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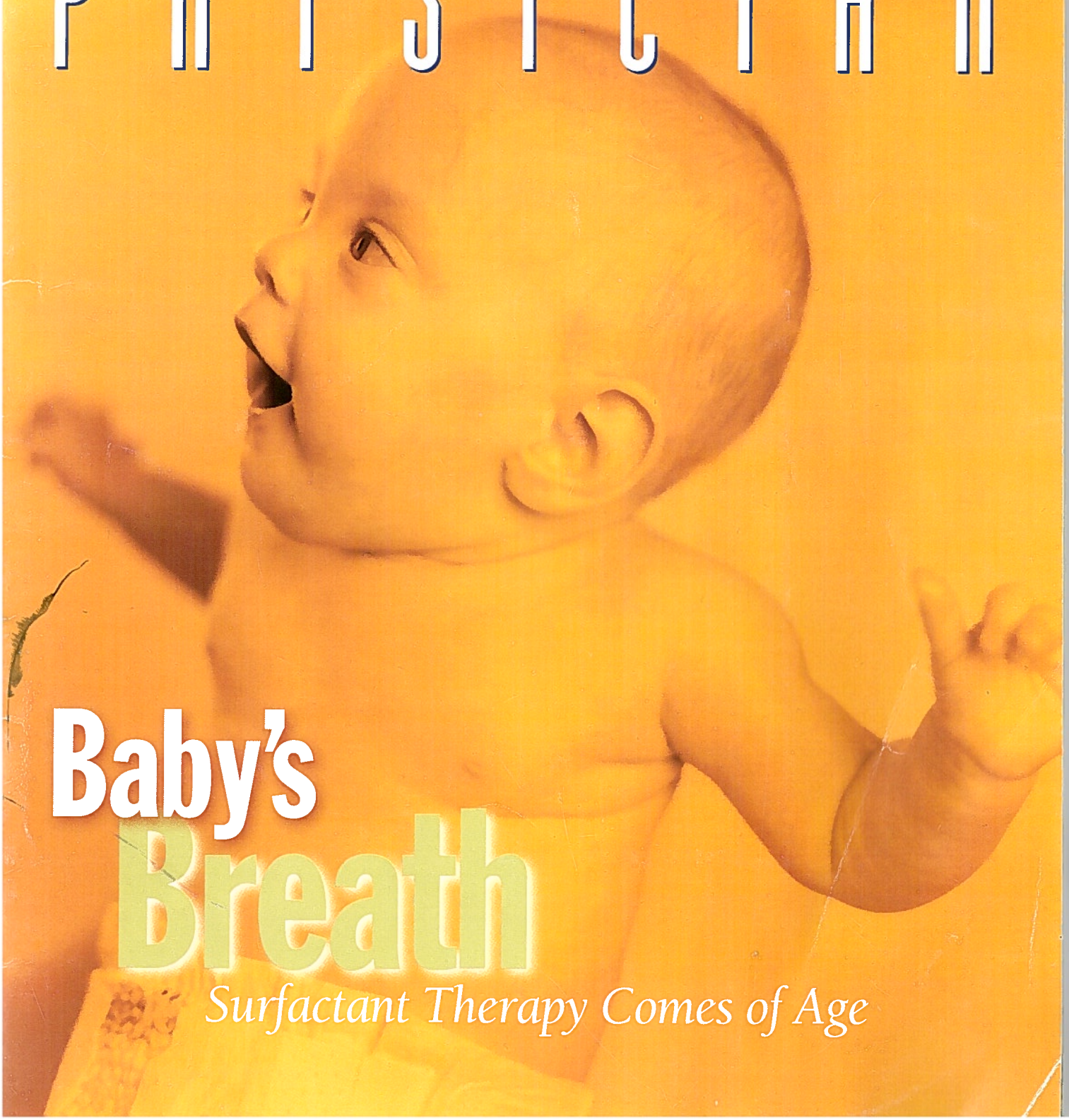
Special Report
The Surfactant Story



