FALLOT'S TETRALOGY

DEVELOPMENTAL ASPECTS OF TETRALOGY OF FALLOT

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In the normal heart the parietal band, crista supraventricularis and septal band of the right ventricle are continuous with each other forming an inverted U-shaped structure. The crista supraventricularis is always prominent, easily recognized as a saddle-shaped muscular structure lying immediately superior and in front of the tricuspid valve separating this valve from the right ventricular infundibulum. A small papillary muscle located at the junction of the crista supraventricularis and the septal band receives chordae tendineae from the anterior and septal cusps of the tricuspid valve. This papillary muscle, while constant in position varies greatly in size from being a small but well-formed structure, to being reduced simply to a small tendineous patch, particularly in adult individuals.

A number of tiny papillary muscles located at the postero-inferior border of the septal band receive chordae tendineae from the anterior half of the septal cusp of the tricuspid valve. Of these, the superior most is located behind and close to the medial papillary muscle. The septal band of the right ventricle in some hearts is well delineated and easily seen. In many others, however, particularly again in hearts of adult individuals, it is more or less completely incorporated in the ventricular septum and not at all well defined. Its position in both cases can still be recognized, however, by the position of the series of small papillary muscles noted above.

In tetralogy of Fallot the parietal band and the septal band are in their usual position but the crista supraventricularis is abnormal both in appearance and location (Fig. 1). It appears to be displaced anteriorly relative to the parietal and septal bands, particularly its septal extremity which in many cases appears to have formed a trabecula-like structure running parallel and antero-superior to the septal band. The normal inverted U-shaped structure, therefore, appears to have been broken up. The actual appearance of the crista supraventricularis in tetralogy of Fallot varies greatly. It may be large and stout but very often it is hypoplastic, sometimes to an extreme degree, particularly in those cases where the anterior displacement is marked. Because of the anterior displacement the right ventricular outflow tract is narrowed to a variable degree. In some cases the infundibular obstruction is very mild and in others it is extreme to the point of causing infundibular atresia.

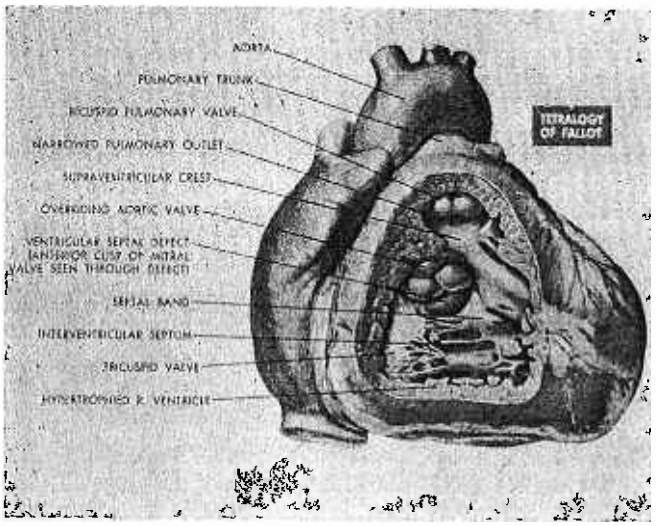

Fig. 1. Tetralogy of Fallot (reproduced from Netter1).

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A medial papillary muscle is not present in tetralogy of Fallot. Its function has been taken over by the superior most small papillary muscle of the series located along the posterior border of the septal band. Since in the normal heart this papillary muscle is located so close to the medial or conal papillary muscle it is often misinterpreted as actually being the medial papillary muscle in cases of tetralogy of Fallot.

A ventricular septal defect, almost always very large, is present behind the anteriorly displaced crista supraventricularis. As compared to the normal heart, the right coronary sinus of Valsalva of the aorta is located in a somewhat higher position, the cusp arising from the roof of the right ventricle, and the aorta can easily be entered from the right ventricle. In fact, in many cases of tetralogy of Fallot, particularly those where the infundibular stenosis is severe or extreme, the aorta appears to arise almost wholly from the right ventricle. In other words, overriding of the aorta is always present, sometimes to a very marked degree. In rare cases, the ventricular septal defect is obstructed by ectopic fibrous tissue resembling valve tissue. Such cases may functionally resemble severe right ventricular outflow obstruction with intact ventricular septum and lead to massive right ventricular hypertrophy to a degree not ordinarily occurring in tetralogy of Fallot.

