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The Formal Genesis of the Transposition of the Great Arteries

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Summary. The formal genesis of transposition of the great arteries is treated in four parts: 1. Presentation of vectorial bulbus rotation on the basis of findings made on the human embryonal heart. 2. Interpretation of the different froms of transposition as disturbances of vectorial bulbus rotation. 3. Comments on other concepts relating to the morphogenesis of transposition: De la Cruz' theory of a straight bulbotruncal septum; Grant's interpretation of an abnormally developed heart skeleton; and Van Praagh's conal growth hypothesis recently advocated by Bankl and comparable to Keith's concept of an anomalous absorption of the bulbus. 4. Discussion of the main terminological problems of transposition.

Vectorial bulbus rotation proves to be a correct interpretation of the more important stages in the development of the arterial end of the heart. The different forms of transposition can be easily explained on the basis of the pathogenic principle of an arrest of vectorial bulbus rotation.

The conal growth hypothesis can be understood, in a causal sense, as an extension of the formal concept of vectorial bulbus rotation, but like the concepts of De la Cruz and Grant it is inadequately supported by the known facts of human cardiogenesis.

Zusammenfassung. Die formale Genese der arteriellen Transposition wird in 4 Abschnitten behandelt:

1. Darstellung der vektoriellen Bulbusdrehung anhand von Befunden an menschlichen embryonalen Herzen.

2. Interpretation der verschiedenen Transpositionsformen als Störungen der vektoriellen Bulbusdrehung.

3. Stellungnahme zu weiteren Konzeptionen über die Morphogenese der arteriellen Transposition: die Auffassung von De la Cruz eines gestreckt angelegten Septum bulbotruncale als Ursache für die Transposition, die Theorie von Grant eines abnorm angelegten und entwickelten Herzskeletes und die mit der Keithschen Konzeption einer anomalen Bulbusrückbildung verwandte Conuswachstumshypothese von van Praagh, die vor kurzem von Bankl vertreten worden ist.

4. Erörterung der wichtigsten terminologischen Probleme der arteriellen Transposition.

Die vektorielle Bulbusdrehung erweist sich als zutreffende Interpretation für die wichtigsten Ereignisse der Entwicklung des arteriellen Herzendes. Die verschiedenen Transpositionsformen lassen sich zwanglos anhand des pathogenetischen Prinzipes einer Arretierung der vektoriellen Bulbusdrehung erklären.

Die Conuswachstumshypothese läßt sich als *Ergänzung* der vektoriellen Bulbusdrehung im kausalen Sinne verstehen, sie ist jedoch, ebensowenig wie die Konzeption von De la Cruz und Grant, nicht ausreichend durch reale Fakten der menschlichen Kardiogenese gestützt.

Transposition of the great arteries as a central problem of cardiac anomalies has been subject of numerous investigations and has led to a number of different theories concerning the normal and pathological development of the heart. The

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following important concepts regarding the genesis of transposition should be mentioned: Rokitansky's theory (1875) of a faulty anlage of the bulbotruncal septum as the cause for transposition; the modification of this theory by Mönckeberg (1924); Keith's viewpoint (1909) of an anomalous absorption of the bulbus; Spitzer's (1923) phylogenetic theory; Bremer's concept (1928) of an anomalous torsion at the arterial end of the heart; and finally, the ontogenetic theory by Pernkopf and Wirtinger (1935) of the *septatio aberrans transponans bulbi*.

After careful analysis of these theories, Doerr (1938, 1943), in agreement with Spitzer (1923), Bremer (1928) and Bredt (1936), came to the conclusion that the nature of transposition was to be found in an anomalous torsion at the arterial end of the heart. In support of Spitzer (1929) and contrary to Pernkopf (1926, 1937), Doerr considered *inversion* as a phenomenon not formally connected with transposition. As a next important step to further understanding these cardiac anomalies, Doerr definied the *formal principle* of *vectorial bulbus rotation* (1952, 1955a). Thus, by the very arrest of vectorial bulbus rotation, the teratologic "series" as recognized by Doerr (1951) (Eisenmenger complex, tetralogy of Fallot, Taussig-Bing anomaly and crossed transposition), is clearly understood as disturbances of the same process. Contrary to the hypotheses of Spitzer and of Pernkopf and Wirtinger, which were based on postulates that could not be verified, neither in ontogenesis nor in phylogenesis, the above concept by Doerr originated as an inductive abstraction from the then known phenomena of normal and pathological cardiogenesis. The results obtained by Goerttler (1955, 1956a, b), De Vries and Saunders (1962), and Asami (1969), may be considered as verification of vectorial bulbus rotation. With regard to pathogenic mechanisms, arrest and dislocations (Goerttler, 1958, 1963b, 1968a, b) are yet to be verified in this segment of the heart.

Doerr's comments on the theories of Spitzer, and Pernkopf and Wirtinger may also be valid regarding Lev's and Saphir's concept of transposition (1945).

New concepts pertaining to the genesis of transposition were then formulated by De la Cruz *et al.* (1956), Grant (1962a) and van Praagh and van Praagh (1966). De la Cruz *et al.* assume a straight bulbotruncal septum, Grant an anomalous development of the heart skeleton, and van Praagh and van Praagh an anomalous growth of the conal musculature as being the underlying cause for transposition. These are esentially the most outstanding hypotheses cited in the anglo-american literature regarding to the transposition theory. In support of the conal growth hypothesis, Bankl (1971a, 1972) just recently tried to refute Doerr's concept of the formal genesis of transposition.

The subject of this paper is to critically evaluate the above mentioned theories and to analyse Bankl's objections. This evaluation is based on examinations carried out on embryonal human hearts, the results of some of which have already been published (Bersch, 1971, 1972; Chuaqui, 1972; Chuaqui and Bersch, 1972). In addition, the more important publications on the problem of transposition in man have been considered.

Our investigations covered the following four interrelated topics:

I. Presentation of the vectorial bulbus rotation with specific consideration of recent findings in human cardiogenesis.

II. Interpretation of the different forms of transposition as disturbances of vectorial bulbus rotation.

III. Evaluation of the following theories pertaining to the genesis of transposition:

a) The theory of De la Cruz *et al.* (1956).

b) Grant's concept (1962a).

c) The conal growth hypothesis by van Praagh and van Praagh (1966).

d) Bankl's objections to Doerr's concept.

IV. Comments on the terminology of transposition.

I. Vectorial Bulbus Rotation

(Doerr, 1952, 1955a, b; 1960, 1970)

The heart tube represents a frontal loop in the XIII. horizon; it consists of six segments connected in series: sinus venosus, atrium, proampulla, metampulla, bulbus and truncus (De Vries and Saunders, 1962; Los, 1960, 1968; Streeter, 1945, 1948; Tandler, 1913; van Mierop *et al.*, 1963) — for terminology pertaining to the cardiac segments cf. De Vries and Saunders, 1962; O'Rahilly, 1971; van Mierop *et al.*, 1963.

