

Editorial

Coxsackie virus infections and heart disease

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The causative factors of most congenital anomalies remain unknown in spite of voluminous literature published on the subject during the last three decades. The relatively large number of known determinants of abnormalities, such as genetic factors, chromosomal aberrations, endocrine disturbances, drugs and chemicals, radiation, physical injury, malnutrition, and infection, although well documented, leave more than 50 per cent of anomalous births unexplained. In fact, several recent surveys have estimated that less than 2 per cent of anomalous infants were known to have been exposed to proved teratogenic agents. One of the most frequently encountered abnormal conditions of the infant is congenital heart disease. This defect has been observed to occur approximately six times in every 1,000 live births.¹⁻³ As stated in a recent review by Higgins,⁴ the causes of malformations of the heart remain essentially unknown. The relative role of hereditary and environmental factors has been subject to considerable investigation in recent years,¹⁻⁵ but, with the exception of rubella virus, genetic factors, and recessive inheritance, little is known of the etiology of this condition. Furthermore, except for epidemic years, only about 2 per cent of the malformations of the heart have been shown to be caused by rubella infections.¹

Other viruses, and Coxsackie viruses in particular, represent logical targets for incrimination as teratogenic agents.⁶ The affinity of these infectious agents for heart tissue has become increasingly well documented in recent years. Experimental studies in young mice and in monkeys by Burch, DePasquale, and their associates,⁷⁻⁹ have demonstrated that Coxsackie type B4 virus induces both valvular and mural endocarditis in significant numbers of infected animals. Of added significance is the fact that virus was recovered from heart tissue and was also detected *in situ* by the fluorescent antibody technique, which suggests strongly that the virus is capable of invading the endocardium. Lou, Wenner, and Kamitsuka¹⁰ also produced mural endocarditis and mitral valvulitis in monkeys with this agent. Burch and his group¹¹ have extended their studies to man where group B Coxsackie viruses were identified by the FA procedure in 17 of 55 hearts obtained at autopsy. A high percentage of the virus-positive specimens were from children and infants, some of whom were premature or anomalous.

The ability of these agents to cause myocarditis in adults¹² and especially in the newborn child is well documented.^{13,14} Many infants with neonatal myocarditis appear to have acquired the infection during the intrauterine period and, sig-

nificantly, their mothers characteristically showed no more than mild illness or completely subclinical infection.

The widespread occurrence of these infections which are predominantly subclinical in adults, the viremia which would enable such very small agents (28 $m\mu$) to cross the placental barrier easily, and the proved greater susceptibility of young, rapidly metabolizing tissue to viruses, all together point clearly to the fetus as a logical target for invasion and subsequent damage in the form of congenital heart disease. Evidence which strongly suggests that this is the case has recently been reported by Brown and Evans.¹⁵ Over 10,000 pregnant women were studied prospectively, and paired sera of mothers of anomalous infants together with matched specimens from mothers of normal children were tested for serologic evidence of infection with various viruses during pregnancy. A significantly greater incidence of infection with Cocksackie group B and type A9 viruses was observed in mothers of infants with congenital heart disease than in their matched controls. Types B3 and 4 were most frequently associated with malformed infant hearts. The greater frequency of maternal infection associated with abnormal infants was observed regardless of the severity of the condition, which ranged from ventricular or atrial septal defects, aortic or tricuspid atresia, and transposition of great vessels to mild patent ductus arteriosus and low-grade murmurs. Inclusion of this latter category was felt to be justified in view of other reports of the development of diastolic and systolic murmurs in patients several months after recovery from group B Cocksackie virus myocarditis.¹⁶ Rubella associated congenital heart cases were discarded from the evaluation and, although infections with other viruses were detected, their occurrence was essentially the same in both the anomaly and the control groups.

Final proof of the incidence of congenital heart disease induced by Cocksackie virus must await extended and additional serologic studies as well as virologic evidence through isolation or visualization in affected heart tissue. In the meantime the pursuit of studies such as described herein constitutes an exciting approach to the

solution of a difficult and important problem.

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