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On the Importance of the Bulboauricular Flange for the Formal Genesis of Congenital Heart Defects with Special Regard to the Ventricular Septum Defects

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Summary. The development and fate of the bulboauricular flange are described from information obtained from the literature and from the author's own investigations which are based on serial sections of embryonic hearts from critical age groups and a wax-plate model.

The significance of the bulboauricular flange for congenital heart defects is discussed, and the importance of the bulboauricular ridge (complementary ridge — Pernkopf and Wirtinger, 1933) in ventricular septum defects is stressed.

The discussion leads to the proposal of classifying ventricular septum defects according to purely embryological views.

Finally, the classification is briefly compared with the schemes of Becu *et al.* (1956) and Kl. Goerttler (1960).

Introduction

In cardiogenesis, His' papers (1880, 1882, 1885), which describe essential embryonic heart structures in man, were the first to supply fundamental findings. We are in debted to Born (1889) for the nomenclature, still valid, of the most important elements and the earliest comment on the conditions of the septa in the human heart, including an instructive and detailed reproduction by the wax plate method which he introduced. Tandler's monographs (1913) supplied a homogeneous description of the entire process of cardiogenesis. Spitzer (1919, 1921, 1923, 1929) will always be remembered for his attempts at a phylogenetical interpretation of cardiogenesis and for having recognized the significance of hemodynamic factors for the non-autochthonous formation of the septum. Pernkopf and Wirtinger (1933, 1935) deserve special appreciation for having elucidated cardiogenesis even further by means of trying an ontogenetic interpretation, and above all for their extensive description and painstaking investigations of human embryonic hearts. They also provided important indications for the transformation of primitive heart segments as regards the definitive heart chambers and for the problem of symmetry. Kramer (1942) emphasized the unity of the bulbus-truncus segment and gave his opinion on the process of septation. The recognition of the formal principle of the vectorial torsion of the bulbus in the normal human heart and its central bearing on the most important heart malformations, also an intelligible explanation and a critique of the theories of Spitzer, Pernkopf, and Wirtinger are due to Doerr (1938, 1938/39, 1943, 1955, 1960). Goerttler (1954/55, 1958) proved the validity of hemodynamic blood stream effects on cardiogenesis, in particular on septation, and confirmed Doerr's principle by his perfusion experiments with glass models of embryonic human cardiogenic plates. Asami (1969) succeeded in presenting and demonstrating photographs of human embryonic hearts prepared under magnification, as well as verifying Doerr's principle.

I was unable to find in the literature any homogeneous presentation on the subject of the bulboauricular flange. For this reason, despite all important papers and contributions mentioned above, I have ventured to comment, in the interest of a better understanding of cardiogenesis, on the formal development of heart defects, with reference to the region described in normal cardiogenesis as "Konfliktzone" (conflictzone), (Fig. 1; Doerr, 1943; Shaner, 1951).

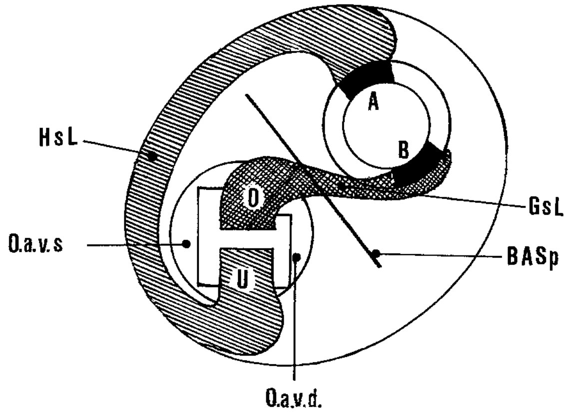


Fig. 1. Projection of the ventricle and the bulbus against the base of the chamber near the beginning of the vectorial torsion of the bulbus. The principal septum ridges (*HsL*) are shown from U to A and the complementary ridges (*GsL*) from O to B (Pernkopf and Wirtinger, 1933); the bulbus cushions A and B, the principal endocardial cushions U and A, and the plane of the bulboauricular flange (*BASp*) are also shown. *O.a.v.s.* ostium atrioventriculare sinistrum; *O.a.v.d.* ostium atrioventriculare dextrum. Modified according to Doerr (1943)

In attempting to solve this task, I posed three questions:

1) What is the bulboauricular flange?

2) What development stages does the bulboauricular flange go through?

3) What bearing has the bulboauricular flange on congenital heart defects, especially ventricular septum defects?

I aim in this paper to answer these questions after making the following investigations:

1) Taking essential literature into account in defining the bulboauricular flange and reviewing it.

2) The author's own investigations and documentation of the anatomic conditions of this region on the basis of serial sections of human embryonic hearts in the critical age groups and a heart model produced according to Born's wax plate method.

