen, AVO = atrioventricular orifices. The ovulation age is given in days ($\pm$ 1).

Serial sections (6 μ thickness, hematoxylin and eosin stain) were prepared from the embryos. This proved to be important control material since just in this second half of cardiogenesis, which Asami only investigated stereomicroscopically, exact accounts according to Streeter's horizons are widely lacking in the literature. Earlier work (Auer, 1948; Barry, 1951; Congdon, 1922; Goerttler, 1963a, b; Grünwald, 1938; Hackensellner, 1955; 1956; McClure and Buttler, 1925; Odgers, 1934/35, 1937/38, 1938/39; Tandler, 1913), done only with reference to the length of the embryos, can only be approximately co-ordinated with a definite horizon. A deviation of ±1 horizon, apart from individual variations, is to be expected.

The results are presented in tabular form (Table 1). The horizon in question is associated with the age of ovulation in days and the average length in mm.

The ensuing discussion of the findings is divided into general and special parts. The special part contains the analysis of the malformations which come into consideration during the critical phases. The formal genesis of cardiac malformations will be gone into only when absolutely necessary; whereas the causal genesis is not considered. The supposed periods of determination do not refer to the moment when a teratogenic peristatic or genetic factor must act in order to eventually cause a malformation.

Discussion

I. General Part

The three principle cardiac developmental phases recognizable from the summary table are designated *early phase*, *critical phase*, and *late phase*.

1. The *early phase* extends from the IX. through the XIII. horizons. It begins with the appearance of the cardiogenic plate. Shortly thereafter the cardiac tubes fuse with one another, the cardiac segments differentiate — X. horizon (Davis, 1927; Heuser and Corner, 1957) — and the cardiac loop forms (see also Tandler, 1913). The 180 degree tilting of the auricular canal about a frontal axis also takes place in this phase (XI. horizon, Doerr, 1955a; Streeter, 1942) (Fig. 1). The tilted auricular canal lies to the left in the cardiac loop during the XII. horizon (Streeter, 1942, 1945). From this position the auricular canal begins to migrate medially and dorsally and rotate clockwise (with regard to the direction of flow) about its own vertical axis (vectorial rotation of the auricular canal, Goerttler, 1958, 1963a). Meanwhile the sinoatrial orifice has formed (XII. horizon, Streeter, 1942, 1945) which reaches its final position in the XIII. horizon (Los, 1960, 1968). By this means the left sinoatrial fold develops, with which later the Septum primum connects.

2. The *critical phase* of cardiac development extends from the XIII. through the XX. horizons. In this phase three essential processes take place: connection of the auricular canal to the metampulla, vectorial rotation of the bulbus, and cardiac septation.

a) Connection of the Auricular Canal to the Metampulla. Through the enlargement of the metampulla (Asami, 1969; de Vries and Saunders, 1962; Pernkopf and Wirtinger, 1933; Streeter, 1945, 1948) and the migration of the auricular canal, this orifice connects to the metampullary segment in the XVI. horizon (Asami, 1969; de Vries and Saunders, 1962) (Fig. 2). This process implies a reorganisation in the dorsal region of the heart. The pro- and metampulla, at first connected in succession, move to their final position as parallel cardiac chambers (see Pernkopf and Wirtinger, 1933; Goerttler, 1958, 1963a).

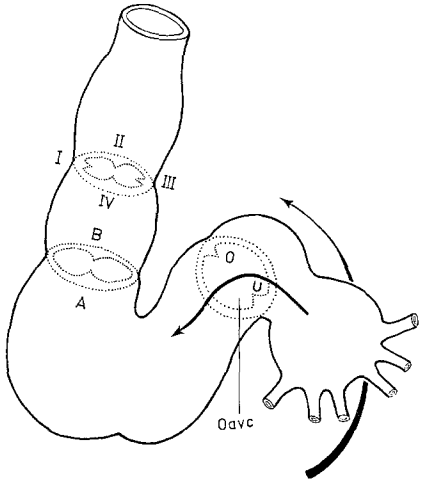


Fig. 1. Tilting of the common atrioventricular canal (*Oavc*) about a frontal axis. Position of the future proximal bulbar cushions (*A*, *B*) and the distal bulbar cushions (*I*, *II*, *III*, *IV*) prior to bulbar backtorsion and bulbotruncus torsion (modified from Doerr, 1955a)

