A New Breath of Life

Dr. William Truog researches ways to protect premature infants from chronic lung disease.

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The first breaths of life aren't always easy. For some infants, the delicate tissue of their lungs isn't used to the outside world. They may begin to have breathing problems, including wheezing, grunting, and tiring easily after feeding.

These are signs of chronic lung disease (CLD), which is caused by damage to part of the lungs. CLD often results when a newborn is born prematurely. More than 70 percent of babies born earlier than 26 weeks of gestation develop CLD because their lungs are underdeveloped and vulnerable to injury.

Treatments can help aid the newborns' breathing, but there is no definitive cure. About 10 percent of infants with CLD will die. Those newborns that survive may require treatments into early childhood, such as oxygen therapy and medication.

"Every month (at Children's Mercy), we probably have at least one premature baby who's been referred here with very severe chronic lung disease," says William Truog, M.D., professor of pediatrics, Sosland Family Endowed Chair in Neonatal Research at Children's Mercy Hospital in Kansas City. "Many of these babies continue to have breathing problems long after their discharge, even extended out for a couple of years after birth."

To help find better treatments for these newborns, Dr. Truog is involved in several research studies into chronic lung disease in infants. Two of these studies have received grants from the National Heart, Lung, and Blood Institute. In the first, Dr. Truog is a co-principal investigator in a multi-center study using nitric oxide as a treatment for premature babies with CLD. In the second study, Dr. Truog is studying how inflammation of the lungs in premature babies leads to CLD.

Nitric Oxide Test

Over the past 15 years, Children's Mercy Hospital has been the regional center for a therapy called ECMO (extra corporeal membrane oxygenation). This machine provides life support for babies who develop lung disease shortly after birth and can't get enough oxygen. The machine withdraws blood from a vein in the body, removes the carbon dioxide and replenishes the blood with oxygen before returning the blood back to the body. Dr. Truog says that while this therapy helps to save lives, researchers at Children's Mercy have been searching for less invasive therapies.

"ECMO is a complex therapy that is basically heart-lung bypass treatment for babies," says Dr. Truog. "We knew it would be much easier on the newborns if we could use other supportive therapies to help them get through this problem."

Over the last six years, researchers at Children's Mercy Hospital have been investigating a treatment called inhaled nitric oxide for full-term babies with chronic lung disease. The treatment has been shown to be helpful in most full-term infants with acute lung disease and is now a standard treatment used in hospitals throughout the United States. According to Dr. Truog, about 60 percent of full-term infants respond well to this therapy and can avoid heart-lung bypass treatment. The nitric oxide helps regulate their body functions and increases effective breathing.

Photographs by John Carmody

While nitric oxide is an established treatment for full-term babies, it has not been proven yet for premature infants. Today, Children's Mercy is one of the lead centers in a multi-center trial looking at the effects of nitric oxide in reducing CLD in premature babies.

"The lung function of full-term babies is quite different from premature babies," says Dr. Truog. "Part of our goal is to determine if it ought to be part of the routine care for premature babies when they are on a ventilator."

As of now, the common treatment for premature babies needing some breathing assistance is use of a mechanical ventilator and extra oxygen. However, use of these life-sustaining treatments over a long period of time can actually damage the babies' delicate, underdeveloped lungs, resulting in CLD.

"Every month, we have a premature baby who's referred here with very severe chronic lung disease," says Dr. Truog. "It would be terrific to have therapies that would have prevented that process that could have been applied right after birth. We need safe and effective therapies that don't add to the other problems premature babies have."

The trial, which is being conducted in 15 medical centers throughout the nation, received a $7.5 million grant from the National Heart, Lung, and Blood Institute (NHLBI). The researchers plan to enroll about 700 premature babies in the study, with about half enrolled so far. For about three and one-half weeks, half of these babies are receiving a small amount of nitric oxide mixed with the inhaled gas they receive in mechanical ventilation, while the other half are being given a placebo. Neither the investigators nor the families know which treatments the babies are receiving.

The physicians will keep track of the infants' progress through two years after the treatment to see if they will have less severe evidence of chronic lung disease. Dr. Truog says this will help them learn if the nitric oxide can improve the babies' lung function as well as overall development.

"In addition to breathing problems, these babies are also at risk for having growth problems and neuro-developmental problems down the road," says Dr. Truog. "So it's important to know if by affecting the severity of chronic lung disease, we can improve other parts of these children's outcomes as well, not just in the short term."

Inflammatory Response

In addition to studying the treatments of chronic lung disease, Dr. Truog is also looking at the causes. In 2002, he received a

$950,000 grant from the NHLBI to study the role of the immune system in CLD. Specifically he hopes to find out how inflammation of the lungs leads to CLD in some infants.

According to Dr. Truog, the premature babies' lungs may become inflamed when exposed to an irritant. For example, oxygen can be an irritant when the premature infants lungs are suddenly exposed to much more oxygen than they were used to during fetal life. The oxygen acts as a toxic substance, which can promote an inflammatory response. This inflammation may lead to injury in the tissues of the newborn's lungs, which can later affect lung development.

In order to study the molecular process of inflammation, Dr. Truog is collecting 100 to 150 lung fluid secretions from babies in Kansas City, Seattle, and Philadelphia. These secretions will be used to measure the proteins and messenger RNA found on the surface of the inflammatory cells. These proteins serve as a pathway for how the inflammatory cells respond to various irritants. By looking at these substances, Dr. Truog hopes to find out why some proteins react inappropriately to these irritants, causing lung injury.

"We want our approach to be much more targeted, knowing what course a baby should follow and what kinds of therapies would be appropriate, so we can avoid undertreatment and overtreatment," says Dr. Truog. "The long-term objective is to come to an era with much more individualized care."

Dr. Truog says the ultimate goal of both studies is to find the best therapies for these babies that will help them to recover quickly and live normal lives.

"We know that we're not doing the best possible job for premature babies yet," says Dr. Truog. "Given that these babies continue to be born too early, and given that with modern knowledge and technology, a high percentage of these babies survive, our job is to get them off to the best start in life that we can." ■

(Top Left) William Truog, M.D., stands besides the Quantitative PCR Analyzer in his lab at the School of Medicine. The equipment is used to measure RNA in samples taken to research chronic lung disease in infants. (Top Right) – Mo Rezaiekhaligh, research associate, prepares samples for analysis as Dr. Truog looks on. (Bottom Left) – Dr. Truog discusses the research with Mike Norberg, research associate, and Rezaiekhaligh.