3) Conclusions based on these findings concerning the importance of the bulboauricular flange in congenital heart malformations, having special regard to the ventricular septum defects.

I. Description of the Bulboauricular Flange

The entire process of cardiogenesis in man takes place within about 25 days. It starts with the junction of a bilateral system, interspersed with gaps, to form the endothelial tube of the heart in Streeter's horizon X which equals a length of embryo of 2 mm 22 days after ovulation. This development is complete at the end of the embryonic period, i.e. in Streeter's horizon XXIII, at a crown-rump-length of 28–30 mm 47 days after ovulation.

It was Greil's (1902) achievement to have described the formation of the bulboauricular flange in reptile hearts as a structure homologous to human ones; this

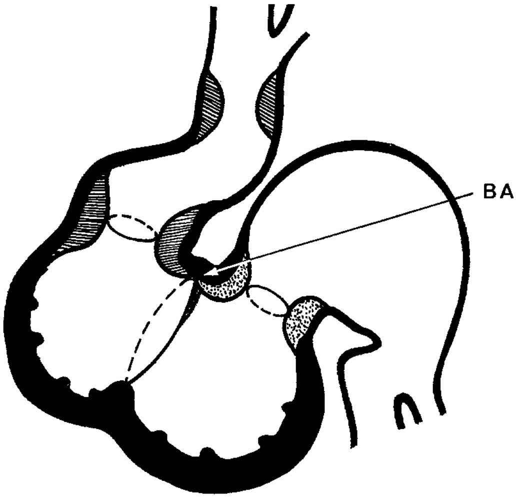


Fig. 2. First appearance of the bulboauricular flange (*BA*) as a sagittal ridge in the upper part of the interampullar ring. The flange passes between the endocardial cushion O (on the right) and the bulbus cushion B (on the left). Modified according to Pernkopf and Wirtinger (1933)

was confirmed by Benninghoff (1933). The first appearance of the bulboauricular flange is as a sagittal ridge (in the following sagittal always refers to the body axis and not to the heart axis). This ridge, being the upper part of the interampullar ring, subdivides the common ventricular space in the cranial direction (Tandler, 1913; Pernkopf and Wirtinger, 1933). It passes between the oval cross-section auricular canal on the left and the bulbus inflow tract on the right (Spitzer, 1928). The first trace of what will later be the septum interventriculare appears at the same time as an interampullar crest in the lower part of the interampullar ring (Tandler, 1913; Pernkopf and Wirtinger, 1933; Fig. 2).

As regards the age grouping, this development takes place in the embryonic stage at a crown-rump-length of 4.7 mm (Keibel's table of standards no. 14) or in Streeter's horizon XIII. This formation of the ridge, i.e. the bulboauricular flange is first conditioned by the shift in the position of the sinus and the primitive atrium in the cranial direction, which then causes a tilting of the ostium atrioventriculare about a frontal axis, and lastly by the sinking in the caudal direction of the bulboventricular roof which was originally dextroverted. The auricular canal and the bulbus tube are thus brought nearer to each other. At the outer relief of the heart, the bulboauricular sulcus corresponds to the bulboauricular flange. The bulboauricular sulcus is formed by the shifts described above ,while the bulboventricular sulcus, which formerly passed horizontally and is to be seen at the outer relief of the heart, assumes a more vertical position, and finally fuses with the depression at the right end of the auricular canal into the bulboauricular sulcus (Tandler, 1913).

Now the bulbus tube shifts to the left and ventrally, and the auricular canal to the right and dorsally (Pernkopf and Wirtinger, 1933). Due to this and the complex sequence of movements summarized as "vektorielle Bulbusdrehung" (vec-

