

# This Week's Citation Classic

Rudolph A M, Drorbaugh J E, Auld P A M, Rudolph A J, Nadas A S, Smith C A & Hubbell J P. Studies on the circulation in the neonatal period. The circulation in (he respiratory distress syndrome. *Pediatrics* 27:551-66, 1961. [Dept. Pediatrics, Harvard Med. Sch.; Boston Lying-In Hospital; Children's Medical Center, Boston, MA]

**Cardiac catheterization studies in newborn infants demonstrated that the ductus arteriosus is usually closed functionally in normal gestationally mature babies within 15-20 hours. Premature infants with respiratory distress had a widely patent ductus arteriosus with a large shunt, predominantly left-to-right, within the first 20 hours after birth. [The SC<sup>®</sup> indicates that this paper has been cited over 250 times since 1961.]**

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"At the time this work was done, a large proportion of premature infants were dying as a result of hyaline membrane disease (idiopathic respiratory distress syndrome). I had observed that many of these infants had a cardiac murmur, and this, combined with reports of the presence of hyaline membranes in the alveoli of children dying of cardiac failure, led me to consider that the respiratory distress syndrome was due to left ventricular failure associated with persistent patency of the ductus arteriosus. I proposed a study to confirm this hypothesis by performing cardiac catheterization studies in a series of normal infants and infants with respiratory distress. Extensive discussions regarding the ethics of these studies followed for a period of about six months before it was agreed that the studies were justified. In view of the high incidence of morbidity and mortality in infants of diabetic mothers, these families were most cooperative in granting permission for the procedures.

"In reflecting on the changes in attitude regarding human research over the past 15 years, I doubt that I would have considered performing these studies, or that approval would have been granted by an institutional committee in the present era. The study was, however, extremely important in formulating our current concepts about the high incidence of persistent patency of the ductus arteriosus in premature infants, and the role of large left-to-right shunts through the ductus, either in causing cardiorespiratory difficulties or in aggravating symptoms in premature infants with hyaline membrane disease.

"It is also of interest that the information presented in this paper was neglected for some years because, soon after it was published, the role of immaturity of pulmonary surfactant in preventing adequate lung expansion and causing hyaline membrane disease, received most attention. It was suggested that inadequate ventilation would cause hypoxia and pulmonary vasoconstriction and, if the ductus arteriosus were patent, a right-to-left, rather than a left-to-right shunt, would result.

"Later, it became apparent that although lack of pulmonary surfactant accounted for inadequate lung expansion, large left-to-right shunts through the ductus arteriosus often complicated the course of premature infants with respiratory distress syndrome. This paper first clearly documented the importance of left-to-right shunts with resultant cardiac failure in contributing to respiratory distress in premature infants, and stimulated us, as well as others, to recommend ligation of the ductus arteriosus to treat these infants. This has proved to be very effective in selected cases. More recently, prostaglandin synthetase inhibitors have been used to close the ductus arteriosus by pharmacologic means."