The pulmonary valve is commonly, but not always, stenotic. Often it is cone-shaped with a small central or paracentral orifice, very often it is bicuspid. In about one-third of the cases, however, there is no obstruction at the pulmonary valvar level and in about half of these there is a normally formed, tricuspid pulmonary valve which may or may not be hypoplastic depending upon the severity of the infundibular obstruction and the degree of reduction of pulmonary blood flow. In slightly over one-fourth of cases of tetralogy of Fallot, the pulmonary valve is atretic and, in rare cases, it may be absent.

No one to date has had the opportunity of actually studying the pathogenesis of tetralogy of Fallot (or for that matter of any other congenital cardiac anomaly) by direct observation in human or other mammalian embryos. Still, a reasonably working hypothesis can be arrived at by correlating the findings obtained from the observation of normal and abnormal hearts with those acquired from the study of normal development of the human heart. Let us then briefly review the events which take place during the fifth and sixth week of human ontogeny, at which time cardiac septation results in a four-chambered organ from which arise the two great arteries, and the atrioventricular and arterial valves are formed.

In a human embryo of 4-5 mm. crown-rump (C-R) length, the heart externally resembles the adult condition with the two atria and ventricles indicated. Internally, however, only rudiments of the atrial and the muscular ventricular septum are present, otherwise the heart is still essentially a single, be it convoluted tube (Fig. 2a). The essentially common atrium still discharges its blood through a single ostium, the atrioventricular canal, into the left side of the bulboventricular part of the heart. This portion of the heart, already trabeculated at this age, will form the major part of the left ventricle and may be referred to as the primitive left ventricle. It communicates by means of a somewhat narrowed area,

the primary interventricular foramen, with the proximal, also trabeculated one-third of the bulbus cordis from which will develop a portion of the right ventricle and, therefore, may be referred to as the primitive right ventricle. The middle one-third of the bulbus cordis, from which eventually will develop the outflow tracts of both the right and left ventricle, is still completely devoid of any septa as is the truncus arteriosus which after partitioning will form the arterial roots and valves, the ascending aorta and the pulmonary trunk.

In embryos between 5-6 mm. C-R length, we see the almost simultaneous appearance of opposing masses of cardiac mesenchymal tissue in the atrioventricular canal, the conus cordis and the truncus arteriosus. Of these three pairs of swellings or cushions, those in the truncus arteriosus initially grow the fastest. In embryos of 6-7 mm., they have approached each other and have begun to fuse, thus executing the division of the truncus arteriosus into a pulmonary and an aortic channel. Growth of the atrio-ventricular endocardial cushions is somewhat slower and the conus cushions lag even further behind.

To accommodate the rapidly growing truncus cushions the truncus arteriosus at this stage of development has increased considerably in diameter while the right sixth arch has shifted somewhat to the left fusing with its opposite member forming a short common stem. At the same time the right posterior wall of the trunco-aortic sac between the origins of the fourth and sixth arches and distal to the truncus septum has begun to invaginate. The leading border of the invaginated portion of the trunco-aortic sac approaches the distal face of the developing truncus septum and eventually will fuse with it, thus completing the partitioning of the arterial end of the heart. Meanwhile, two smaller cardiac mesenchymal cushions have formed in the truncus arteriosus, one in the pulmonary channel and the other in the aortic channel. These minor swellings will eventually form the anterior cusp of the pulmonary valve and the posterior or non-coronary cusp of the aortic valve. The other two cusps of each of the arterial valves will be formed by the truncus swellings themselves (8-9 mm. embryo, Fig. 2b).

The atrioventricular canal cushions meanwhile have continued to grow and have begun to approach each other. Here, as in the truncus arteriosus, two additional, lesser cushions, the lateral atrioventricular canal cushions, have made their appearance on the right and left side of the atrioventricular canal and alternating in position with the major cushions. These will contribute to the formation of the tricuspid and mitral valves. The conus cushions continue to grow very slowly and have not yet begun to fuse, i.e., the conus cordis remains undivided.