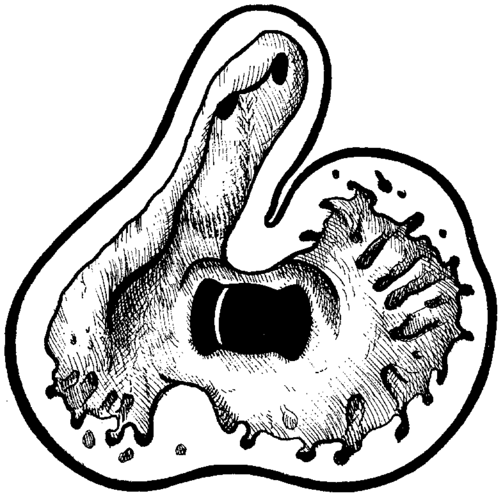
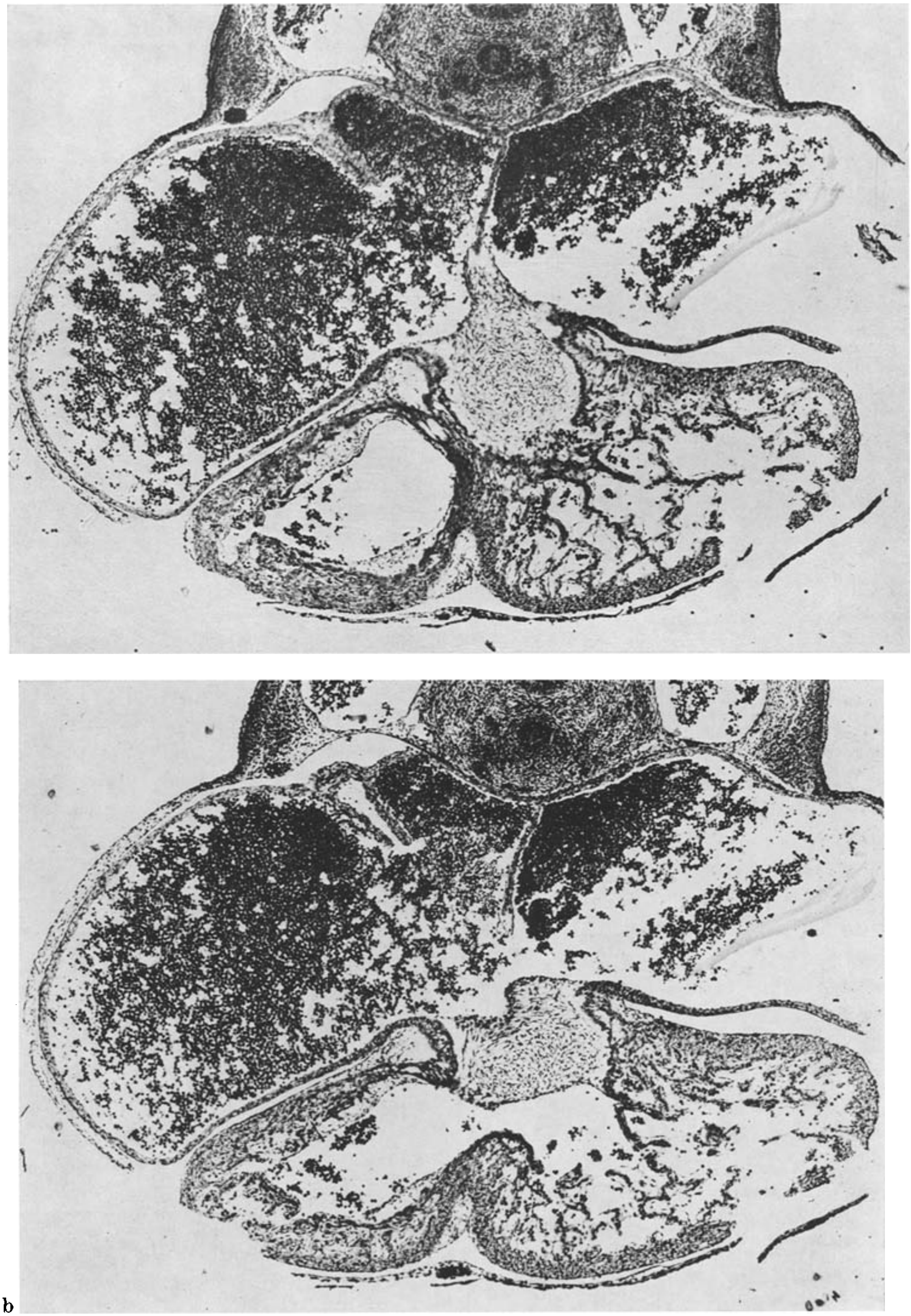


Fig. 3. More frontal course of the bulboauricular flange in the base of the chamber (shown as a line which is lightly concave downwards). Modified according to van Mierop *et al.* (1962)

torial torsion of the bulbus), (Doerr, 1955), the bulboauricular flange is not only forced out of its sagittal course, but is also highly compressed (Pernkopf and Wirtinger, 1933). The initially muscular tissue becomes largely fibrous (Pernkopf and Wirtinger, 1933). The bulboauricular flange is now seen in a more frontal plane, and divides almost in an "S"-shape the ostium atrio-ventriculare from the ostium ventriculo-bulbare. Thus the right curve, which is convex to the rear of the reclining "S", is the compressed tissue located between the bulbus cushion B and the endocardial cushion 0 (Spitzer, 1928). The bulboauricular flange now separates the inflow from the outflow tracts of the heart. Due to the development of the so-called aortic conus, the flange increasingly recedes upwards and backwards at the cardiac base while vanishing gradually behind it (Spitzer, 1928; Van Mierop, 1962; Asami, 1969; Fig. 3). This development can clearly be demonstrated in Streeter's horizon XVIII (Asami, 1969). To recapitulate: the bulboauricular flange changes its course from the sagittal to the frontal direction, its tissue developing from a primarily muscular to a secondarily largely fibrous tissue.