Pernkopf and Wirtinger (1933) made a significant contribution to an understanding of the complex reorganization processes leading from this cardiac loop to the parallel position of the left and right vascular system of the fully developed heart; basically, analogous reorganization processes take place at the auricular canal and at the arterial end of the heart:

1. The right portion of the auricular canal, in the XIII. horizon solely connected with the proampulla, joins the metampulla in the XVI. horizon (Asami, 1969; De Vries and Saunders, 1962). This process is of great importance for the morphogenetic interpretation of the so-called "double inlet left ventricle" (De la Cruz and Miller, 1968) and other related malformations of the atrioventricular valves (see Lev *et al.*, 1969; Liberthson *et al.*, 1971). A detailed description of this process is given by Goerttler (1958, 1963a).

2. At the arterial end of the heart the aortic portion of the bulbus is incorporated in the proampulla (Asami, 1969; De la Cruz *et al.*, 1956, 1967, 1971a; De Vries and Saunders, 1962; Goerttler, 1958, 1963a; Grant, 1962a; Kramer, 1942; Los, 1960, 1966, 1968; Mall, 1912; Odgers, 1937/38; Patten, 1960, Pernkopf and Wirtinger, 1933; Tandler, 1913; van Mierop *et al.*, 1963). This process, which takes place prior to the termination of the ventricular septation (Asami, 1969; Chuaqui and Bersch, 1972; Doerr, 1952, 1955a, b; Goerttler, 1958, 1963a), was *formally* explained by Doerr as *vectorial bulbus rotation* and stereomicroscopically confirmed by Asami (1969) in the embryonal human heart. This complex process can be explained as resulting from the following three components:

a) Displacement of the bulbus *in toto* to the left with almost concomitant enlargement of the metampulla (Asami, 1969; De Vries and Saunders, 1962) from the XIII. through the XVIII. horizon, shrinkage of the bulbus, and elongation of the truncus during the last three horizons (XVI–XVIII) (Asami, 1969).

b) A torsion of the bulbus at the bulboventricular orifice in a 45° clockwise twisting (in the direction of the blood flow). Asami (1969) was able to clearly

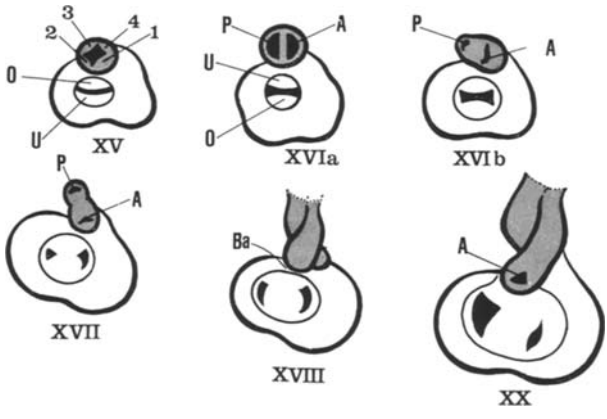

Fig. 1. Stages of the bulbotruncal torsion in the human embryo. Top view (atria removed). At top ventral, at bottom dorsal. The Roman numerals designate developmental stages (horizons); *1, 2, 3* and *4:* distal bulbar swellings. *P* pulmonary, *A* aortic orifice. From stage XV to stage XVII a rotation of the bulbotruncal orifice and the arterial orifices respectively can be seen. In stage XVIII the bulboauricular flange (*Ba*) is still visible. Stage XX: final position of the aortic orifice after recession of the bulboauricular flange. *O* anterior, *U* posterior endocardial cushion. (According to the original photograms by Asami, 1969, these here schematically illustrated)

illustrate this bulbar backward torsion by the change in position of the proximal bulbar swellings during the developmental phase from the XV. through the XVI. horizon.

c) A counterclockwise rotation at the bulbotruncal orifice in 150° (in the direction of the blood flow), likewise stereomicroscopically observed by Asami (1969), which takes place between the XV. and the XX. horizons. Asami found that the aortic bed at the bulbotruncal orifice is located ventrally to the right at the beginning of vectorial bulbus rotation, and that the pulmonary bed is located dorsally to the left; however, after completion of the bulbotruncal torsion (third component) the aortic and the pulmonary orifices are found to be in almost reverse positions (Fig. 1). Consequently, prior to this movement the bulbar ridges run in a markedly twisted spiral (Fig. 2a). It is by the bulbotruncal torsion, the shrinkage of the bulbus, and the backward torsion of the bulbus that the extent of this spiral is considerably reduced (Fig. 2b), whereas at the same time the truncal septum is twisted in 150°. This means that the aortic region is located ventrally in the cranial region of the truncus, and dorsally in the caudal region. As found by Asami (1969) in 58 embryos, bulbus septation does not start until horizon XVII is reached. i.e. at a time when the truncal septum is already developed and the aortic orifice is located dorsally behind the pulmonary orifice. This implies that the ultimate separation of the two vascular beds at the bulbus is not accomplished until complete bulbar backward torsion and extensive torsion of the bulbotruncal segment—as already described by Doerr (1952, 1955a)—are effected. Of particular interest in this reorganization process are two additional events which go hand in hand with the incorporation of the bulbar aortic area

into the proampula. These are, firstly, the recession of the bulboauricular flange and secondly, the development of the counter-ridge. In horizon XV the aortic region is bordered at the bulboventricular orifice ventrally to the right by the proximal bulbar swellings, and dorsally to the left by the primitive muscular bulboauricular flange (Fig. 3a). This muscular spur first separates the proximal aortic area from the endocardial cushion located dorsally farther to the left at the auricular canal. The bulboauricular flange, however, is then compressed by bulbus shifting to the left and degenerates; thereby a direct continuity between the left dorsal part of the aortic proximal bed and the anterior endocardial cushion is achieved (Fig. 3b). (This process has been discussed in detail by Bersch, 1971). During this developmental phase the proximal bulbar swellings both fuse, and the initially fibrous, later muscular counter-ridge B–0 is formed, which represents the ventral as well as the medial wall of the proximal aortic area. This ridge (bulboauricular ridge, Bersch, 1971) subsequently fuses with the crest of the ventricular septum (main ridge), thereby closing the interventricular foramen (Asami, 1969; Bersch, 1972; Pernkopf and Wirtinger, 1933). The His bundle runs directly underneath of this zone of fusion, which can be discerned as a line of fusion in horizons XIX and XX (Bersch, 1972; Chuaqui and Bersch, 1972; Fig. 4).

II. Disturbances of the Vectorial Bulbus Torsion

Both the concepts formulated by Spitzer and by Doerr explain the formal genesis of apparently unrelated cardiac malformations by one pathogenetic principle—as is the case in the arrest of cardiac torsion—and interpret different forms of malformations as a teratogenic "series". Categorization of these morphogenetically linked forms into strictly separated complexes satisfies the need for morphological classifications rather than the continuous character of the phenomena, since it is known that transitional forms often occur between recognized classical complexes. Fig. 1 clearly illustrates these malformations as a discrete series. The various malformations, i.e. the crossed transposition and the Beuren anomaly (1960), the Taussig-Bing anomaly (1949), the tetralogy of Fallot, and the Eisenmenger complex (1897, 1898) can be easily deduced from the diagram. In such anomalies the decisive factor is the extent of arrest of bulbotruncal torsion. In addition to the arrest of the arterial orifices in crossed transposition and Beuren anomaly, we may assume, as already described by Doerr (1955a), an anomalous development of bulbar ridges A-III and B-I on the following grounds: (i) as already mentioned by Asami (1969), the bulbar ridges A-I and B-III are not continuous in horizon XV; (ii) we have been able to prove the existence of a relatively thick layer of endocardial reticulum along the lines A-III and B-I in the embryo in horizon XV (Fig. 5). These findings support the assumption that the bulbar ridges cannot fuse into a normal septum *until after* decrease of spiralization caused by bulbotruncal torsion.