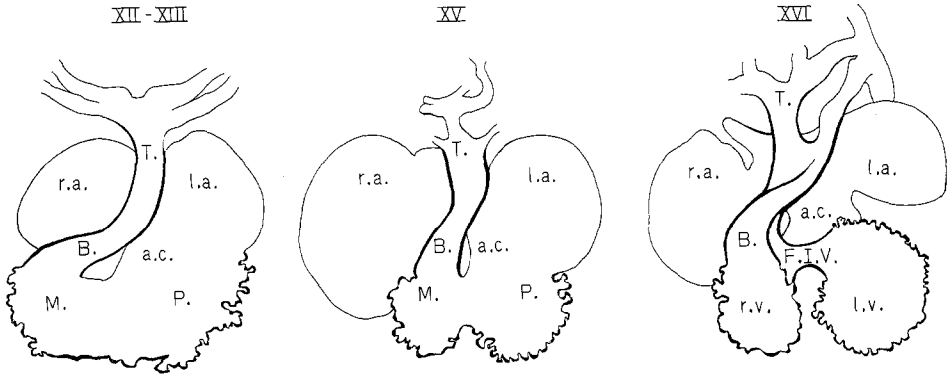


Fig. 2. Progressive growth of the metampulla and rightward displacement of the auricular canal. Both processes take place simultaneously, and serve to connect the right border of the auricular canal (future tricuspid orifice) to the developing right ventricle. The first component of vectorial bulbar rotation (leftward displacement of the entire bulbus) is also represented in the figure. *T* Truncus, *B* Bulbus, *M* Metampulla, *P* Proampulla, *ac* Auricular canal, *la* left Atrium, *ra* right Atrium, *FIV* Interventricular Foramen, *lv* left Ventricle, *rv* right Ventricle (modified from de Vries and Saunders, 1962)

b) The Vectorial Rotation of the Bulbus. This process, which Asami (1969) could confirm stereomicroscopically, consists of three component movements: 1. a leftward displacement of the bulbus, 2. a clockwise 45 degree torsion of the bulbus (bulbar backtorsion) and 3. a 150 degree counterclockwise torsion of the bulbustruncus (Doerr, 1951; 1952, 1955b, 1960). The first component takes place almost concurrently with the enlargement of the metampulla (Fig. 2), and occurs together with a bulbar shrinkage between the XVI. and XVIII. horizons (Asami,

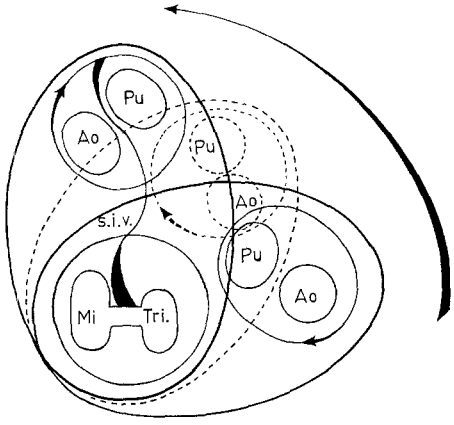
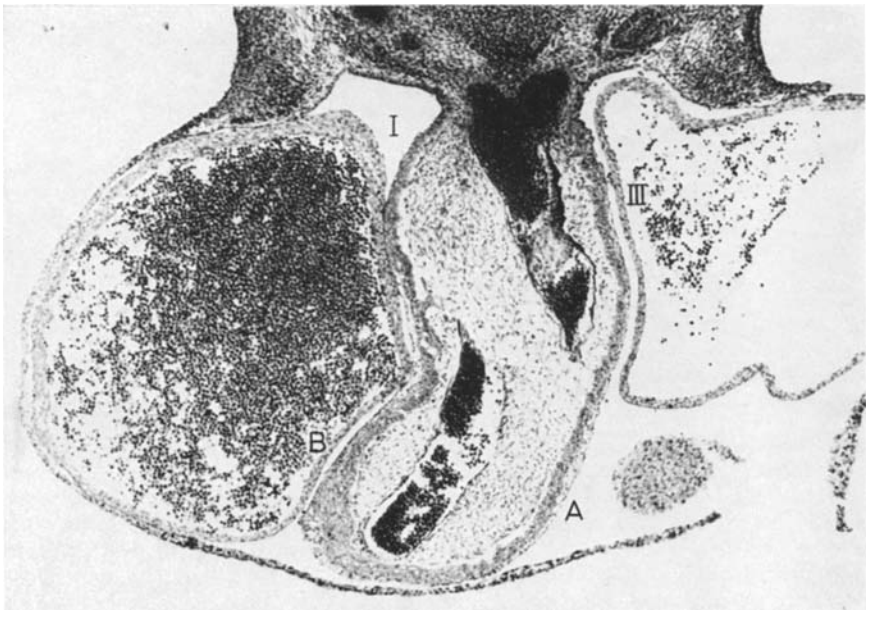