At the same time the proximal bulbus cushions, the principal endocardial cushions and the septum ridges are developing. A distinction must be made between the two principal endocardial cushions O, cranial and anterior, and U, caudal and posterior, on the one hand, and the proximal bulbus cushions A, ventral and left, and B, dorsal and right, on the other. The septum ridges are now developing into the principal ridge, passing between the endocardial cushion U and the bulbus cushion A, and the complementary ridge passing between the endocardial cushion O and the bulbus cushion B. The complementary ridge O–B is especially important because of its relationship with the bulboauricular flange. First, the part of the complementary ridge which runs to the endocardial cushion O becomes attached to the cranial and left side, and the part running to the bulbus cushion B becomes attached to the dorsal and right side of the bulboauricular



a

b

Fig. 4. a Almost sagittal course of the bulboauricular flange between the endocardial cushion O (on the right) and the bulbus tube with the bulbus cushions B (at the top) and A (at the bottom). (Serial sections of Streeter's horizon XV; HE stain; ×40). b From the right lobes of the endocardial cushion O and from the left branches of the bulbus cushion B accumulate at the bulboauricular flange. (Serial sections of Streeter's horizon XV; HE stain; × 40)

flange. In its later development it runs under the bulboauricular flange (Pernkopf and Wirtinger, 1933; Asami, 1969) thus forming an angle with the plane of the bulboauricular flange (Doerr, 1943, 1955). However, in the later development, the bulbus cushion B alsways remains to the right of this plane. The tissue called bulboauricular flange thus lies as a secondarily fibrous material above and behind the complementary ridge, along which the final closure of the foramen interventriculare takes place, due to a fusion of the principal and the complementary ridges with the joined endocardial cushions (Asami, 1969; Conte *et al.*, 1966; van Mierop *et al.*, 1962; Bredt, 1936, and others).

After these largely converging observations, the opinions in literature now diverge as regards the position of the bulboauricular flange in the "finished heart".

Thus Spitzer (1928) describes in the case L. Brings—which does not even concern the bulboauricular flange but a crista saliens as defined by Doerr (1959)—the course which the flange takes in the finished heart, as follows: It starts on the left at the aortic cusp of the mitralis and forms the basal part of this in its anterior section. The flange then passes on to the posterior margin of the septum membranaceum, forms the septum in its sagittal course forward, leaves it at its anterior border, and then ends along the anterior tricuspidal cusp. On the contrary Pernkopf and Wirtinger (1933) define the flange in the finished heart on the one hand as a secondarily fibrous margin and a component part of the heart skeleton, on the other hand they agree with Benninghoff (1933), Doerr (1955, 1960, 1967, 1970), Goerttler (1960, 1963), Odgers (1937/38/39) and others that the last remnant of the foramen interventriculare is closed by the fusion of the septum interventriculare with the basal part of the bulboauricular flange (Pernkopf and Wirtinger, 1935). Tandler (1913), as well as Pernkopf and Wirtinger, think one remnant of the flange is located in the crista supraventricularis.

II. The Author's Own Investigations

1. Material and Methods

Three human embryos (Streeter's horizons XV, XVIII, and XXIII), a human fetus (at a crown-rump-length of 80 mm), and a model reproduced from the fetal heart according to Born's wax plate method, are available for examination. The thoraces of the three embryos were separated from the head and abdomen, fixed in formalin and embedded in paraffin; serial sections, 6 μ in diameter, were made in the frontal direction and stained with HE. The thorax of the fetus (fixed in formalin) was dissected from its head and embedded in celloidin; serial sections, 30 μ in diameter, were made in the horizontal direction and stained with azan. The heart and the great vessels were reconstructed (enlargement X 25) according to Born-Peter's method; every other section was marked, the intermediate section being projected on to the preceding one for checking, the resulting diameter thus being 0.75 mm.