The more general term of the so-called "double outlet right ventricle" may be applied to the not quite uniform group of malformations, which includes the Taussig-Bing anomaly (Neufeld *et al.*, 1961a, 1962), cases with extreme dextropositioned aorta as transition to the tetralogy of Fallot (Braun *et al.*, 1952; Lintermans *et al.*, 1964; Neufeld *et al.*, 1961b; Venables *et al.*, 1966) and primi-

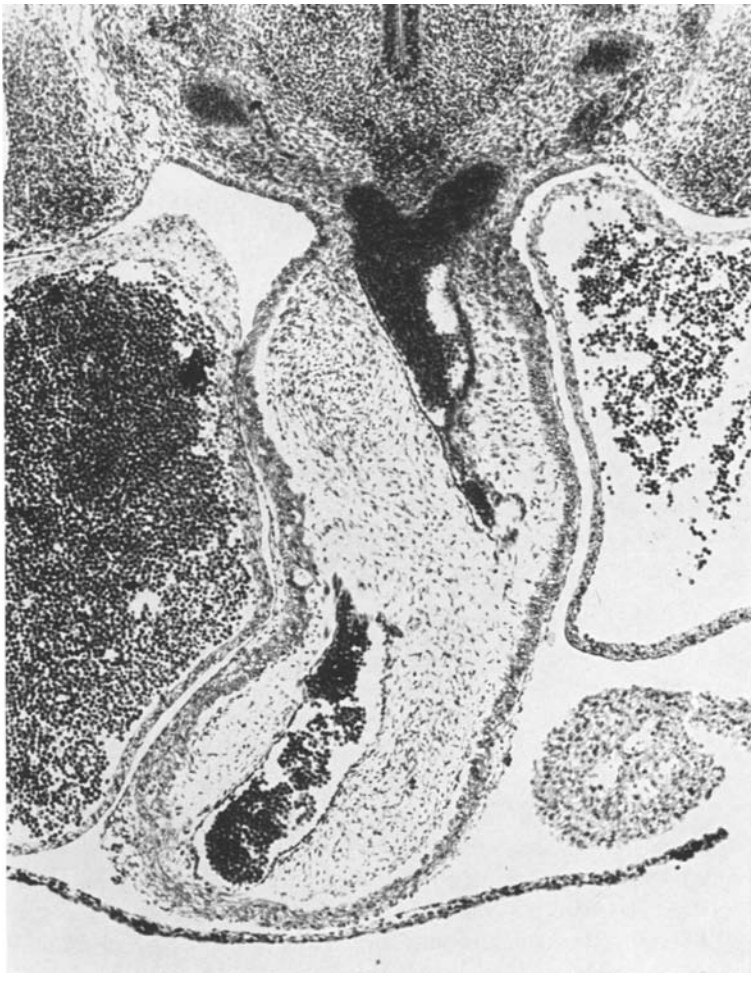

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Fig. 2. a Human embryo in stage XV; segment of the long bulbus, with markedly twisted ridge A-I. At the upper right the distal bulbar swelling III, at the lower left, at the bulboventricular orifice, the proximal bulbar swelling *B* can be seen (about × 60, H-E). b Human embryo in stage XVIII; section of the shrunk bulbus, revealing the almost straight ridges fused into the bulbar septum. *A* and *B:* proximal bulbar swellings (about × 100, H-E)

tive cardiac malformations (Bankl and Wimmer, 1971) in the sense of the "primitive levocardia" of Goerttler (1958, 1963b) as well as the "single ventricle" of Lev (Lev *et al.*, 1969). The origin of both arterial trunks from the right ventricle or the bulbometampullar segment, in this category of malformations may be considered as evidence of an arrest of the bulbus shifting to the left as well as of lack of incorporation of its aortic bed into the proampulla in agreement with Harley's findings (1958) and those of van Mierop and Wiglesworth (1963a). This has also been confirmed experimentally by Gessner and van Mierop (1970). In

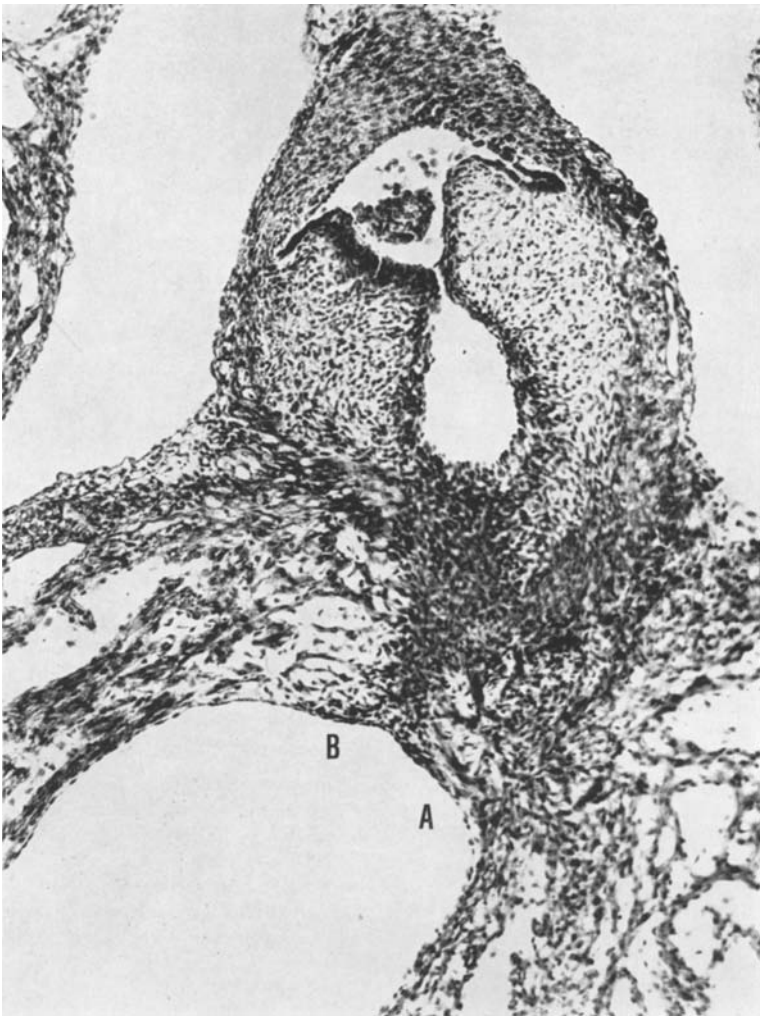

Fig. 2b

this connection the position of the arterial orifices is also an indication of an arrested torsion of the bulbotruncal segment, the extent of which in the more primitive forms is usually, but not always, that found in transposition. The remaining different positions of the great vessels in double outlet right ventricle have also been commented on by Mehrizi (1965), in particular in the Taussig-Bing anomaly by Lev *et al.* (1966), and in the common ventricle in a broader sense by Anselmi *et al.* (1968), Elliot *et al.* (1963a, 1964) and van Praagh *et al.* (1964). Some of these positions of the great vessels within the bulbar segment are interpreted by Goerttler as asymmetrical rotations around the aortic or the pulmonary axis (1963b, 1968a, b). Goerttler's assumption that these orifices might be dislocated with regard to the ligamentum aortopulmonale is supported by Rowlatt's findings (1962). In this group of malformations mention should be

