Doerr's theory of morphogenesis of arterial transposition in light of recent research

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SUMMARY Doerr's theory of the morphogenesis of transposition is discussed with special reference to recent studies by Goor and co-workers and Anderson and associates. The views advanced by all these authors coincide in three points: (a) the description of the reorganisation process occurring at the arterial end of the embryonic heart (a process called by Doerr vectorial bulbus rotation); (b) the pathogenetic interpretation of transposition as the result of an arrest of vectorial bulbus rotation; (c) the recognition of a teratological series or spectrum of anomalies pathogenetically related to transposition. Vectorial bulbus rotation is explained mainly as the result of three largely simultaneous events: bulbar shift, bulbus torsion, and truncus torsion. The spectrum of anomalies related to transposition appears as a close-knit series. Bulbar retraction does not seem to be a necessary condition for the connection of the aorta to the left ventricle.

During the 1970's, Goor and associates in the United States (Goor *et al.*, 1972; Goor and Edwards, 1973; Goor and Lillehei, 1975) and Anderson *et al.* (1974a, b) in Britain have developed similar theories concerning the morphogenesis of transposition, which coincide in their main features with that formulated by Doerr 26 years ago (Doerr, 1952). This concordance of 3 independent sources is the more significant, since Doerr's contributions to the subject (Doerr, 1952, 1955a, b, 1960, 1970) seem to have been unknown to the later authors. There is also a remarkable similarity in the arguments used by Doerr (1938, 1943) and by Anderson's group (Anderson *et al.*, 1974a; Macartney *et al.*, 1976) to refute the pathogenetic concept of the straight bulbotruncal septum (Rokitansky, 1875) which in recent years has been postulated by de la Cruz and Pio da Rocha (1956) and de la Cruz *et al.* (1959, 1967, 1971).

Agreement exists on 3 essential points:

(1) The morphological features of the reorganisation occurring at the arterial end of the embryonic heart, a complex process denoted by Doerr *vectorial bulbus rotation* (see Fig.); (2) an arrest of this process as the main pathogenetic mechanism causing transposition; and (3) the existence of a teratological series, or spectrum, of anomalies pathogenetically related to transposition.

However, Anderson and associates depart from Doerr and from Goor and co-workers in assigning a similar significance to bulbar shrinkage as bulbar atrophy has in Keith's theory (1909), to which Van Praagh's conal growth hypothesis (Van Praagh and Van Praagh, 1966, 1967; Van Praagh *et al.*, 1967, 1971) is also related (cf. Anderson *et al.*, 1974a; Chuaqui and Bersch, 1973). But Van Praagh's concept of *conal inversion* (Van Praagh and Van Praagh, 1966)—(unfortunately, Goor and associates use the same expression with a very different meaning, namely that of the normal bulbotruncal torsion)—shows some relation to Pernkopf and Wirtinger's belief in the inverse development of the septum bulbi as the cause of transposition (Pernkopf and Wirtinger, 1933, 1935; Wirtinger, 1937). In fact, according to Van Praagh's definition of the conus (Van Praagh and Van Praagh, 1966), the position of the great arteries depends also on how the bulbar septum develops. This is why the objections of Goor and Edwards (1973) to the conal growth hypothesis are also valid with respect to the concept of (using Doerr's expression) the *septatio aberrans transponans bulbi*. With almost the same words as those used by Doerr (1955a), they conclude that transposition is determined before the bulbar septum develops, and that the presence or absence of a conus is incidental rather than causal. As for the contribution of Pernkopf and Wirtinger it is especially important to distinguish between its

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Fig. Diagram of the vectorial bulbus rotation (caudal view; ventral: top of the figure). I: initial state, II: end state. Outer circles: bulbotruncal orifice (solid line: aortic bed; broken line: pulmonary bed); inner circles: bulbometampullar orifice. α : bulbus displacement. O: a point of reference dorsal to the bulbotruncal segment. The combination of rotation of the bulbus around its long axis and rotation around the fixed point O resembles movement of a planet round the sun; hence the term vectorial bulbus rotation.

descriptive and its interpretative aspects, the former having been widely confirmed by several authors, including Doerr, but the latter representing the antithesis to Doerr's views (for a detailed discussion of this topic, see Goerttler, 1963).