2. Development and Fate of the Bulboauricular Flange

a) Embryo of Streeter's Horizon XV: In this age group the bulboauricular flange is a strong, arched, muscular flange which projects from the cranial direction into the common ventricular space and has an approximately sagittal position. As a deeply incising ridge, it separates the bulbus from the auricular canal. De Vries' (1962) opinion that the concept of a bulboauricular flange is "speculation" remains all the more incomprehensible since he presents it himself. If one follows the flange in its sagittal course, delicate lobes of the already developed

Fig. 5. a Horizontal course of the bulboauricular flange whose two ends are to be seen: the one on the right between the left atrial wall and the developing mitralis; the other on the left between the right atrial wall and the endocardial cushion O. Between the two ends the remnant of the aorta. (Serial sections of Streeter's horizon XVIII; HE stain; $\times$ 27). b Fibrous plate of the fused endocardial cushions O and U, U lying broadly on the crest of the septum interventriculare. (Serial sections of Streeter's horizon XVIII; HE stain; $\times$ 27)

endocardial cushion O and the bulbus cushion B may be seen accumulating (Fig. 4a and b). Seen from the front to the rear, this accumulation occurs in the field of the endocardial cushion O on the cranial and left side, in the field of the bulbus cushion B on the dorsal and right side of the muscle cuneus. However, what is striking is that there is so far no connection between these branches. The appear-

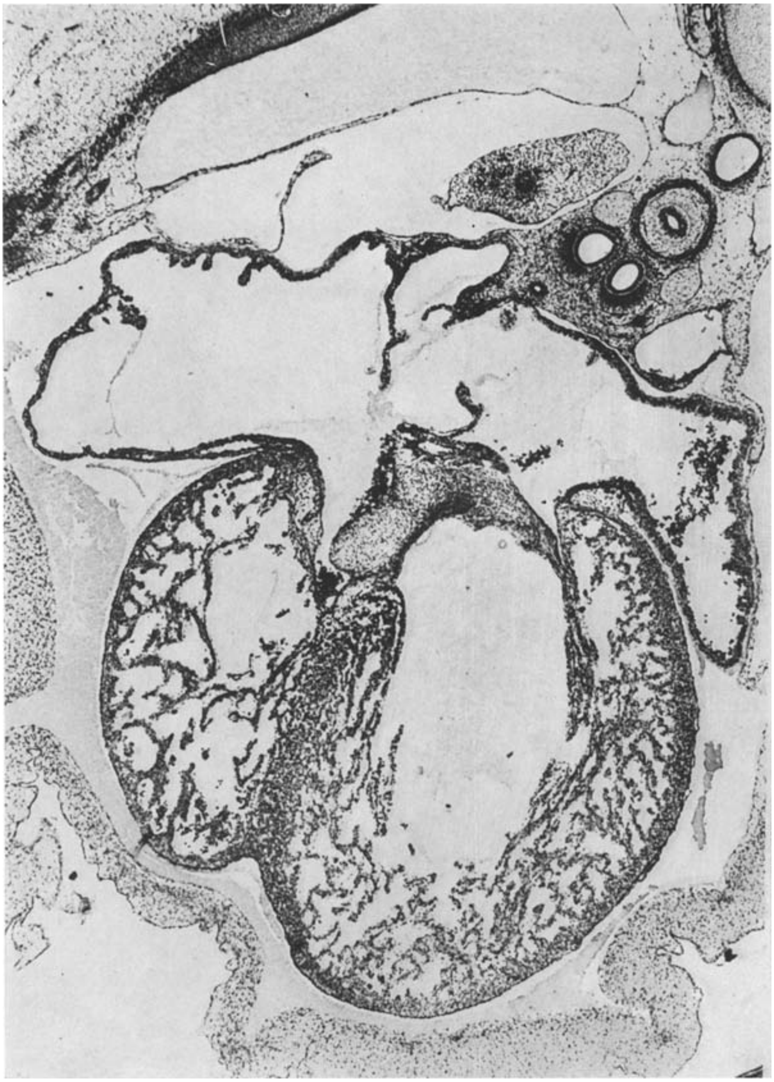


Fig. 5 b

ance of the septum interventriculare as an interampullar crest, on whose closing ridge (principal ridge) the anterior and posterior endocardial cushions already lie, may also be seen.

b) Embryo of Streeter's Horizon XVIII: Due to the vectorial torsion of the bulbus, which at this time is for the most part complete, the bulboauricular flange now passes in a largely frontal direction. A beginning transformation of its connective tissue can be observed, especially behind the developing aortic conus. The formerly almost sagittal ridge assumes the shape of a reclining, lightly curved "S", the curve, which is convex to the rear, lying between the bulbus cushion B and the endocardial cushion O, while the part curving in the frontal direction