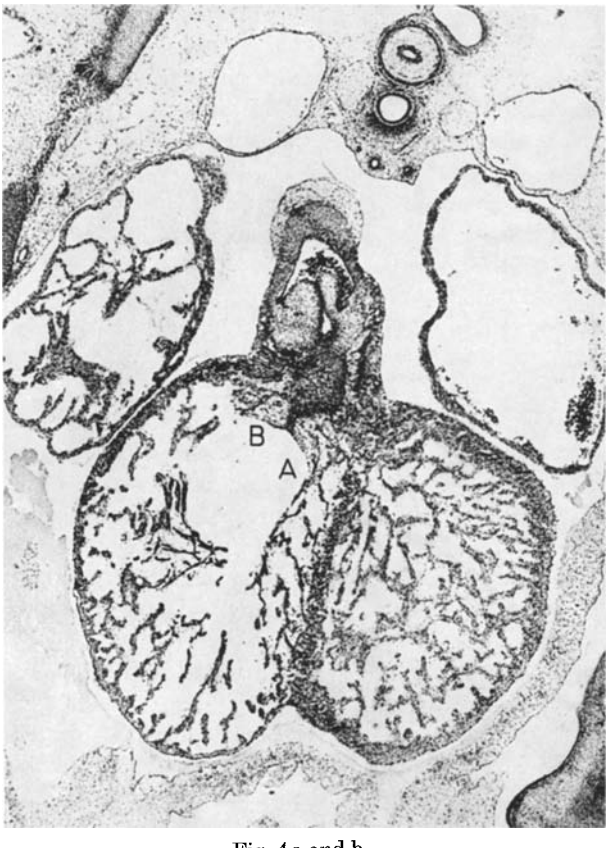
Fig. 3. Three positions in the course of vectorial bulbar rotation. View of the base of the heart from above. On the right is represented the primitive position of the bulbus and the arterial flow tracts at the level of the future arterial orifice. The normal relationships in the completed heart (above, center) are achieved through: a) leftward and ventral displacement of the bulbus (I. component) and b) bulbustruncus torsion (III. component). The backtorsion running in the plane of the bulbar orifice (II. component) is not represented. A normal intermediary stage is presented in dashed lines. *Ao* Aorta, *Pu* Pulmonary Artery, *Mi* Mitral, *Tri* Tricuspid, *siv* Interventricular Septum (modified from Doerr, 1970)

1969). The second component is recognized through a change in position of the proximal bulbar cushions—XV. through XVI. horizons (Asami, 1969)—The third component—accompanied by a truncus elongation from the XVI. through the XVIII. horizons—takes place from the XV. through XIX. horizons. As the last act of this process, the aortic orifice experiences an additional leftward displacement in the XIX. through XX. horizons, as the interventricular foramen is closing (Asami, 1969). The entire process is clarified by one of Doerr's diagrams (Fig. 3). The strongly twisted bulbar ridges A-I and B-III, which during the XV. horizon course in a spiral of 180 degrees (Fig. 4a), are extended during the XVIII. horizon (Fig. 4b) by virtue of the bulbustruncus torsion.

c) Cardiac Septation. Atrial septation is realized through two septa developing after one another; the septum primum (Fig. 5) and the septum secundum. The XVII. horizon, in which the ostium primum closes and the dorsal and ventral endocardial cushions fuse with one another (Asami, 1972), represents the transition point between the end of septum primum growth and the initation of the septum secundum. Ventricular septation is likewise realized through the development of two septa: ventricular and bulbar. The interventricular foramen only closes after the bulbus backtorsion, the septation of the bulbus and truncus, and the greatest part of the truncus torsion are complete. The aorta still rides over the interventricular foramen (Fig. 6) during the XVIII. horizon. The line of fusion between complementary and principal ridges can be recognized (Fig. 7) in the XIX. and also the XX. horizon (see Bersch, 1971, 1972). The aortic orifice is connected to the left ventricle by this process, which draws a part of the metampulla and the bulbus into the proampulla (Pernkopf and Wirtinger, 1933; see also Goerttler, 1958, 1963a).