Thus, viewed historically, theories on transposition have evolved in a cyclical manner, classical pathogenetic ideas re-emerging to be argued on a

more secure basis, though Spitzer's phylogenetic theory (1923), reformulated by Lev and Saphir (1945), in combination with Pernkopf and Wirtzinger's ontogenetic theory, seems to have remained separate from this evolution.

What follows in this brief paper is subdivided into 3 parts: comments on (a) vectorial bulbus rotation as verified in recent studies; (b) the concept of a teratological series with special reference to the spectrum of transposition; (c) the significance of bulbar shrinkage.

(a) Vectorial bulbus rotation

This complex process may be conceived as the result of 3 components which occur more or less simultaneously (Fig.).

(i) Leftward shift of the bulbus *in toto* with concomitant enlargement of the metampulla (horizons XIII-XVIII, de Vries and Saunders, 1962; Asami, 1969) and with shrinkage of the bulbus and elongation of the truncus (horizons XVI-XVIII, Asami, 1969; Chuaqui and Bersch, 1972, 1973; horizons XVI-XIX according to Goor *et al.*, 1972).

(ii) Torsion of the bulbus at the bulbometampullar orifice through 45° clockwise rotation (looking downstream) (horizons XV-XVI, Asami, 1969).

(iii) Torsion of the truncus at the bulbotruncal orifice through 150° counterclockwise rotation (looking downstream) (horizons XV-XX, Asami, 1969; Chuaqui and Bersch, 1972, 1973; through 90-110° according to Goor *et al.*, 1972).

The sequence of these events is illustrated in Table 1. For the timing of ventricular septation (development of ventricular septum, truncus and bulbus septation, and closure of the interventricular foramen) see de Vries and Saunders (1962), Asami (1969), Goor *et al.* (1970), and Chuaqui and Bersch (1972, 1973). However, some discrepancies exist about the data presented in Table 1. Thus, for example, the ventricular septum is already present in horizon XIII according to Goor *et al.* (1970). Completion of the truncal septum is variously

Table 1 Components of vectorial bulbus rotation and ventricular septation

Horizon*	XIII	XIV	XV	XVI	XVII	XVIII	XIX	XX
Ovulation age (days)	28	29	31	33	35	37	39	41
Bulbus shifting								
Bulbus torsion								
Truncus torsion								
Bulbar shrinkage								
Ventricular septum								
Truncus septum								
Fusion of bulbar ridges								
Closure of interventricular foramen								

*After Streeter (1945, 1948, 1951).

Table 2 Teratogenetic periods of main prototypes in transposition series

Horizon*	XIII	XIV	XV	XVI	XVII	XVIII	XIX	XX
Ovulation age (days)	28	29	31	33	35	37	39	41
Cor bulboventriculare								
Beuren transposition								
Complete transposition								
Taussig-Bing anomaly								
Tetralogy of Fallot								
Eisenmenger complex								

*After Streeter (1945, 1948, 1951).

thought to occur at the following points: horizon XVI (Goor *et al.*, 1972; Anderson *et al.*, 1974b), horizon XVIII (Neill, 1956), horizon XIX (O'Rahilly, 1971); bulbar septation is completed in horizon XVII according to Anderson *et al.* (1974b).

Before bulbotruncal torsion the bulbar ridges run in a conspicuously twisted spiral, whereas at the truncus a straight septum develops. Torsion of the bulbotruncal orifice produces different effects on these septa: at the truncus it causes the primarily straight-structured septum to become helical, and at the bulbus it considerably reduces the extent to which the ridges spiral; torsion of the bulbometamullar orifice and bulbar shrinkage also contribute to this last effect (Fig.) (cf. Los, 1966, 1968; Chuaqui and Bersch, 1972, 1973; Goor *et al.*, 1972; Anderson *et al.*, 1974b).

(b) Concept of teratological series

This concept was introduced by Schwalbe (1906) and applied to cardiac teratology probably for the first time by Spitzer (1923). In the following brief account, previous ideas (Chuaqui, 1971) are elaborated, taking into account Bersch and Doerr's recent contribution (1976).