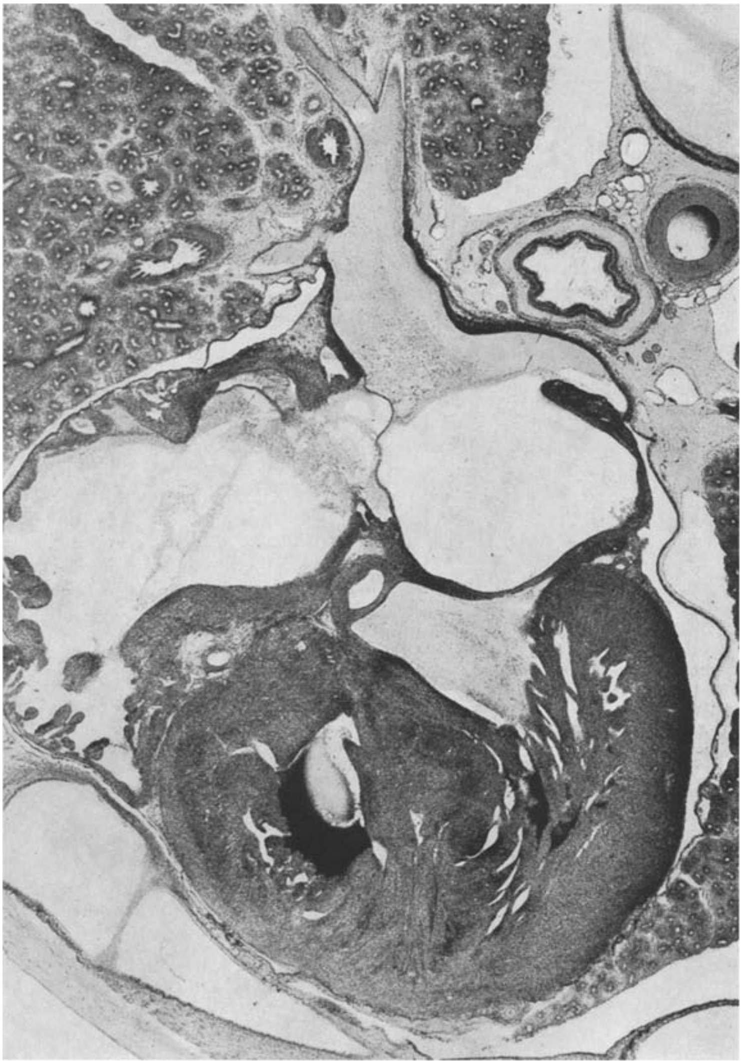


Fig. 6. a Course of the fibrous bulboauricular flange from the regio mitroaortalis (the lamella separating the left atrium from the aortic conus) behind the aorta to the right passing between the right atrium and the ventricle. (Serial sections of the fetus at a crown-rump-length of 80 mm; azan stain; × 25). b Region of the bulboauricular flange in the wax plate model which was constructed according to serial sections of the fetus at a crown-rump-length of 80 mm

passes in front of the developing tricuspidal orifice (Fig. 5a). At this stage, the two principal endocardial cushions have largely fused and form an arched plate which is open towards the ventricular chamber (Fig. 5b). The two proximal bulbus cushions A and B have fused here and there, though a raphe is clearly to be seen. To the rear, the right part of the lower endocardial cushion U lies broadly on the ventricular septum; to the front, the bulbus cushion A fuses with the ventricular