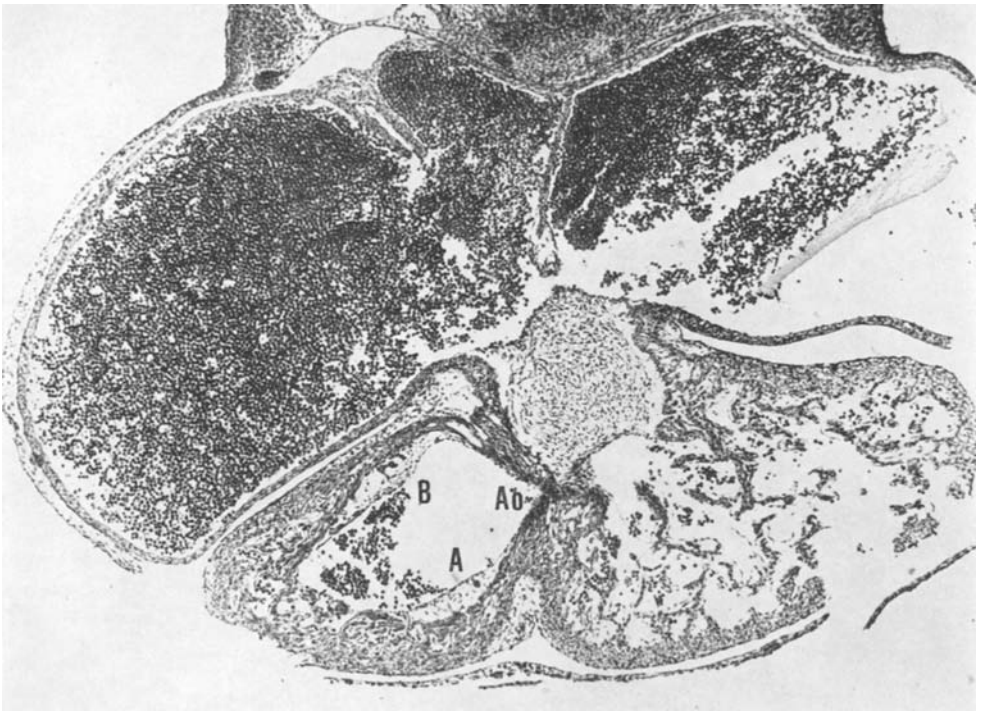

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Fig. 3. a Frontal section of the heart (human embryo in stage XV). The muscular bulboauricular flange extends between the aortic bed *Ao* in the bulbus and the anterior endocardial cushion. In the bulbar area the proximal swellings *B* (at top) and *A* (at bottom) are seen (about × 48, H-E). b Frontal section of the heart (human embryo in stage XVIII). The aortic bed *Ao* is directly bordered by the above extending fibrous strand of the anterior endocardial cushion. Directly below the tricuspidal niche (*T*) horizontally extending muscle fibres of the primitive bulboauricular flange can be still recognized (about × 48, H-E)

made of the crista supraventricularis, the deformities of which have already been refered to by Lev (1953) and Lev *et al.* (1966). In these malformation complexes the crista often lies in an almost parasagittal plane. This anomalous position of the crista, which occurs in the Beuren anomaly, may be understood as due to an arrest of the bulbar backward torsion. It is difficult to evaluate its various components in the so-called "aortic ventricle" because of lack of sufficient differentiation of the musculature of the bulbometampullar segment; consequently, we can hardly refer to this primitive musculature as a crista in the classical sense. Whether or not primitive components of the crista are at all discernible does not seem to have been established; only few authors have analyzed the normal development of this structure (Asami, 1969; Grant, 1962b; Grant *et al.*, 1961; Pernkopf and Wirtinger, 1933).

Another noteworthy finding in this group of malformations is the frequent lack of a fibrous connection between the mitral and the aortic valves (Neufeld

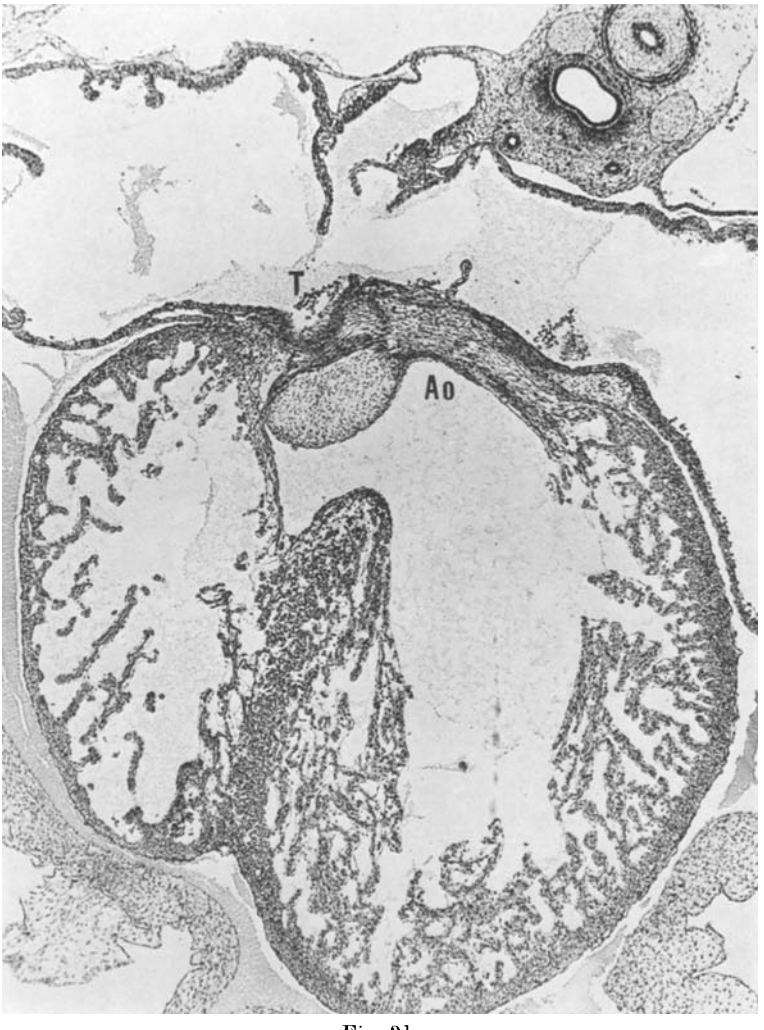

Fig. 3b

et al., 1961a, b, 1962). This fibrous discontinuity is found also in cases where the ventricular septum is intact (Ainger, 1965; Davachi *et al.*, 1968; MacMahon and Lipa, 1964; Oppenheimer-Dekker and Gittenberger-De Groot, 1971). In accordance with van Mierop and Wiglesworth (1963a) and on the basis of researches carried out by Bersch (1971) on the bulboauricular flange in man and stereomicroscopical observations on the development of this structure by Asami (1969), anomalous musculature between the mitral and the aortic valves may be considered as a muscular remnant of the bulboauricular flange. In the more primitive malformations of this category the bulboauricular flange can be recognized more distinctly (Bankl and Wimmer, 1971; Goerttler, 1958, 1963b). In cases where an intact ventricular septum is present, fusion of the ventriculars eptal crest with the bulboauricular flange can be assumed to have taken place.