It is to Doerr's credit that he recognised in the apparently heterogeneous group of malformations known as Eisenmenger's complex, Fallot's tetralogy, the Taussig-Bing anomaly, and complete transposition, the existence of a teratological series (Doerr, 1951), and inferred from it the morphogenetic relation between these anomalies (Doerr, 1952).

A teratological series is a set of developmental anomalies that may be thought of as varieties of a similar basic morphological pattern. The members of such a series are thus related to one another in their visible form. However, the great heuristic value of this concept lies in the fact that these various entities may each represent distinct manifestations of a similar disturbance occurring at different times in development, in which case the members of the series are also morphogenetically linked. The series is then limited, on the one extreme, by the earliest,

usually the most severe malformation, and on the other, by the last-occurring anomaly, representing the least deviation from normal. In the case of transposition, the morphogenetic accident involved is an arrest to a varying extent of vectorial bulbus rotation. The teratogenetic periods of some exemplars of this series are presented in Table 2 (cf Chuaqui and Bersch, 1972, 1973). Viewed the other way, analysis of the transposition series can serve to clarify the nature of a hypothetical, and complex, process of development, if this means that each member of the series has to be explained by a disturbance of that process. Such analysis then shows that the original series can be extended by additional entities which appear as transitional forms between the classical members (Chuaqui, 1969), for example, the cor bulboventriculare of Goor and Edwards (1972), equivalent to Goerttler's primitive laevocardia (1958, 1963, 1968), and Beuren's transposition (1960) (cf Chuaqui, 1969). This has happened more and more in recent years and the teratological series of transposition could now be described as a close-knit one in the sense that it is possible to conceive of a transitional anomaly between any two existing members. Thus, by the very recognition of the quasicontinuous nature of the series, one may infer that the underlying mechanism producing it ought to have the character of a biological continuum, as indeed a process of bulbus rotation has. This explains why it is impossible to categorise all its manifestations into a progression of well-defined, fixed entities; in systematisation one can only consider the intervals where well-recognised prototypes recur. Conventional distinctions seem of no decisive importance. In the Anglo-American papers concerning transposition and related lesions the expression *spectrum* or *continuous spectrum* of anomalies is used with a similar meaning to that of teratological series (Gessner, 1966; Gessner and Van Mierop, 1970; Lev *et al.*, 1972; Goor and Edwards, 1973; Anderson *et al.*, 1974a; Patterson *et al.*, 1974; Becker *et al.*, 1975; Rosenquist *et al.*, 1976).

From this approach it should not be concluded that the anomalous forms of the transposition series

represent normal stages of cardiac development; processes of adaptation occur and there are likely to be other and different disturbances of vectorial bulbus rotation (cf Goerttler, 1963; Chuaqui and Bersch, 1973; Anderson *et al.*, 1974a), thus multiplying the possibilities.

(c) Comments on significance of bulbar retraction

Bulbar shrinkage is a proven fact which is particularly evident in horizon XVII (Asami, 1969; Goor *et al.*, 1972; Anderson *et al.*, 1974b). According to Goor *et al.* (1972) it begins after bulbar migration when half of the truncal torsion is completed. Nevertheless, as Chuaqui and Bersch (1973) point out, it is difficult to establish whether bulbar retraction merely accompanies vectorial bulbus rotation or is partly a cause of it. Anderson *et al.* (1974a, b) adopted the second alternative in considering it to be the cause of bulbar migration, and thus assigned to it a decisive role in the connection of the aorta to the future left ventricle. A failure of bulbar retraction would then imply, besides persistence of the bulboauricular flange and a lack of mitral-aortic fibrous continuity, at least an overriding aorta. Until the case described by Bersch *et al.* (1975) it was impossible to know whether this introduction of an additional factor was correct or not, but here, as so often, teratology came to the rescue. These workers reported for the first time a malformation characterised by normally positioned great vessels, adult type morphology of the ventricles, except for a long muscular aortic conus measuring 4 cm, and absence of mitral-aortic fibrous continuity. Bulbar retraction, therefore, may be vital for the atrophy of the left portion of the bulboauricular flange and for the establishment of mitral-aortic fibrous continuity (cf Chuaqui and Bersch, 1973; Anderson *et al.*, 1974a, b), but this case shows that it is not a necessary condition for the connection of the aorta to the left ventricle.

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