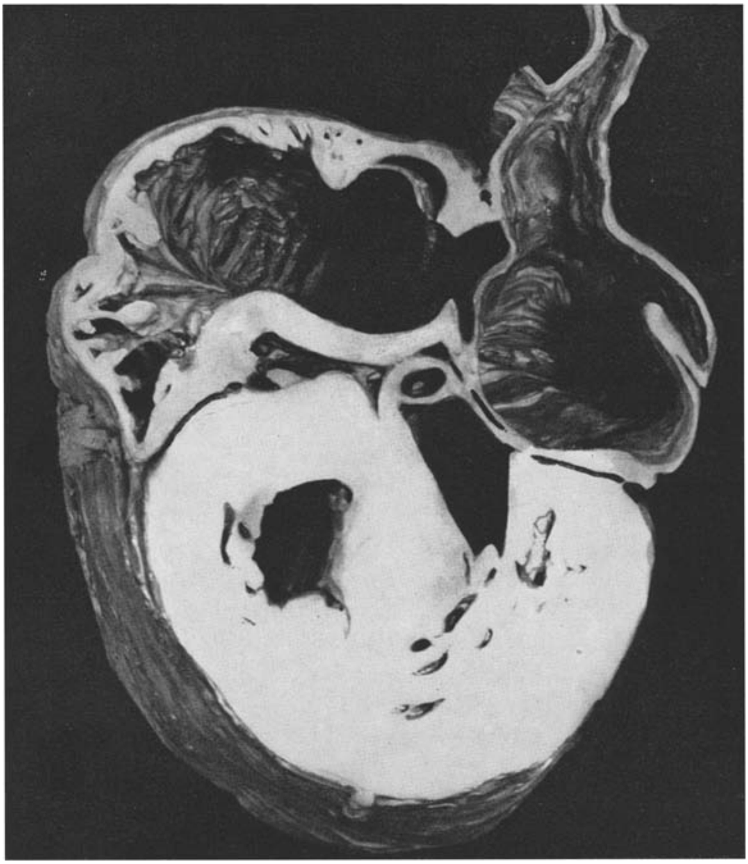


Fig. 6b

septum (principal ridge—Pernkopf and Wirtinger, 1933). A chord may be followed which passes as a continuous ridge from the bulbus cushion B to the principal endocardial cushion O (complementary ridge—Pernkopf and Wirtinger, 1933). This tissue formation runs under the bulboauricular flange from the right front to the left rear in a diagonal direction. It thus forms together with the flange a sharp angle which is open to the right front. The foramen interventriculare, which is already present at this stage, is thus bounded by the two right knobs of the former endocardial cushions O and U, the crest of the free margin of the septum interventriculare (principal ridge), and the branches of the fused bulbus cushions A and B (complementary ridge), but it is not bounded by the bulboauricular flange.

c) Embryo of Streeter's Horizon XXIII: The bulboauricular flange is here seen to be a chord which is placed frontally between the inflow and the outflow tracts and is largely fibrously transformed and compressed. Since its course is similar to the one described in Streeter's horizon XVIII, I do not give an extensive description.

d) Fetus at a Crown-Rump-Length of 80 mm and Heart Model: In this age group, cardiogenesis is already complete. I may thus apply the anatomic findings, which can be made here concerning the bulboauricular flange, to its position in the "finished heart". The remnants of the bulboauricular flange now stretch, as a fibrous cuneus, which is clearly to be seen when stained with azan, between the inflow and the outflow tracts. The top left of this fibrous lamella, which already comprises collageneous fibrous chords, is situated in the insertion margin of the septal cusp of the mitral valve, the remainder bending convexly to the rear and passing behind the aortic conus. Here, on the right side of the conus, branches run downwards and end near the septum atrioventriculare. On the right, the fibrous chord disappears between the origin of the anterior tricuspidal margin and the bulbus cushion B, whose position is identical with that of Luschka's muscle (Pernkopf and Wirtinger, 1933; Figs. 6a and b).

III. The Importance of the Bulboauricular Flange for Congenital Heart Malformations with Special Regard to the Ventricular Septum Defects

The bulboauricular flange is first sagittal and muscular, then changes its course in later cardiogenesis and is transformed into fibrous tissue. Its left end is identical with the regio mitroaortalis, its right end lies near Luschka's muscle. Since these findings indicate that the flange is largely enclosed in the so-called heart skeleton, it does not very often seem to be responsible for congenital heart defects. However, it may be assumed that with some early appearing malformations the developments of the bulboauricular flange as described above are arrested, but this is probably only part of a more extensive disturbance of cardiogenesis in the stage of the bulboventricular loop. In such cases, the heart always shows a kind of loop shape, and the regio mitroaortalis is underdeveloped. "A lack of continuity between the mitral and aortic valves" (Edwards, 1968). The malformation of the so-called double outlet chamber (Edwards, 1968) is an example of this. According to Neufeld *et al.* (1962), a distinction can be made between type I with a ventricular septum defect below the crista supraventriculare and type II which is identical with the Taussig-Bing-complex. The so-called primitive levocardia and dextrocardia (Goerttler, 1963) may also be given as examples. It would go beyond the scope of this paper to discuss to what extent this is only a question of the retardation of the bulboauricular flange or of a more complex process and hence a retardation of the vectorial torsion of the bulbus (Doerr, 1943, 1955), which for example could be due to an overgrowth or untimely persistence of endocardial tissue (Shaner, 1949/1951).

The situation is completely different as regards the complementary ridge (O–B; Pernkopf and Wirtinger, 1933). Since it passes from the bulbus cushion B to the endocardial cushion O thus presenting a clear and direct "bulboauricular" connection, it may in this sense be called the "*bulboauricular ridge*". In congenital heart defects, i.e. ventricular septum defects, special importance may be attributed to this bulboauricular ridge. For it passes, in addition, as has been described, beyond the bulboauricular flange, crossing it at a sharp angle which is open to the right (Doerr, 1943/1955) and thus, while fusing with the principal ridge,