a



b

Fig. 4a and b

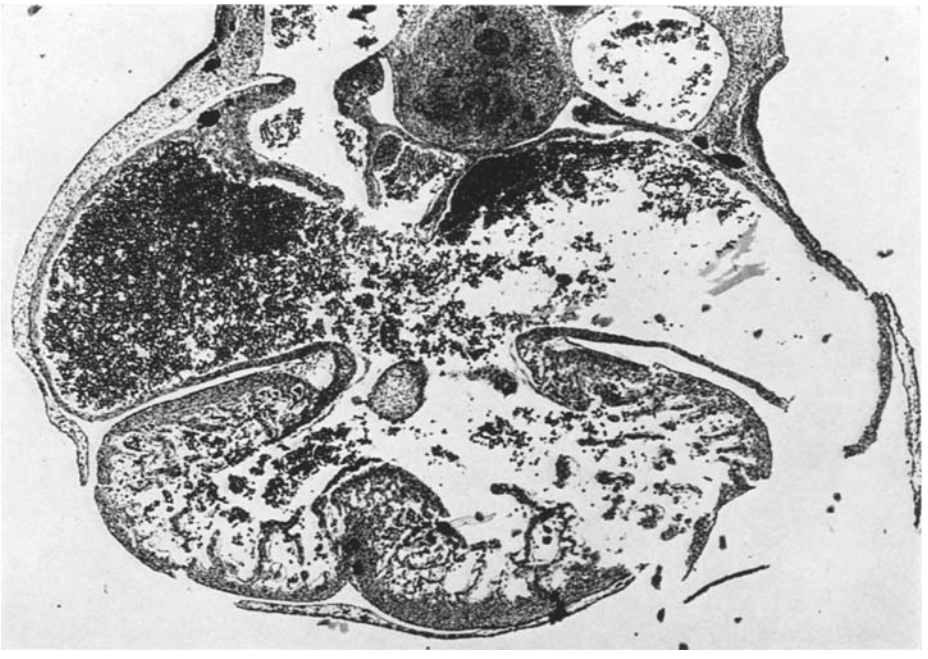


Fig. 5. Frontal section through the heart in the XV. horizon. The auricular canal and the sectioned posterior endocardial cushion stand in the center. Below, between the metampulla on the left and the proampulla on the right, lies the anlage of the ventricular septum. From the atrial roof hang from left to right the Valvulae venosae and the Septum primum, the lower edge of which delimits the wide ostium primum (about ×40, HE)

3. The *late phase* extends from the XX. through the XXIII. horizons, and for some structures, for example the A-V valves, to the fetal period (Odgers, 1938/39). The most important transformation processes are already concluded by this time.

II. Special Part

Cardiogenic Plate and Fusion of the Cardiac Tubes. Malformations, which can be traced back to an absent cardiogenic plate anlage or to a complete separation of the cardiac tubes, are unknown in man. Acardia (see Doerr, 1955a) is instead explainable through a secondary destructive process involving the already

Fig. 4. a Human embryo (XV. horizon). The strongly twisted bulbar ridge *A–I* is sectioned upon the longitudinally extended Bulbus cordis, which lies in the center surrounded by the atria. Bulbar cushion *B* is recognizable on the left beneath the bulboventricular orifice, and above to the right the distal bulbar cushion *III.* is seen. These anlages display a connective tissue structure at this horizon (about 100×, HE). b Frontal section through the heart (XVIII. horizon). In comparison with a the bulbus shows a pronounced shrinkage and extended ridges fused to the bulbar septum. An extensive muscular transformation is recognizable in the middle of the bulbar septum, beneath the fusion line between bulbar cushions *A* and *B*, above the semilunar valves (about ×24, HE)