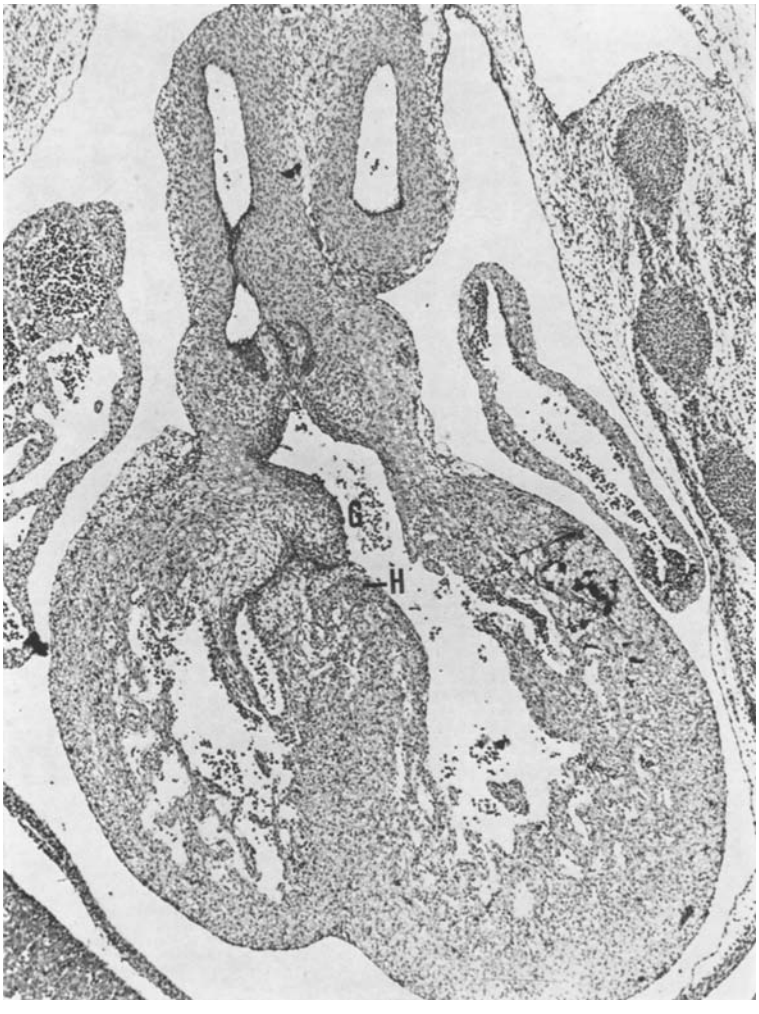

Fig. 4. Frontal section of the heart (human embryo in stage XVIII). In the centre, the fusion line is seen between the transversely cut counter-ridge *G* located, below the aortic valve, and the crest of the ventricular septum. Directly below this zone of fusion, the His bundle (*H*) is seen (about × 48, H-E)

III. Comments on Further Theories Pertaining to the Genesis of Transposition

a) The Theory of De la Cruz et al. (1956, 1959, 1962, 1967, 1971a, b; cf. also Anselmi *et al.*, 1963; Espino-Vela *et al.*, 1969, 1970)

Basically this theory corresponds to Rokitansky's concept (1875) in which a faulty anlage and development of the bulbotruncal septum are assumed to be the cause of transposition. According to De la Cruz *et al.* the normal origin of the great vessels is determined by a bulbotruncal septum winding in a 180° spiral,

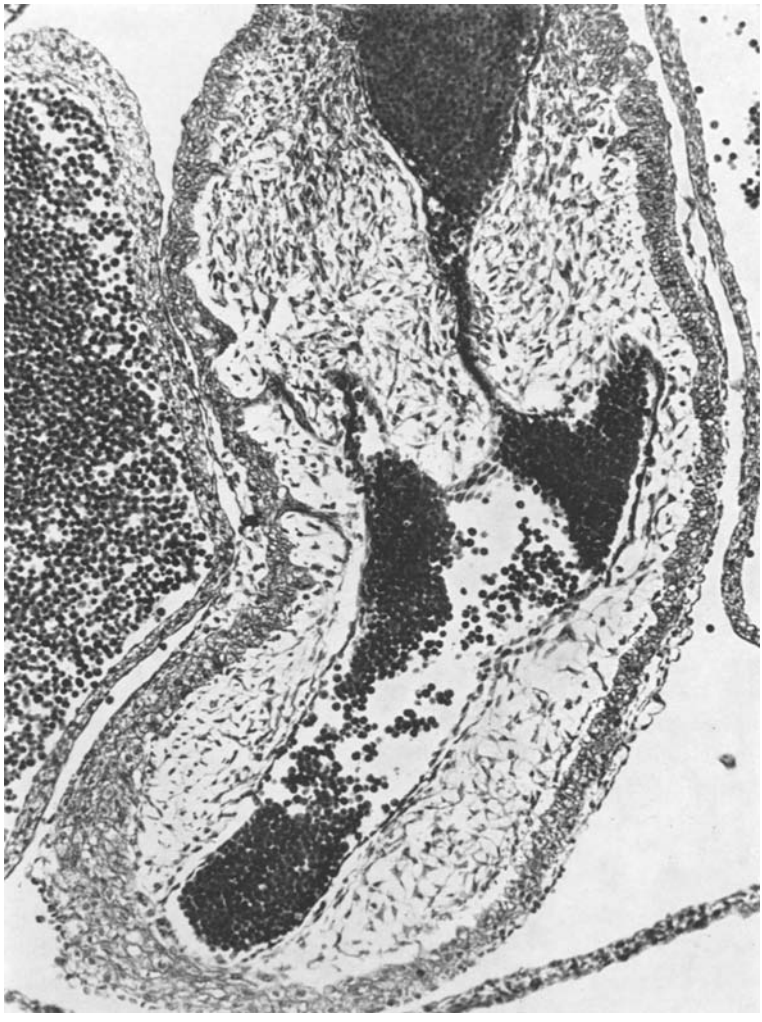

Fig. 5. Human embryo in stage XV; segment of the bulbus. At the top the distal, at the bottom the proximal bulbar swellings. At both sides there is a thick layer of subendocardial reticulum between the bulbar swellings *B* and I (to the left in figure) as well as between *A* and III (to the right) (about × 100, H-E)

whereas the transposition is caused by the development of a straight bulbotruncal septum. As stated by van Mierop and Wiglesworth (1963 b), this anomalous septum would develop as a result of a premature appearance of the distal bulbar swelling II and IV. However, the anomalous truncal septum—as previously described—is not to be regarded as the *cause* but as the *result* of arrested bulbotruncal torsion. The torsion at the bulbotruncal orifice produces different effects on the bulbus and the truncus respectively: at the truncus it determines the spiral course of the already structured septum, and at the bulbus the almost

