NEW OPTIONS NEW HOPE

WALL CENTER UPDATE Fall 2004

VERA MOULTON WALL CENTER FOR PULMONARY VASCULAR DISEASE AT STANFORD

NO Therapy May Prevent Pediatric PH

Stephen H. Abman, M.D.

The Fourth Annual Dunlevie Family Lecture in Pediatric Cardiopulmonary Medicine

The Wall Center was pleased to host the Fourth Annual Dunlevie Family Lecture at Stanford University Medical Center, where invited lecturer Stephen H. Abman, M.D., discussed his innovative research into the developing lung. Through their research, Abman and his team at the University of Colorado School of Medicine have discovered that Nitric Oxide (NO) plays a pivotal role in lung growth and function.

Dr. Abman has long been associated with the University of Colorado, having completed his internship, residency, and fellowship training there. Today, he is a Professor of Pediatric Pulmonary Medicine and Director of the Pediatric Heart-lung Center in the Department of Pediatrics at the University of Colorado Health Sciences Center and The Children's Hospital, Denver. He has been the recipient of many awards including, most recently, the James B. Strain Award which recognizes a physician best exemplifying the values of the American Academy of Pediatrics.

"This is a really exciting time for cardiovascular biology," Abman remarked at the start of his talk, noting that the past 15 years have brought significant advances in pediatric cardiac, pulmonary, and neurological disorders. Pulmonary hypertension (PH) is often involved in the disorders. To survive, newborns with PH must rely on mechanical ventilation—which can cost between $50,000 and $70,000 per infant. Tragically, many neonates with PH still die due to respiratory failure.

Abman went on to describe the vascular differences between healthy infants and those with PH. While the vessels of all babies are constricted in the womb, those of healthy infants dilate at birth, allowing oxygen-rich blood to pass. Vessels of ill neonates remain constricted even after their births. This vessel malfunction led Abman and his team to ask, "What are the prenatal changes that must occur for a normal transition to take place?"

They found the answer in the endothelial cells that line vessel walls.

They found the answer in the endothelial cells that line vessel walls. During healthy vascular development, an enzyme within the cells known as eNOS, or endothelial NO Synthase, comes in contact with several factors, like VEGF (vascular endothelial growth factor) and hormones. These factors prompt eNOS to convert one of its amino acids into another, releasing NO in the process. NO molecules then adhere to underlying smooth muscle cells, discouraging the excessive cell production that can clog vessels and impede blood flow. At birth, the NO molecules trigger another cellular component, cyclic guanylic acid (cGMP), which dilates the vessels. The pioneering research of Stanford's own Marlene Rabinovitch, M.D., Dwight and Vera Dunlevie Professor of Pediatrics and Research Director of the Vera Moulton Wall Center, confirms that this transition begins before birth. When examining vessels in newborns who died from PH, Dr. Rabinovitch found that the vessels had been "injured," preventing their cells from producing NO. As a result, they displayed abnormal muscular growth down to the smallest vessel.

"Several complex conditions could set the stage for this vascular injury," said Abman, including chronic hypoxia (oxygen deficiency), lung inflammation, genetic factors, and even hypertension itself.

Abman's work in the laboratory supports his findings. For example, he has revealed that suppressing eNOS in premature lambs leads to a 50-percent reduction in vessel flow. Other lambs receiving small, inhaled doses of NO experience "dramatic, sudden, and sustained" vessel dilation. Yet, Abman observed, the doses don't adversely affect systemic blood pressure—making them good therapeutic candidates. Abman also cited the success of NO therapy in premature, severely ill infants who would typically need ECMO (extra corporeal membrane oxygenation) to survive. After receiving low doses of inhaled NO, those infants required less ECMO.

Although NO therapy has proven successful for babies outside the womb, Abman acknowledged that "the ongoing challenge is how to treat preterm infants with NO deficiencies." Abman concluded by calling for the continued investigation of these and other therapies, with the ultimate goal of improving outcomes for all infants with PH—both before and after delivery.