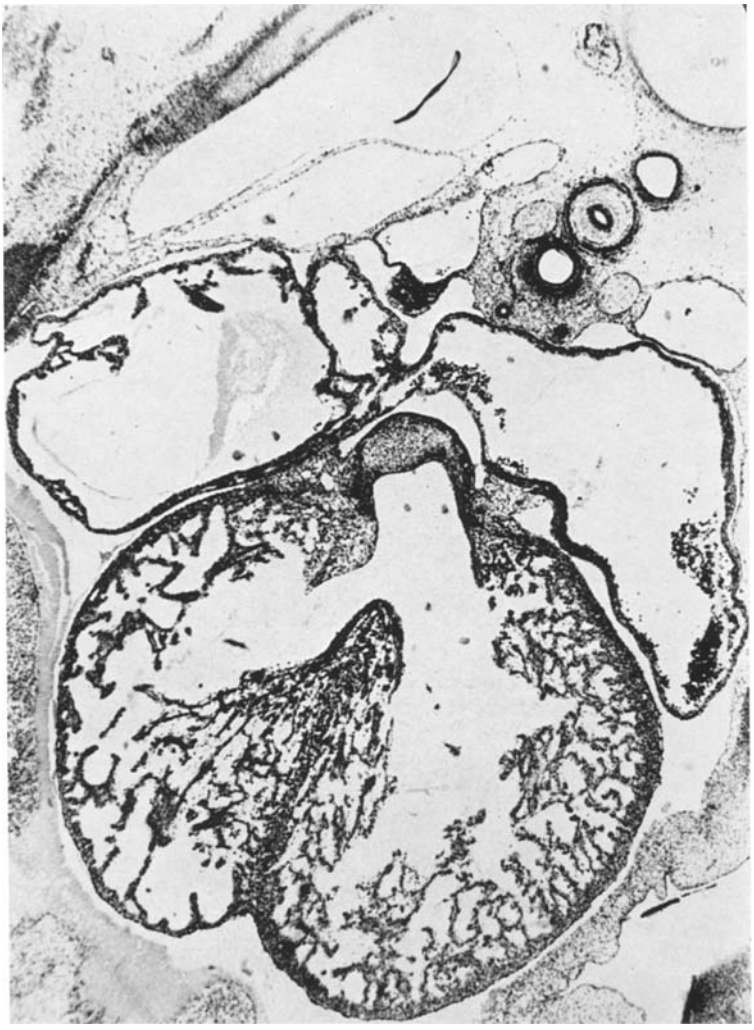


Fig. 6. Horizon XVIII. Frontal section of the heart. In the center the aorta rides over the interventricular foramen. A transverse section of complementary ridge B–O can be seen at the right border of the aortic conus (about ×27, HE)

laid down cardiac tube (Goerttler, 1963b, 1971). Partial duplication of the heart in conjointed twins are explicable by a faulty fusion of the cardiac tubes (horizon X).

Cardiac Loop. Three malformations can appear in this period of development (X.–XI.): symmetrical cor biloculare, dextrocardia, and ventricular inversion.

a) Cor biloculare can originate in the X. horizon, before the bilaterally asymmetrical cardiac loop has formed. In the case of this anomaly the absence of the atrial and ventricular septum is seen as a secondary malformation. On the other hand it is also possible, as Goerttler declares (1963b), that a cor biloculare arises in a later phase through a direct developmental inhibition of the atrial

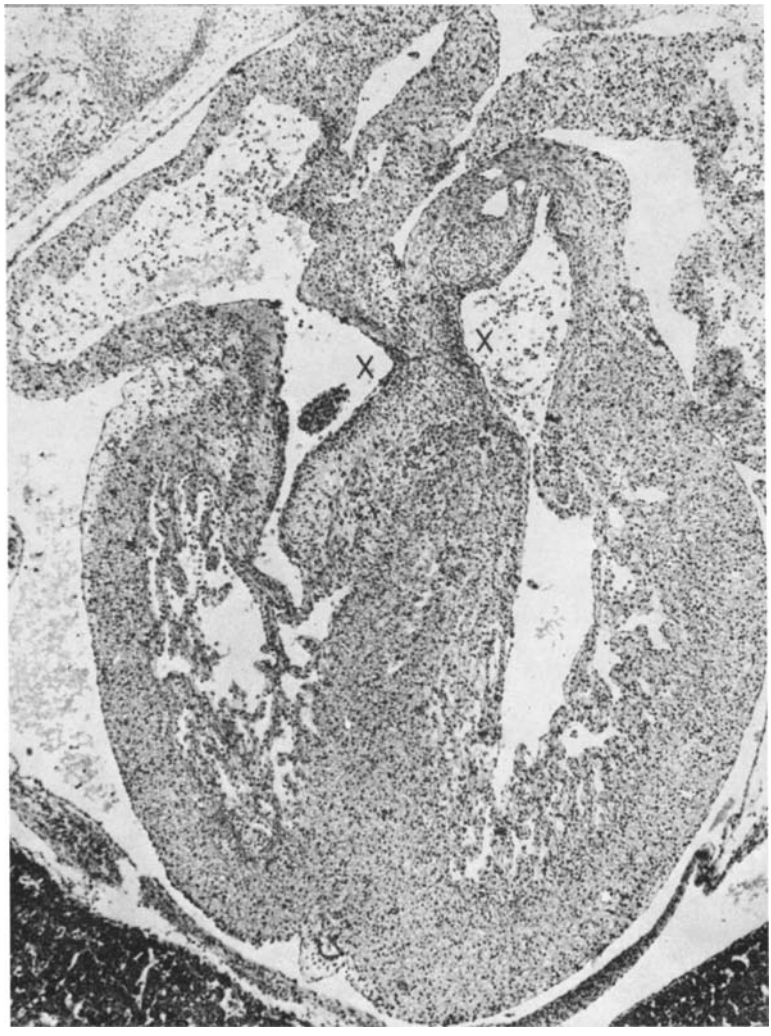


Fig. 7. XIX. horizon. Frontal section of the heart. The incorporation of the aortic conus in the proampulla, which is thereby transformed into the left ventricle, is completed. A fusion line is visible (x–x) between the complementary and principal ridges (about $\times 30$, HE)

and ventricular septum. The determination period of this second type extends at least from the XIII. (Patten, 1960; Tandler, 1913), the ventricular septum in XIV horizon (de Vries and Saunders, 1962)—Again by this second type an absent septum secundum, the anlage of which first appears in the XVII. horizon (Asami, 1972), is regarded as a secondary inhibition.