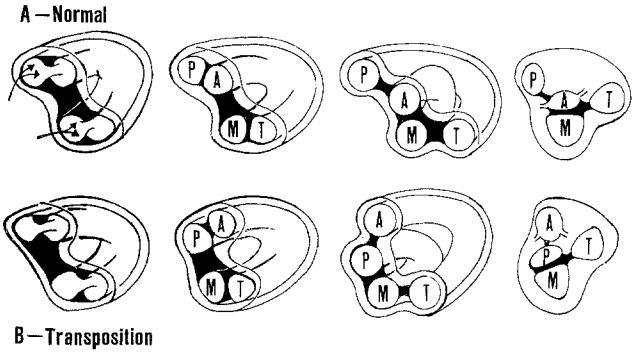

Fig. 6. Schematically illustrated development of the heart skeleton and the resulting positions of the valvular orifices according to Grant. Top view (arterial trunks and atria not outlined). The upper row shows normal development, the lower that of transposition (for more details see text). (After Grant, 1962a, modified)

straight course of the ridges A-I and B-III. In this context note should be taken of Los' investigations (1966, 1968). This author likewise attributes the helical course of the truncal septum as being due to the torsion of the truncus and not to a primarily spiral-structured septum. The straight septum of transposition and the consequent lack of twisting of the vessels is therefore not the *cause*, but the morphologic symptom of this anomaly. De la Cruz *et al.* and Rokitansky ascribe both pulmonary and aortic stenosis to an asymmetrically structured, i.e. laterally displaced, truncal septum. Further discussion of this hypothesis is not necessary here, for it has already been analyzed in detail by Barthel (1960), Bredt (1936), Doerr (1955a), and Goerttler (1958, 1963b).

b) The Concept of Grant (1962a, b)

Grant's theory is not related to any of the currently known concepts pertaining to the nature of transposition. For the purpose of explaining the ultimate position of the great vessels in the normal heart and in particular of the close relation of the aortic orifice with the mitral valve, Grant lays down two fundamental theses:

1. The myocardium has a greater growth activity than the fibrous tissue of the heart.

2. A fibrous continuum is located at the concavity of the cardiac loop.

According to Grant, this fibrous mass grows from the external surface into the bulbotruncal region and into the auricular canal. Thus, on the one hand development of the truncal septum would take place, and on the other the fibrously interconnected orifices form at the venous and arterial ends of the heart. The major portion of this fibrous continuum extends normally between the prospective aortic orifice and the future mitral valve. After formation of the different valvular orifices the growth activity of this fibrous mass ceases, whereas the myocardium continues to grow fast (Fig. 6). Due to the fibrous matrix the aortic orifice is fixed to the mitral valve, while the pulmonary orifice is shifted away

from the atrioventricular valves by the myocardial growth. Hence, transposition would now be due to an anomalous shift to the left of the fibrous tissue continuum, the major portion of which would expand between the prospective pulmonary orifice and the future mitral valve (Fig. 6). According to this concept, bulbotruncal septation takes place normally in the case of normotopic great vessels as well as in transposition. Hence, according to Grant, the essential morphologic equivalent of transposition is the absence of the fibrous continuity between aortic and mitral valves.

Comments on Grant's concept:

1. According to Los (1966), the truncal septum is actually formed by fibrous tissue penetrating from the external surface; he fails, however, to verify the existence of the postulated fibrous continuum between the bulbar ridges and the endocardial cushions during the critical developmental stages of the heart (see also Asami, 1969). Contrary to Grant's theory, during these developmental stages the *muscular* bulboauricular flange lies between the endocardial structures of bulbus and the atrioventricular endocardial cushions, and the continuous transitional musculature extends between the atria and ventricles (Chuaqui, 1972). The muscular tissue does recede progressively at these sites, however, without revealing the required *penetration* of fibrous tissue.

2. Experiments on chicken embryos have revealed—as Grant postulates—that the growth activity of the myocardium is greater than that of the endocardium (Grohmann, 1961). These results rather indicate that the formative factors can be ascribed to the myocardium and not to the highly plastic embryonal fibrous tissue.

3. According to Grant, the prospective aortic orifice represents, from the very beginning, a fixed centre around which only the pulmonary orifice revolves. Consequently, the movement of the aortic orifice is only apparent and not real (Grant, 1962a). Contrary to this concept, the stereomicroscopic studies by Asami (1969) unequivocally demonstrate that the aortic orifice migrates from the right ventrally to the left dorsally during bulbotruncal rotation.

4. Displacement of the cardiac skeleton, as the pathogenetic principle of transposition which, moreover, can hardly be explained by the effect of peristatic factors, renders it difficult to understand the multiple transitional forms. Malformed hearts showing *different* positions of the arterial orifices *despite* the lack of mitro-aortic fibrous continuity (e.g. double outlet right ventricle) remain unexplained.

5. Even authors who have accepted the criterion of an absent mitroaortic fibrous continuity as the basic morphologic manifestation of transposition have not succeeded in coordinating this symptom with the position of the arterial trunks and thus have not been able to develop a consistent terminology (cf. van Praagh and van Praagh. 1967; van Praagh, 1971; van Praagh *et al.*, 1971).

c) The Conal Growth Hypothesis by Van Praagh and Van Praagh (1966)

The conal growth hypothesis by van Praagh (van Praagh and van Praagh, 1966, 1967; van Praagh *et al.*, 1967, 1971) is closely related to Keith's theory of bulbar atrophy (1909). Keith assumes a symmetrical cardiac loop located in the sagittal plane. The normal or transposed position of the great vessels then depends

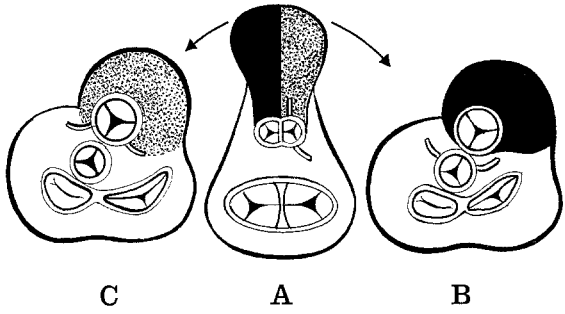

Fig. 7. Schematic representation of normal and transposed arterial orifices according to Keith. Top view (arterial trunks and atria not outlined). A: primitive stage, B: normal development after atrophy of the right bulbar portion (dotted), C: transposition due to the absorption of the opposite bulbar area. (After Keith, 1909, modified)

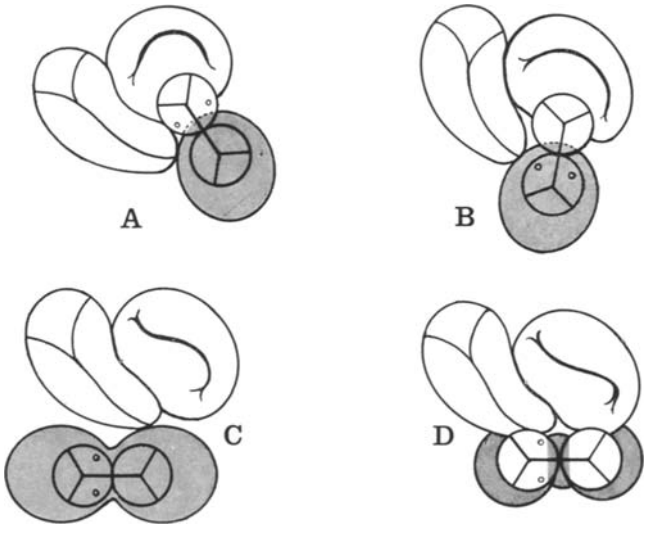

Fig. 8. Development of the conus musculature according to van Praagh. A: normal case, B: subaortic conus in transposition, C: anomalous bilateral conus, D: bilaterally deficient conus (after van Praagh and van Praagh, 1967, modified)

on whether the right (normal position) or the left (transposition) portion of the bulbus recedes (Fig. 7).