In embryos of about 9-10 mm. C-R length, division of the truncus arteriosus and trunco-aortic sac have been completed while the primordia of the two arterial valves are clearly recognizable. At about this stage of development the atrioventricular canal cushions will fuse, thus executing the partitioning of the atrioventricular canal into right and left ostia. Meanwhile, the atrioventricular canal region, presumably by a process of differential growth, has shifted further to the right so that direct communication is established between the atrial portion of the heart and the primitive right ventricle. At the same time, the conus cordis has shifted to the left while the fold between the conus cordis and the primitive left ventricle, the bulboventricular fold or flange effaces. This allows blood from the primitive left ventricle to directly enter the conus cordis rather than having to go by way of the primary interventricular foramen and primitive right ventricle. Once this has been accomplished, the conus cushions grow more rapidly and fuse with each other and in turn with the already established truncus septum distally (16 mm. embryo, Fig. 2c). Thus, the conus cordis is divided into a postero-medial part which joins the primitive left ventricle to form its outflow tract, while the

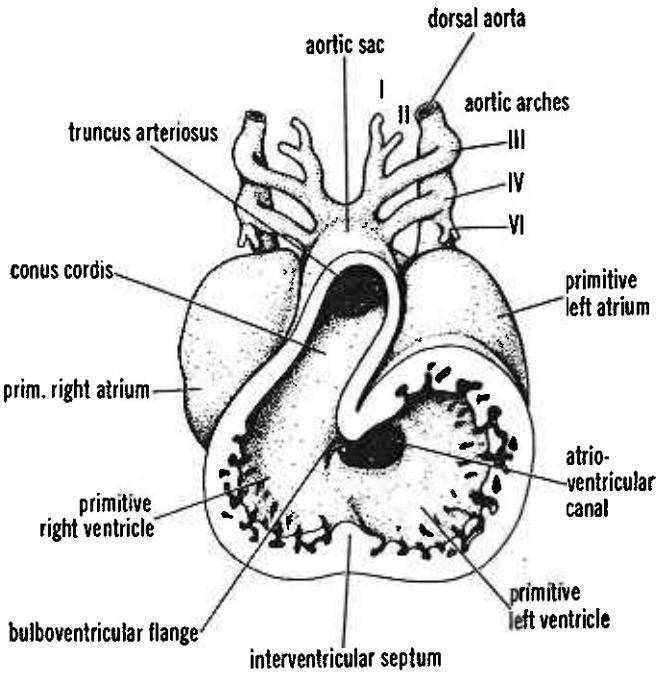

Fig. 2(a). Frontal section through the heart of a 5 mm. human embryo.

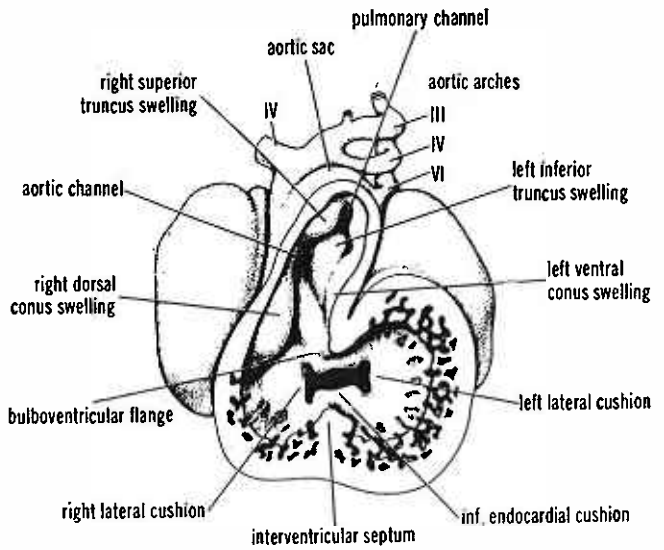

Fig. 2(b). 9 mm. embryo.

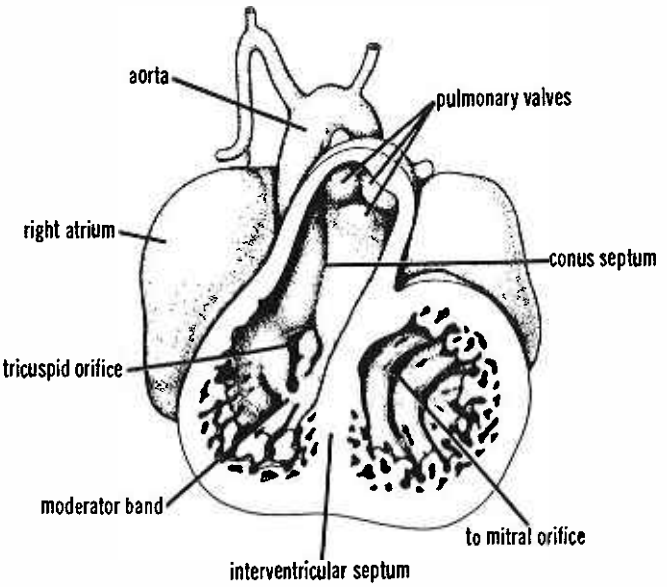

Fig. 2(c) 16 mm. embryo. (From Langman's "Medical Embryology"2, after Van Mierop3).