b) Dextrocardia (mirror image dextrocardia) is explained through an inverted lay out of the cardiac loop. Period of determination: from X. through XI. horizons.

c) Ventricular inversion: The hypothesis of Lochte (1898), that ventricular inversion is determined through an anomalous rotation of the cardiac loop, has

proven correct to the present time (for discussion see Chuaqui, 1969). Two determination periods are possible for this malformation: one the interpretation of De la Cruz *et al.* (1959, 1967) and Los (1968), the other the view of Goerttler (1958, 1963b). According to the two first named authors a ventricular inversion originates in the same phase as dextrocardia (X.–XI. horizons) through an inversion of the ventricular loop alone (therefore not the atria!), according to Goerttler, however, by means of a leftward directed swinging of the bulbometampullary portion, and indeed between the XIII. and XVI. horizons (1963b, 1968a).

Connection of the Auricular Canal to the Metampulla. Arrest of the vectorial rotation of the auricular canal leads to the so called primitive levocardia (Goerttler, 1958, 1968b). It manifests itself as a looped heart, in which case the persisting pro- and metampulla are connected in succession and the atria are only connected with the proampulla ("Double-Inlet left ventricle", De la Cruz and Miller, 1968). The migration of the auricular canal, and also often the vectorial bulbar rotation, are arrested. The so called juxtaposition of the atrial appendages is an important morphological sign of this arrested development.

The pro- and metampulla show a particularly rapid growth from the XIII. through XVII. horizons. One may trace the origin of hypoplastic ventricular inflow tracts, that is to say without involvement of the conus, back to this time. The Ebstein-anomalie is such a hypoplasia affecting the right ventricle (concerning the formal genesis see Goerttler, 1963b).

The Sinuatrial Orifice. The sinoatrial orifice and left sinoatrial fold develop in the XI. through XIII. horizons as an expression of the rightward displacement of the entire sinus venosus (Los, 1960). An arrest of this process leads to the atrial septal defects of the venous cardiac entrance (Goerttler, 1958, 1963b; Los, 1968). These defects lie between the atrial septum and the defective left sinoatrial fold.

Dorsal and Ventral Endocardial Cushions. The dorsal and ventral endocardial cushions appear in the XIII. horizon (Patten, 1960; Tandler, 1913) and fuse with one another according to Patten (1960) and de Vries and Saunders (1962) in the XVI. horizon, according to Asami (1972) not until the XVII. horizon. Odgers (1938/39) finds all atrioventricular leaflets present in the XVIII. horizon (embryos between 14,5 and 15,5 mm in length). Therefore, a disturbance in fusion of the dorsal and ventral endocardial cushions must occur in the period of time from the XVI. through XVIII. horizons. This time span can, however, when a common atrioventricular canal with rudimentary, widely separated leaflets is present, go back to the XIII. horizon. Ventricular septal defects lying below the unfused dorsal and ventral endocardial cushions arise in the XV. through XVII. horizons (see Bersch, 1971).

Septum Primum, Ostium Secundum and Septum Secundum. The development of the septum primum takes place from the XIII. (Patten, 1960; Tandler, 1913) through the XVII. horizons (Asami, 1972). This span is therefore valid as the period of determination of a persisting ostium primum. According to Asami (1972), the ostium secundum has already appeared in most embryos by the XV., according to Patten (1960) in the XVI. horizon. It was not recognizable in our embryo (XV. horizon). A defect in the region of the ostium secundum can arise through a hypoplasia of the septum primum (XIII–XVII) as well as the

septum secundum (XVII—XXIII). In either case the ostium secundum is not completely covered by the septum secundum. Consequently an ostium secundum defect may originate anytime from the XIII. through the XXIII. horizons. (The following times are given in the literature for the appearance of the septum secundum: XVI. horizon by Patten (1960), XVII. horizon by Asami (1972), XVIII. horizon (inconstant!) by Vernall (1962), and about the XIX. horizon (embryos of 17.5 mm and 19 mm length) by Odgers (1934/35). The anlage of the septum secundum was recognizable in our embryo (XVIII. horizon).

Ventricular Septum. The anlage of the ventricular septum appears in the XIV. horizon (de Vries and Saunders, 1962). In the XVII. horizon it has fused with the dorsal and ventral endocardial cushions (Asami, 1969). Defects of this primary septum may therefore originate from the XIV. through the XVII. horizons.

