Tetralogy of Fallot With Absent Pulmonary Valve
Clarification of a Complex Malformation and of Its Therapeutic Challenge

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The many different fields of medical research can be categorized under three main headings: etiology (causes of diseases), pathophysiology (underlying mechanisms), and therapeutics (efficient ways to prevent or treat). In this issue of Circulation, the report by Momma et al1 on an experimentally created model of tetralogy of Fallot (TF) with absent pulmonary valve in rats is a remarkable example of research that succeeds in touching upon all the above-mentioned categories.

The etiologies of congenital cardiac malformations are generally considered multifactorial, with two predominant elements—genetic background and environmental influence. An important role is being increasingly ascribed to cranial neural crest cells in the pathogenesis of certain forms of congenital heart defects, especially conotruncal anomalies.2 Of interest is that the agent used in their study, bis-diamine, interferes with neural crest cells. Although the fact that the syndrome of TF with absent pulmonary valve could be created by administration of this chemical teratogen does not necessarily support the environmental factor as solely responsible for the appearance of this malformation in humans, it does make it a strong probable contributor. It remains to be seen whether the experimentally created malformation has all of the morphological features of the human syndrome. Neural crest–related heart malformations are known to be associated with defects involving glandular derivations of the pharyngeal pouches such as the thymus and parathyroids.3 Finally, the role played by the hemodynamic and flow–related effects of a primary lesion on its final morphology must also be taken into account. In this respect, it will be interesting to see whether bis-diamine can produce the same malformation in other species, particularly in animals with larger fetuses suitable for hemodynamic and ultrasonographic studies.

As far as the pathophysiology is concerned, it must be emphasized that this disease has been puzzling pediatric cardiologists and cardiac surgeons for years. It is agreed that the main element responsible for the morbidity of this malformation is the aneurysmal dilatation of the pulmonary arteries. Factors such as the orientation of the infundibulum6 or the degree of valvular stenosis4,5 have been held responsible, directly or indirectly, for this vascular dilatation. However, no specific comments and presumably no specific findings have been mentioned about the orientation of the infundibulum in the rats with TF and absent pulmonary valve. Furthermore, in the present study, the finding of a lesser degree of pulmonary arterial dilatation in the presence of most severe stenosis gives as much support to the post-stenotic dilatation theory as does the possible effect of volume flow into and out of the pulmonary arteries in the absent pulmonary valve syndrome. That frequently no trace of a ductus arteriosus can be found in TF with absent pulmonary valve, as observed in the rats with this syndrome, prompted the hypothesis that lack of decompression of the pulmonary circulation through the ductal outlet could be responsible for the intrauterine pulmonary artery dilatation.3 This theory, although attractive at first, has no real hemodynamic foundation. In the presence of a large ventricular septal defect, the pressure in the fetal pulmonary artery will never exceed the level of the systemic pressure. Without the normal valvular separation between the right ventricle and the pulmonary artery, the only consequence of an intrauterine closure of the ductus arteriosus is a massive shunting of blood flow from the right to the left ventricle through the unrestrictive ventricular septal defect. In these circumstances, the role of decompression of the right-sided circulation, usually played by the fetal ductus, is to some extent undertaken by the ventricular septal defect.4 It must also be kept in mind that

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rare cases of absent pulmonary valve with an identified patent ductus arteriosus have been reported. In these cases, however, dilatation of the pulmonary artery has also been documented. These observations and the massive sizes of the aneurysms sometimes observed in babies with this syndrome are arguments for the hypothesis that the dilatation of the pulmonary artery might be a primary event. Histological evidence of cystic medial necrosis of the pulmonary arterial walls has induced some researchers to draw a parallel between the pulmonary artery of the TF with absent pulmonary valve and the vascular wall structures described in Marfan syndrome. It will be interesting to see whether the same histological changes are present in the dilated pulmonary arteries of the rats.

Finally, will this report on animals help us adopt a rational therapeutic approach to this complex disease in human infants? The answer is deductive and, unfortunately, grim. One of the most striking findings in the fetal rat with TF and absence of pulmonary valve is the intrauterine presence of bronchial deformities and bronchi with smaller diameters than normal, suggesting a secondary (or primary) involvement of the bronchial tree as part of the syndrome. In these circumstances, isolated correction of the cardiovascular malformation will fail to prove of much benefit because of the persistence of pulmonary problems, even if early intrauterine correction is attempted. Only patients with mild lung impairment can be expected to be successfully managed; even then, they will have an uncertain long-term future. Such pessimistic views have been supported by studies that showed abnormal branching patterns of the pulmonary arteries in severely affected infants. These somber predictions were confirmed by a report on early and late results of surgical treatment showing combined early and late mortality of 58.3% in a group of 12 markedly symptomatic infants. Due to the relatively low incidence rates of these cases, multicenter studies appear mandatory to obtain a sufficient study population in a short period of time to determine the long-term cardiopulmonary status of the survivors.

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