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This Week's Citation Classic®

Friedman W F, Pool P E, Jacobowitz D, Seagren S C & Braunwald E. Sympathetic innervation of the developing rabbit heart: biochemical and histochemical comparisons of fetal, neonatal, and adult myocardium. *Circ. Res.* **23**:25-32, 1968.
[Cardiology Branch, Natl. Heart Inst., Bethesda, MD, and Dept. Pharmacology, Univ. Pennsylvania, Sch. Med., Philadelphia, PA]

The sympathetic innervation of the rabbit heart as a function of age was studied by measuring cardiac catecholamine concentrations and observing the anatomic distribution of sympathetic nerves by the monoamine fluorescence technique. Quite low levels of cardiac norepinephrine rose progressively from the late gestation stage to reach adult values by three weeks of age. Unlike the heart, the adrenal glands were found to contain abundant catecholamine stores. [The *SCI*® indicates that this paper has been cited in over 185 publications.]

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After completing clinical training as a pediatrician at the Johns Hopkins Hospital, and following two years as the pediatric cardiology clinical associate in the Cardiology Branch of the National Heart Institute (NHI), I was vexed by the clinical observation that newborn infants with heart disease were remarkably fragile and labile when compared to older children and adults. It appeared reasonable to suggest that the intrinsic physiological properties of the developing heart and circulation were uniquely age-dependent. There existed, in 1966, an important focus of interest concerning the manner in which the autonomic nervous system, and particularly adrenergic mechanisms, provided support to both the healthy and abnormal heart and circulation. Eugene Braunwald, the chief of the Cardiology Branch of the NHI, was enthusiastic about my proposal to employ pharmacological, biochemical, and histochemical techniques to compare fetal, neonatal, and adult myocardium with respect to sympathetic and parasympathetic innervation.

In the paper so frequently cited, we studied the sympathetic innervation of the rabbit heart as a function of age, by measuring the cardiac concentrations of catecholamines. David Jacobowitz at the University of Pennsylvania had perfected the monoamine fluorescence technique to observe the anatomic distribution of sympathetic nerves, and he was pleased to collaborate with us. Thus, it was necessary to transport tissue from our laboratories in Bethesda, Maryland, to Philadelphia, Pennsylvania. Peter Pool had just obtained a license to fly a single-engine airplane, and his maiden flight as a solo pilot transported me and rabbit myocardium to Philadelphia on a cold and rainy day. The trip defies description; that we arrived safely was truly a miracle, and it was a long time before I regained the courage to fly again. Nonetheless, the data from our study were exciting and showed clearly the gradual development of complete sympathetic innervation early in life. I think our paper was quoted widely because great interest existed thereafter in understanding the limited cardiac reserve in the newborn, particularly in response to disease states and physiologic stimuli.[1]

These findings, for example, provided a springboard for many future studies of cardiac autonomic control mechanisms,[2,3] cardiac ultrastructure, and the mechanical properties of the developing heart and for a host of investigations of the influence of growth on myocardial energy metabolism, the responses of the developing circulation to cardioactive drugs, and subcellular, cellular, isolated, and *in situ* cardiac responses of the fetus and newborn to cardiocirculatory stress. All of these efforts led to a focus on the pharmacological properties of the ductus arteriosus in fetal and newborn life.[4] We had the good fortune of pinpointing the critical, controlling role of prostaglandins in determining the caliber of the ductus arteriosus before and after birth and of finding a pharmacological substitute for cardiac surgery to close the patent ductus of premature human infants. The latter is an important therapeutic advance for improving the outcome of many thousands of infants yearly.[5]

1. **Friedman W F & George B L.** Medical progress. Treatment of congestive heart failure by altering loading conditions of the heart. *J. Pediatrics* **106**:697-706, 1985.
2. **Friedman W F.** The intrinsic physiologic properties of the developing heart. *Progr. Cardiovasc. Dis.* **15**:87-111, 1972. (Cited 175 times.)
3. **Geis W P, Tatooles C J, Priola D V & Friedman W F.** Factors influencing neurohumoral control of the heart in the newborn dog. *Amer. J. Physiol.* **228**:1685-9, 1975. (Cited 50 times.)
4. **Friedman W F, Printz M P, Kirkpatrick S E & Hoskins E J.** The vasoactivity of the fetal lamb ductus arteriosus studied *in utero*. *Pediat. Res.* **17**:331-7, 1983.
5. **Friedman W F.** Patent ductus arteriosus in respiratory distress syndrome: a historical review. *Pediat. Cardiol.* **4**(Suppl. II):3-9, 1983.