Analogous to the above concept, van Praagh interprets the different positions of the great vessels as resulting from conal musculature development; in the normal heart conal musculature develops solely below the pulmonary orifice (subpulmonary conus), whereas in transposition it develops below the aorta (subaortic conus) (Fig. 8). Van Praagh distinguishes two additional developmental possibilities of the conal musculature, i.e. the absence of conal musculature (absent conus) on the one hand, and its development below both vessels (bilateral conus) on the other. For the present, it should be emphasized that neither van

Praagh's nor Keith's opinion contradict Doerr's concept. As shown in Fig. 7, it is the absorption of part of the bulbus that causes a torsion of the great vessels which can be interpreted as bulbotruncal rotation. According to Keith's diagram this torsion takes place, in case of transposition, in exactly the opposite direction to that in the normal case. Van Praagh himself has pointed out that the great arteries of the embryonal heart are normally "transposed" (aorta on the right and pulmonary artery on the left). They would then, however, *due* to the development of the conal musculature, and depending of which cone develops, be caused to turn from this initial position to a normal pattern or to maintain the pathological one. These two theories, as well as Grant's interpretation, represent an attempt to explain causally the formal changes at the arterial end of the heart. They so belong to a cognition level different from Doerr's *formal* concept. The causes for these changes are—according to Grant, Keith, and van Praagh—the topographic growth differences of the myocardium. This concept is in agreement with Doerr's interpretation. This author, as early as 1955, emphasized that more likely the causes for vectorial bulbus rotation were better sought for in the growth differences of the myocardial mantle (Doerr, 1955a). A simplified model of the bulbus movements caused by these growth differences has been postulated by Bremer (1942), and Robertson (1913/14) also explains some forms of transposition in a similar way. Though different growth activities of the embryonal myocardium have been experimentally verified by various methods (Goerttler, 1956a; Grohmann, 1961; Sissman, 1966; Stalsberg, 1969), further research work needs to be done in order to coordinate more accurately such topographic growth differences with the formal changes at the arterial end of the heart. Furthermore, it is obvious that the transformations of the bulbar musculature, as assumed by Keith and van Praagh, become manifest, at least to some extent, in the phenomena of the bulbus shrinkage. The question as to whether vectorial bulbus rotation is caused solely by bulbus shrinkage has not, as yet, been clarified. Such a shrinkage has been stereomicroscopically detected only in the last developmental stages. Doerr's and van Praagh's concepts could complement each other. However, it should be pointed out that, contrary to the conal growth hypothesis, which up to now has been outlined in only purely schematic form (Fig. 8) in the available literature, vectorial bulbus rotation has been verified by Goerttler's (1955, 1956a, b) and Asami's investigations (1969). Furthermore, van Praagh assumes, with reservations, that the pulmonary conus in the embryonal heart is located dorsally in relation to the aortic conus (van Praagh and van Praagh, 1966). Neither the primitive musculature nor its intermediary stages have been documented in embryonal sections or schematically outlined in detail. Moreover, the somewhat unique concept postulated by van Praagh regarding the crista supraventricularis renders the conal growth hypothesis difficult to understand: the pars parietalis cristae—the actual crista according to van Praagh—corresponds to the "distal conus", the pars septalis to the "proximal conus" (van Praagh and van Praagh, 1966; van Praagh, 1968). The pars parietalis is not considered to be an intrinsic component of the right ventricle, only the pars septalis is a characteristic part of this chamber. In other words, the pars parietalis cristae could thus appear below the aortic annulus in certain malformed hearts and belongs to the left ventricle. Hence, subaortic musculature, which lies above a

ventricular septal defect and is not distinguished from the normal subaortic musculature, is defined as crista supraventricularis (van Praagh, 1971; van Praagh *et al.*, 1971). This "displaced crista supraventricularis" obviously corresponds to the musculature of the counter-ridge, which can be observed between His' bundle and the aortic conus (Bersch, 1972; Bersch and Chuaqui, 1972; Chuaqui and Bersch, 1972). Van Praagh considers the classical concept of the crista supraventricularis as being absolutely unacceptable (van Praagh and van Praagh, 1966), however, his new concept has not been substantiated embryologically.

d) Bankl's Remarks about Doerr's Concept (Bankl, 1971a, b; 1972)

Bankl's objections to Doerr's concept are as follows:

1. The vectorial bulbus rotation is based on hypothetic assumptions and not on proven facts of cardiogenesis.

2. Bremer (1931/32) and Rychter and Lemez (1957, 1958) do not attribute particular importance to the blood stream as being a formative factor for cardiac septation. Bankl's opinion is that the cardiac septa should be considered as structures whose independent development is the sole cause of the final location of the arterial vessels.

3. The overriding aorta is explained solely by the absence of a muscular support of its annulus (Bankl, 1971a, b). The Eisenmenger complex and the tetralogy of Fallot do not, therefore, belong to the teratologic series recognized by Doerr.

4. In comparison to Doerr's concept, the conal growth hypothesis represents a more precise and simpler explanation of transposition and its related malformations.

These points are worthy of further discussion:

Ref. 1. Previous accounts of vectorial bulbus rotation, based on proven facts of human cardiogenesis, can be accepted as a satisfactory basis for Doerr's concept. The high growth activity of the embryonal myocardium implies that this tissue is particularly sensitive to damaging factors. The pathogenetic principle of an arrest of vectorial bulbus rotation is essentially based on this fact.

Ref. 2. In the case of one chicken embryo, Bremer (1931/32) found that the atrial septum, not however that of the ventricles, develops after excluding a vitelline vein from the circulation. Less importance was therefore attached to the blood stream as a formative factor of the *atrial septum*. Recent investigations on the development of the atrial septum in anuran and chicken embryos, are however, not in agreement with this isolated observation by Bremer (Jaffee, 1962, 1963, 1965). Rychter and Lemez (1957, 1958) have been engaged in experimentally producing cardiac anomalies and have come to the conclusion that localized mechanical interferences produce secondary changes in the development of the cardio-vascular system as a result of *hemodynamic* distrubances (Rychter and Lemez, 1957). Rychter points out that no anomalies of the heart could be observed after exclusion of one vitalline vein. In agreement with Goerttler, Lemez states that cardiac malformations develop mainly from a structural lesion of those parts of the myocardium that have a greater growth potential and are therefore much more easily damaged. That this is in fact the case and is in contradiction to Bankl's interpretation of Rychter's and Lemez' investigations, was substantiated

by these authors in 1958: „Vom Standpunkt dieser Theorie, die mit den Erfahrungen von Doerr und Durchströmungsversuchen von Goerttler im Einklang steht, haben wir uns mit der experimentellen Entstehung der Transposition von großen Schlagstämmen des Herzens beschäftigt" (Rychter and Lemez, 1958, p. 311; "On the basis of this theory, which is in accordance with the findings of Doerr, and the results of blood flow experiments carried out by Goerttler, we have studied the experimental production of transposition of the great vessels"). Regarding the significance of the blood stream as a formative factor in cardiac septation, see Barthel, 1960; Beneke, 1920, 1928; Bremer, 1931/32; Goerttler, 1956a; Romhanhy, 1952.