Vectorial Bulbar Rotation. Disturbances of the vectorial bulbar rotation lead to a teratogenic series recognized by Doerr (1955b, 1951, 1952), in which the following examples are to be regarded as taken from a continuous process (Chuaqui, 1971): Beuren's anomaly (1960), classical transposition, Taussig-Bing anomaly, tetralogy of Fallot, and the Eisenmenger complex. Arrest of bulbustruncus torsion is decisive in the genesis of this teratogenic series. (About further possible disturbances of the vectorial bulbar rotation, e.g. dislocations and asymmetrical rotations, see Goerttler, 1963b, 1968b).

According to the investigations of Asami (1969) the aortic orifice lies ventrally to the right during the XV. horizon and laterally on the right in the XVI. horizon; at these times the pulmonary orifice is found in the opposite position. Moreover, in the XV. horizon continuous bulbar ridges have not yet developed along lines A-I and B-III (Asami, 1969). Either Beuren's anomaly or crossed transposition can arise from the XV. through the XVI. horizons depending upon whether the Pulmonalis is riding or not. The development of anomalous bulbar ridges, namely A-III and B-I, can also be accounted for by an arrest of the bulbustruncus torsion in the mentioned positions, as Doerr (1955b) has already hypothesized for the case of transposition.—In the XVII. horizon the aortic orifice lies dorsally to the right, the pulmonary orifice ventrally to the left. The leftward displacement of the bulbus is not yet completed. The span from the XVI. through the XVII. horizons can therefore be regarded as the determination period for the Taussig-Bing anomaly. It is to be accepted in the case of this anomaly, as well as others in this series yet to be discussed, that normal bulbar ridges A-I and B-III develop (Doerr, 1955b), since continuous ridges already exist in the XVI. horizon.

The aorta still rides over the interventricular foramen during the XVIII. and XIX. horizons. Arrest of the vectorial bulbar rotation in this position leads to the tetralogy of Fallot and the Eisenmenger complex.

Asami (1969) could demonstrate an additional leftward displacement of the aortic orifice from the XIX. through the XX. horizons. The question arises, whether the interventricular foramen can still close normally in spite of the arrest of the aortic orifice in a position corresponding to the XIX. horizon, and if this then provides the congenital basis for a septum sigmoideum developing later in life.

A fusion line between complementary and principal ridges canbe demonstrated in the XIX. and sometimes still in the XX. horizon (Bersch, 1972). The crista

saliens may result from a disturbance in this region (Doerr, 1959). It can be interpreted either as the expression of an excessive (Doerr, 1959) or as an arrested (Köthe, 1966) vectorial bulbar rotation.

Truncus Septum. Bulbar cushions I and II appear in the XIV. horizon (de Vries and Saunders, 1962), II and IV in the XV. horizon (de Vries and Saunders, 1962; Asami, 1969). I and III are halved during the development of the truncus septum (XV.–XVII.). Following the conclusion of this process the still rudimentary semilunar valves differentiate further, while the conus of each ventricle expands. The development of the truncus septum is completed from the XV. to the XVII. horizons (de Vries and Saunders, 1962; Streeter, 1948); according to Neil (1957), O'Rahilly (1971), Los (1966, 1968) and van Mierop *et al.* (1963), however, it has already begun in the XIV. horizon. Neil (1957) finds the development to be complete in the XVIII. horizon, and O'Rahilly (1971) in the XIX. horizon. The septum was already formed in our embryo (XVIII. horizon). The determination period for this septum, which grows contrary to flow (including the persistent truncus arterious) may therefore be set between the XIV. and XVII. horizons (concerning the formal genesis see Heilmann, 1971). In examining the possible periods of determination of the pseudotruncus anomalies, for which a hypoplasia of the arterial segments surrounding the semilunar valves is decisive, it is practical to distinguish the following forms of semilunar valvular stenosis (Barahona and Chuaqui, 1966): a) pure stenosis of the orifice (circumference of the annulus normal), b) pure stenosis of the annulus (true hypoplasia with semilunar valves "en miniature"), and c) stenosis of the annulus with malformed semilunar valves. Pseudotruncus anomalies occur in b and c, atresias only in c. Apparently the period of determination for a stenosis confined to the orifice only begins after the division process of both semilunar valves is concluded (XVII. horizon), and even extends into the phase of fetal development. A hypoplasia of the affected arterial segments is conceivable *also during* truncus septation in the case of b and c (see Barthel, 1960; Goerttler, 1963b).

Septum Bulbi. According to Asami (1969), fusion of the bulbar ridges takes place from the XVII. through the XIX. horizons. Nevertheless, the bulbar septum was already formed in our embryo (XVIII. horizon) and almost completely infiltrated by muscle tissue. The span mentioned is valid as the period of determination for bulbar ventricular septal defects. Since the bilateral conus enlargement also falls into this time span (XVII.–XX.), it can be accepted as the period of determination of conus stenoses and hypoplasia of the completed cardiac chambers (see Bredt, 1936; Doerr, 1955b).