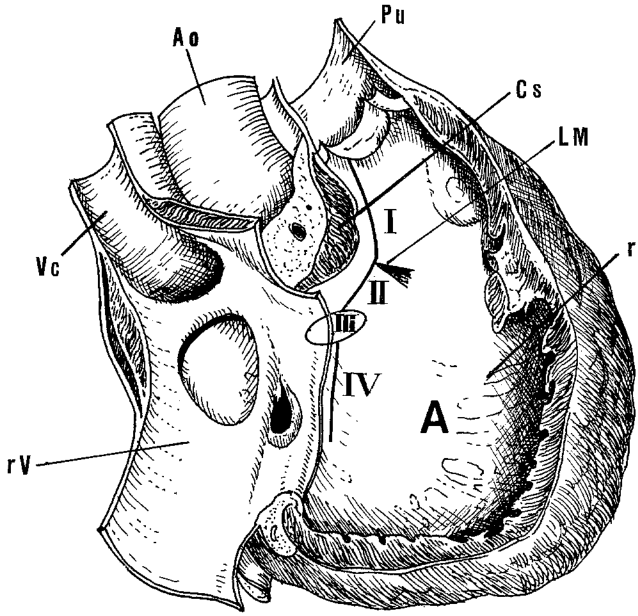


Fig. 7. View from the right of the ventricular septum in the finished heart, illustrating the classification principle of ventricular septum defects. *A* primary ventricular septum; *I* closure zone of the bulbus cushions; *II* raphe of the principal and complementary ridges (bulboauricular ridge); *III* pars membranacea; *IV* fusion zone of the joined endocardial cushions with the principal ridge; *Ao* aorta; *Pu* pulmonalis; *LM* Luschka's muscle; *Cs* crista supraventricularis; *rV* right atrium; *rK* right chamber

contributing largely to the closure of the foramen interventriculare as well as to the building up of the septum membranaceum.

If one considers the structure of this septal region of the heart from the front to the rear, it is simply a series of fusion zones and raphes of:

I. the bulbus ridges;

II. the bulbus cushions A and B;

III. the principal and complementary ridges (bulboauricular ridge);

IV. the principal and complementary ridges with the fused endocardial cushions;

V. the fused endocardial cushions O and U and the principal ridge with the endocardial cushion U.

Thus a classification of ventricular septum defects might perhaps be proposed according to the morphogenetical principle, namely defects of:

A. the primary ventricular septum;

B. the secondary fusion zones of the septum interventriculare:

I. the fusion zone of the bulbus ridges (between the anulus fibrosus and the crista supraventricularis);

II. the principal and complementary ridges (bulboauricular ridge; below and behind the crista supraventricularis);

III. the pars membranacea;

VI. the fused endocardial cushions with the principal ridge (behind the pars membranacea and below the septal cusp of the mitralis and the tricuspidalis), (Fig. 7).

Since it is difficult to define a point of reference of the final raphe of the bulbus cushions A and B in the finished heart—they may be supposed approximately at the height of Luschka's muscle, i.e. the fusion point of the pars septalis with the pars parietalis of the crista supraventricularis—this point has been omitted in the classification proposed above.

As already mentioned, the raphe zone between the principal and complementary ridges (bulboauricular ridge)—under B II in the above classification—deserves special attention since most of the ventricular septum defects are found in this region (Becu, 1956). Only the two most important classifications of those known so far of the ventricular septum defects shall be compared with the classification proposed above. The classification principle described in the following as the scheme of Becu *et al.* (1956) is based on investigations by Becu, Fontana, Du Shane, Kirklin, Burchell, and Edwards (1956). The other principle, described in the following as the scheme of Goerttler (1960) / Doerr (1967), was modified by Goerttler (1960) and revised by Doerr (1967); it was introduced by v. Rokitansky (1875) and Spitzer (1923) and slightly modified by Warden, de Wall, Cohen, Varco, and Lillehei (1956). If one compares these two schemes with what has been said above, the following may be stated:

The raphe mentioned under B II—which Doerr (1970) described with good reason as "Achillesferse" (Achilles heel)—is identical with the fossa subinfundibularis in the scheme Becu *et al.* (1956). Becu tries to localize this region by bounding it by the anulus tricuspidalis and an axis drawn through Luschka's muscle. This axis, which is drawn through a comparatively small point of reference, must show a wide range of variety if no second point can clearly be defined.

This raphe zone—mentioned above under B II—is identical with sections 3 and 4 in the scheme of Goerttler (1960) / Doerr (1967). It may be said to be generally agreed that most of the ventricular septum defects may be found in this region. Moreover, Goerttler (1960) is completely right in saying that the scheme of Becu *et al.* (1956) which, as is known, is based on projecting structures of the right chamber, is only little useful since these points of reference are too variable with larger defects.

The classification scheme introduced by Goerttler (1960) is a comprehensive system in which, however, two classification principles have been combined, an embryological and a topographical one.

The most important result of the statements given is the confirmation of the complementary ridge (Pernkopf and Wirtinger, 1933), here described as *bulboauricular ridge*. It is important because of its relationship on the one hand with the bulboauricular flange and thus the closure of the foramen interventriculare, and on the other with the region of the ventricular septum described by Doerr (1970) as "Wetterwinkel" (storm center), being the raphe where most of the ventricular septum defects are to be found. Perhaps a morphological gap has thus been closed as regards the classification principles of the ventricular septum defects.

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