antero-lateral portion becomes the right ventricular outflow tract or infundibulum. The right-sided or dextro-dorsal conus cushion, because of the shift of the atrioventricular canal and the conus cordis, becomes continuous with the right lateral cushion of the atrioventricular canal while the left-sided, sinistro-ventral conus cushion grows downwards in a plane somewhat to the right of the primary interventricular foramen. It descends along the anterior part of the muscular ventricular septum, grows over the upper part of the septal band and becomes continuous with it. Thus, in actual fact, the primary interventricular foramen serves or comes to serve as the communication between the primitive left ventricle and the postero-medial part of the conus. To the right and posterior of the conus septum, a small communication is still present at this stage of development between the two ventricles. This may be called the secondary interventricular foramen. It will rapidly be closed by growth of the mesenchymal tissue from the conus septum and the right extremities of the two atrioventricular canal cushions, thus completing the ventricular septum.

The atrioventricular valve cusps are elaborated mostly from the wall of the two ventricles by a process of undermining and further trabeculation. On the left side this leads to the formation of the two mitral valve cusps. On the right side the first cusp to be elaborated is the anterior cusp of the tricuspid valve. After the conus septum has been formed and after its right side, i.e., the part arrived from the dextro-dorsal conus swelling, has become continuous with the lateral cushion of the atrioventricular canal, the process of undermining which develops the anterior tricuspid valve cusp extends into the right side of the conus septum. In this way the most proximal, leading portion of the conus septum is separated off the remainder of the septum and will form a small part of the anterior tricuspid valve cusp, the adjacent chordae tendineae and the medial or conal papillary muscle. The posterior cusp of the tricuspid valve is elaborated at about the same time while the septal cusp develops considerably later and will not be completely formed until about the third month of embryonic life.

It is easy to see what would happen if the conus septum would develop in a position too far anterior as compared to the normal:

1. The conus cordis would be divided into two unequal portions at the expense of the antero-lateral part, i.e., the part which normally becomes the right ventricular outflow tract. The result will be a narrowing of the right ventricular outflow tract, the degree of which depends upon the degree of anterior displacement of the conus septum. If the entire conus septum is displaced, a generalized narrowing of the entire infundibulum will result. If it involves mainly the proximal portion, a more localized type of right ventricular outflow obstruction is created while the more distal part of the infundibulum widens again to form an infundibular chamber.
2. The large interventricular communication cannot be closed resulting in a large ventricular septal defect.
3. The aortic valve, and more particularly the right coronary cusp, cannot descend far enough into the central part of the heart and the aorta continues to arise from the right ventricle to a variable extent, i.e., there is overriding of the aorta. In general, the more marked the anterior displacement of the conus septum, the more pronounced the aortic overide.
4. Because of the anterior displacement of the conus septum, its right extremity fails to become continuous with the right lateral cushion of the atrioventricular canal and it, therefore, cannot contribute to the formation of the anterior tricuspid valve cusp and the medial or conal papillary muscle is not formed. The left extremity of the conus septum does not become continuous with the septal band of the right ventricle but descends anterior to it along the right side of the muscular ventricular septum resulting in an apparent second septal band.

Almost certainly, at least in many cases of tetralogy of Fallot, not only the conus septum but also the truncus septum is displaced anteriorly. This may explain why in tetralogy of Fallot anomalies of the pulmonary valves, e.g., a bicuspid and/or stenotic pulmonary valve, are common. It also may explain why the aortic root and proximal part of the ascending aorta in tetralogy are unusually large and more or less cone-shaped.

Tetralogy of Fallot, therefore, may be thought of as due to a single embryological error: development of the conus septum (and probably usually also the truncus septum) in a plane too far anteriorly.

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