Interventricular Foramen. The interventricular foramen closes between the XVIII. and XX. horizons. It is already closed in the XIX. horizon according to our material and that of Odgers (1937/38) and Los (1968). The closing of the bulboauricular canal (investigated by Asami in numerous embryos) ensues between the XIX. and XX. horizons (see Odgers, 1937/38). The fusion of the complementary and principal ridges begins ventral to the bulboauricular canal (Asami, 1969; Bersch, 1971, 1972). The time from the XVIII. through the XX. horizons may also be determination period for ventricular septal defects occuring in these two fusion zones.

Enlargement of the Atrioventricular Orifices. A distinct enlargement of the atrioventricular orifices can be seen after the fusion of the dorsal and ventral

endocardial cushions in the XVII. horizon. It lasts through the XX. horizon (Asami, 1969), and may be regarded as the determination period for annular stenosis of these orifices. This span is just that accepted as the determination period for ventricular hypoplasias.

Coronary Arteries. According to Hackensellner (1955, 1956), the first pouches of the coronary arteries appear in 13 mm embryos (about the XVII. horizon), shortly after truncus septation is concluded. These buds appear first in the XVIII. horizon, according to Patten (1968), and they were easily recognized in our embryo (XVIII. horizon). According to Hackensellner, every distal bulbar cushion—therefore II and IV as well as the pulmonary part of I and III—possesses the potential to form a coronary pouch. Since anomalies of origin of the coronary arteries are to be traced back to this development (see also Hackensellner, 1954/55), their period of determination must be about the XVII. horizon (XVI.–XVIII.).

Pulmonary Veins. The critical developmental phase of the pulmonary veins extends from the XIII. horizon (anlage of the pulmonary venous trunk)—according to Los and Dankmeijer (1957) and Los (1968) the XIV. horizon—through the XV. horizons (extensive connections with the pulmonary plexus; Neill, 1956 (see also Auer, 1948)). The first connections with the pulmonary plexus are, according to Neill, recognizable in the XIV. horizon. The anastomoses with the cardinal venous system have largely receeded by the XV. horizon. The branching process of the pulmonary trunk takes place from the XV. through the XX. horizons, and the inclusion of the spatium pulmonale in the left atrium occurs after the XX. horizon (Los and Dankmeijer, 1955; Los, 1968). The time span from the XII. through the XIII. horizons is acceptable for the transposition of the pulmonary veins to the right atrium (see Neill, 1956), and XIII. through XV. horizons for persistence of the connection between the pulmonary and caval venous systems. It is an open question whether in these latter malformations a pulmonary venous trunk is laid out at all or if it is later reabsorbed. Cor triatriatum sinsitrum would therefore arise after the XX. horizon.

Aortic System. The aortic system develops in two phases: the prebranchial from the X. through the XVII. horizons, and the postbranchial from the XVII. through the XX. horizons (Congdon, 1922). The first phase is distinguished by the bilateral appearance of the aortic arches and the fusion of the dorsal aortas. In the second phase a reorganization of this symmetrical system is realized. First, (XVII. horizon) the dorsal segment of the IV. aortic arch disappears, as well as the segments between the III. and IV. aortic arches bilaterally. One horizon later the right dorsal aorta is reabsorbed distal to the VI. arch; the entire system is displaced leftward (Hackensellner, 1954a, b), and the origin of the left subclavian artery migrates to a position proximal to the ductus arteriosus (XIX.–XX. horizons, Barry, 1951). In view of these facts, malformations of the aortic system may be traced back to the second phase.

Venous System. We prefer to follow here the more precise classification of Grünwald's, from among the two detailed works concerning the development of the inferior vena cava (McClure and Buttler, 1925; Grünwald, 1938). The cardinal venous system is the principal component in the primary stage (embryos from 4 to 13 mm), supplemented below through the sacrocardinal and caudal veins, above through the supracardinal veins, and in the middle through the

lacunar anlage of the subcardinal beins. In the transition stage (embryos from 13–14 mm) two venous systems exist at the same time: the cardinal and subcardinal. The cardinal veins are reabsorbed in the secondary stage (embryos from 13,5 to 20 mm). The final assymmetry of the subcardinal system appears in the definitive stage (embryos greater than 20 mm). The time span from the XVI. through the XIX. horizons should be valid as the determination period for the most important venous malformations, since the transition stage, which is decisive for these malformations, was also described in a few embryos with C.R. lengths of 10 and 17 mm (Grünwald, 1938).

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