Discovery Of A Fundamental Lung Function Leads To Higher Survival Rates For Premature Infants

University of California, San Francisco (UCSF)

A University of California, San Francisco professor dedicated his career to studying how lungs work, then created a treatment that helps babies suffering from respiratory distress syndrome breathe. The result is a dramatic decline in infant mortality caused by RDS.

Not long ago, thousands of newborn babies died in hospitals every year because of a mysterious affliction called respiratory distress syndrome. Up until the mid-1950s, doctors didn't know the cause of this heartbreaking ailment. That's when professor John Clements began to make inroads into doctors' understanding of the human lung that eventually led to a cure for RDS.

Clements had been in the U.S. Army's Medical Research Unit during the Korean War. A trained biochemist and physiologist, Clements had been assigned the task of understanding how nerve gases affect the lungs. His research focused on the defensive aspects of chemical warfare — providing better treatment for soldiers who had been exposed and trying to figure out whether they could be protected against the noxious gas. The knowledge Clements sought for the battlefield would eventually save thousands of lives — not soldiers' lives, but babies' lives in hospital nurseries around the world.

“My studies on lung mechanics led me to think there was a surfactant there,” Clements says, more than a half-century later.

Finding It Was Just the Beginning

> *A surfactant is a substance that reduces the surface tension of liquid containing it. It accumulates at the surface of the lung and occupies the surface of air spaces, which are typically wet and would otherwise have high surface tension. The lung secretes this surfactant to allow the lung to expand in breathing and remain air-filled.*

“I guessed it was there, tested for it, and I found it was there,” Clements says. “It turned out to be very interesting, very complex — and it took me another 25 years to really understand it,” he adds with a laugh.

Clements is now an emeritus professor at the UCSF Cardiovascular Research Institute and the Department of Pediatrics. “It’s only one molecule deep,” he says about the qualities of lung surfactant. “It’s like a sheer nightgown covering the surface of the airspaces of the lung, but it is absolutely critical to life.”

Intrigued, Clements has spent decades Investigating the structure, function and biology of lung surfactant. The problem for newborn babies, especially those born pre-term, is that this life-supporting mammalian function doesn’t become active until late in pregnancy, around 28 to 32 weeks.

“Preemies with RDS don’t have a surfactant,” Clements says. “They have not begun to secrete the protective surface that will enable them to keep their lungs expanded.”

The Connection with Infants

Around the same time Clements was beginning to explore and publish articles about lung surfactant, Mary Ellen Avery, a pediatrician interested in RDS, and Jerre Meade, a pulmonary physiologist who knew about Clements’ research, decided to see if infants with RDS lacked surfactant. Working at Harvard University, they consulted with Clements to learn his methods and in 1959 published data indicating that babies who died with RDS did, in fact, lack surfactant.

Between that time and 1982, Clements explored the intricacies of surfactant in the human lung, using his research knowledge to consult with clinicians about how best to care for premature infants. It was during this time that one of the nation’s first intensive care nurseries was developed at UCSF, with expert input from Clements.

“I consulted on the research aspects of neonatal care, especially in terms of physiology and basic science,” he says. “We brought many supportive measures — blood transfusions, artificial oxygenation and others developed in adult intensive care — to bear on the problems of sick newborns.” Other universities including Columbia University and Vanderbilt University also were introducing these types of facilities, Clements says.

Around 1980, a Japanese pediatrician, Tetsuro Fujiwara, created an artificial surfactant from cow lungs and found it worked well in 10 infants with RDS. Clinicians from the Specialized Center of Research on Pulmonary Disease at UCSF asked Clements what surfactant he would advise for a larger clinical trial. Clements, who was a little concerned about putting animal materials into human lungs, told them that he would design a synthetic substitute for them. Two weeks later, he presented a substance named Exosurf.

Clement's synthetic surfactant was licensed by Burroughs-Wellcome in 1986. Clements says a friend persuaded the pharmaceutical company, now GlaxoSmithKline, to take a look at the substance. The company shepherded the product Through the U.S. Food and Drug Administration approval process, from pre-clinical work through human clinical trials.

But it wasn't an easy road to market. According to the University of California Office of Technology Transfer, the Exosurf invention was disclosed just before the passage of the Bayh-Dole Act in 1980, meaning the university had no legal right to license it. And the preference of the National Institutes of Health for non-exclusive licensing was incompatible with the company's need for exclusivity. So several years of negotiation ensued before the university could offer exclusive rights.

Trials Showed the Impact Was Immediate

When Exosurf finally went into human clinical trials, the impact of the drug on the welfare of newborn babies was immediate. "During the first trials of Exosurf, infant mortality was reduced one-half to one-quarter of what it was with the standard treatment," Clements says.

Exosurf, and other surfactant substitutes developed more recently, have contributed to a dramatic drop in the infant mortality rate in this country and around the world. Between 1988 and 1993, infant mortality in the United States dropped by 16 percent — a remarkable decline in such a short time frame.

In honor of their achievements, Clements and the Burroughs-Wellcome scientists who assisted in the development of the drug received the 1997 Discoverers Award from the Pharmaceutical Research and Manufacturers of America, a membership organization dedicated to the research and introduction of new medicines.

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