Ref. 3. It has already been shown that the anomalous connection between the annulus of the overriding aorta and both ventricles in the tetralogy of Fallot cannot always be explained by the absence of support to the annulus, and that such an anomaly results from a primary heterotopy of the vessel (Chuaqui, 1971). A similar anomalous connection between the aortic annulus and the right ventricle is also likely to occur in the Eisenmenger complex (Bersch and Chuaqui, 1972). Lev (1953) has also referred to such architectonic anomalies of the right ventricle in these malformations. Van Praagh *et al.* (1970) also point out that not every case of an overriding aorta can be explained by a ventricular septal defect and that in tetralogy of Fallot the aortic orifice is often rotated counterclockwise (as viewed from above). This deficient rotation is in complete agreement with Doerr's concept.

Ref. 4. The previously mentioned comments on van Praagh's concept reveal that the conal growth hypothesis supports rather than refutes vectorial bulbus rotation. We are of the opinion that it is the conal growth hypothesis and not Doerr's concept, as Bankl maintains, which requires more conclusive substantiation.

IV. Comments on the Terminology of Arterial Transposition

In our opinion, the main problem regarding transposition lies in understanding of its genesis and not so much in precise terminological designations of its multiple forms. Even simple numbering of the various prototypes would suffice in the classification of the different forms; however, such a classification would obviously not constitute an aid to the understanding of the genesis of transposition.

An important contribution to the simplification of the nomenclature has been made by van Praagh, who points out that isolated atrial inversion cannot occur (van Praagh and van Praagh, 1964). Purely schematic descriptions, in which every theoretically conceivable combination of inversion of the cardiac metamers with transposition (see Cardell, 1956; Shaher, 1963, 1964), can thus greatly be simplified (Chuaqui, 1969). The question of an isolated inversion of the bulbus requires further study; Raghib *et al.* (1966) are probably the first to have observed such an inversion, albeit in a primitive malformation. Coupled with this problem is the question of the morphological characterization of the ventricles. The atrioventricular valves do not seem to be sufficiently reliable structures (Honey, 1962; Goerttler, 1963b; Sato, 1914; van Mierop and Wiglesworth, 1963b; Walmsley, 1930/31).

Another important contribution to the elucidation of the problem of inversion has likewise been made by van Praagh and van Praagh, 1966, 1967): the first

two clear-cut accounts of cases in which isolated ventricular inversion occur (for pertinent transitional forms, cf. Lev and Rowlatt, 1961; for isolated ventricular inversion in situs inversus, cf. Espino-Vela *et al.*, 1970). These cases demonstrate that the inversion of the ventricles constitutes an independent phenomenon that is not formally related to transposition. In agreement with De la Cruz *et al.* (1967, 1971) we are of the opinion that corrected transposition is a *combination* of ventricular inversion and crossed transposition and not a *special* from of transposition (Chuaqui, 1969; regarding the formal genesis of ventricular inversion, see De la Cruz *et al.*, 1967, 1971; Dekker *et al.*, 1965; Grant, 1964; Goerttler, 1958, 1963b; Geipel, 1903; Lewis and Abott, 1915; Lochte, 1898; van Mierop and Wiglesworth, 1963b; van Praagh and van Praagh, 1964).

As to which anomaly is to be considered the essential morphological symptom of transposition depends on the corresponding concept of its genesis. Grant and van Praagh have deduced that the mitroaortic fibrous discontinuity is the characteristic feature. Accordingly, such cases showing no fibrous but muscular tissue between the mitral and the aortic valves as the only anomaly, were defined as anatomically corrected transposition (van Praagh and van Praagh, 1967). Recently, however, van Praagh *et al.* (1971) have reported cases of crossed transposition revealing a fibrous mitroaortic continuity across a ventricular septal defect. These new findings caused van Praagh to change his diagnostic criterion: on the basis of the conal growth hypothesis, which led first to the above concept of mitro-aortic fibrous discontinuity as being characteristic feature of transposition, he now concludes that transposition manifests itself in the reversed arterial-ventricular relation across the ventricular septum. On the basis of this new criterion the above cases of anatomically corrected transposition (van Praagh and van Praagh, 1967) can no longer be considered as transposition. Since the ventricular septum is regarded as the point of reference, the term *transposition* —according to van Praagh—must not be applied to such cases in which the septum fails to develop (regarding further malformations which, in the light of the above criterion, must now be excluded, see van Praagh *et al.*, 1971).

According to the concept which holds an arrest of the bulbotruncal torsion as the pathogenetic principle of transposition, this anomaly manifests itself in the parallel position of the great arterial trunks, i.e. in the absence of twisting. Consequently, transposition frequently, though not necessarily always, occurs in cases in which a ventricular septum is absent (Elliot *et al.*, 1963a, 1964) and in double outlet right ventricle (van Mierop and Wiglesworth, 1963b). Finally, it is incomprehensible why the terminology pertaining to transposition, whose genesis, as consistently stated by all the authors, is to be traced back to the bulbotruncal segment, must not only refer to this segment but also to the presence or absence of the ventricular septum. If the verb *transponere* is to be applied literally to this malformation, as van Praagh (1971), and van Praagh *et al.* (1971) propose, then it certainly proves to be inadequate since, according to van Praagh's definition, *transposition of the aorta* refers to this vessel, which initially lies on the right of the bulbus, as *not* having transgressed the level of the ventricular septum to the left: i.e. the aorta is *not transposed* to the left as would normally be the case. In this sense, the term would only apply to the pulmonary artery, which is in fact *transposed* from the right to the left in case of transposition. In the recently published cases of crossed transposition (van Praagh, 1971; van Praagh *et al.*,

1971) the truncal septum is—according to these authors—not straight but spiral. The illustrations show, however, that *despite* marked dilatation and ventral bulging of the pulmonary artery, the ascending aorta and the pulmonary trunk are parallel. These secondary changes of the pulmonary artery appear to be the reason why van Mierop (1971)., who insists on a ventrally situated aorta and a dorsally located pulmonary artery as being requisite for transposition, does not consider these cases as transposition. According to Doerr's concept, these cases do involve a transposition. However, the possibility cannot be ruled out that the different positions in the dorso-ventral direction of parallel arterial trunks (Elliot *et al.*, 1963b, 1966), may not be caused by additional changes of these vessels, e.g. dilatations, hypoplasias or even by rotation of the heart *in toto*.

Because of the nature of the phenomena, difficulties will always be met with when searching for distinctly separated manifestations in a biologic continuum.

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