# Baby's Breath

## *Surfactant Therapy Comes of Age*

Special Report

# The Surfactant Story

by S. A. Unger

Photos by Paul Francis

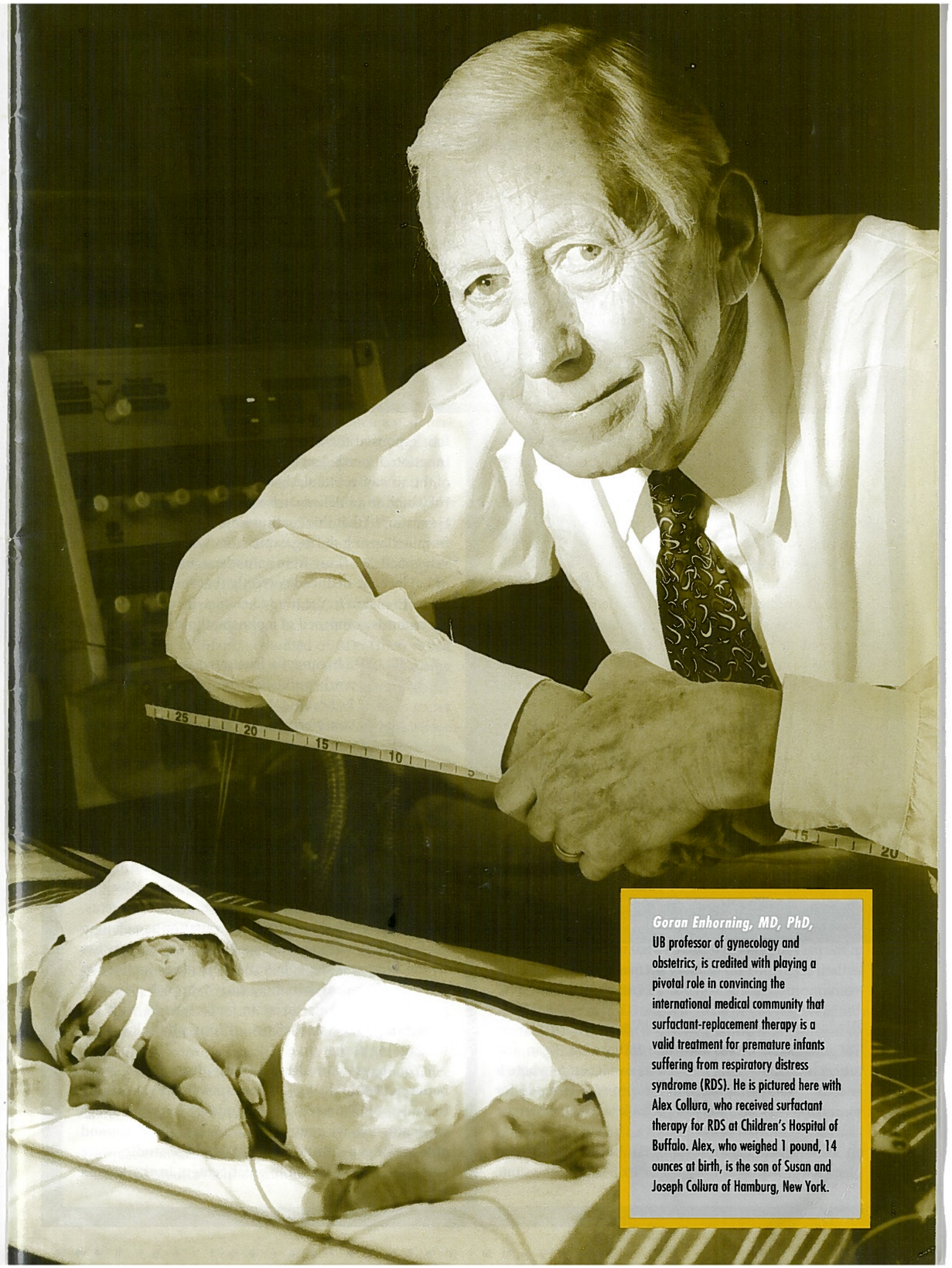
## Buffalo's historic role in surfactant therapy, and the man who led the way

"It hurt me to see that when infants were born too early and had difficulty breathing, really nothing could be done about it. They were just left to die."

In one breath, these are the words spoken by Goran Enhorning, obstetrician, as he talks about his motive for beginning his tortuous, but historic, quest to develop exogenous pulmonary surfactant 35 years ago. His hopes then, as they are today, were simple and straightforward: to alleviate the suffering and prevent the death of premature babies afflicted with respiratory distress syndrome (RDS), a condition that, previous to "the surfactant era," killed 70 percent of its victims.

In his next breath, Goran Enhorning, Swedish research physiologist and inventor, moves away from the realm of the heart and into the mind, where, with softly accented words, he struggles to translate into layman's language the scientific insights he has experienced throughout his controversial career, a career he is still fully engaged in at age 75.

Leaning forward in his chair in his office at the Children's Hospital of Buffalo, he explains that surfactant is a naturally occurring substance in the lungs that helps make breathing possible by decreasing surface tension at the airway-fluid interface in the alveoli. "Surface tension was described by LaPlace's Law—you know, P equals two times T over R, with P representing the pressure that must be generated to overcome surface tension, T, and R representing the radius of the alveolus . . . "



*Goran Enhorning, MD, PhD,* UB professor of gynecology and obstetrics, is credited with playing a pivotal role in convincing the international medical community that surfactant-replacement therapy is a valid treatment for premature infants suffering from respiratory distress syndrome (RDS). He is pictured here with Alex Collura, who received surfactant therapy for RDS at Children's Hospital of Buffalo. Alex, who weighed 1 pound, 14 ounces at birth, is the son of Susan and Joseph Collura of Hamburg, New York.

**In talking with Enhorning, it becomes clear how his affinity for both basic science and medicine enabled him to make crucial contributions that kept the field of surfactant research alive in years past, when leading experts worldwide dismissed its viability. It also becomes clear that his work contributed to making Buffalo, New York, a hub for surfactant research—a place where world-class scientists converged in free-wheeling collaboration to help make real the dream Enhorning first envisioned many decades ago.**

**These scientists include Enhorning's long-time colleague and sometime rival Edmund "Ted" Egan II, MD, professor of pediatrics and physiology at the University at Buffalo School of Medicine and Biomedical Sciences. In the early 1980s, Egan and his collaborators—building on Enhorning's seminal work—spurred on a highly contentious international race to develop the first exogenous surfactant product. Today, despite the behind-the-scenes jostling that continues among these competitors, there are several surfactant products on the market and, as a result, the mortality rate for infants born with RDS has dropped to 5 percent.**

This dramatic, innovative work has not ended in the clinic, however. As the 1990s draw to a close, Buffalo is equally noted for the contributions its scientists are making to basic research in the area of surfactant therapy—contributions that are leading the field into the 21st century, where it promises to impact a wide range of respiratory disorders affecting adults, as well as neonates.

Bruce Holm, PhD, associate dean for research and graduate studies at UB's School of Medicine and Biomedical Sciences, is one of the preeminent scientists recruited to UB in the late 1980s by Enhorning and Egan. Like many others worldwide, he readily acknowledges the pioneering contributions made by Enhorning, whose fortitude against all odds is now as well honored as his science. "If it weren't for Goran Enhorning, we wouldn't have the low neonatal mortality rates we have today," states Holm, "and we wouldn't have been able to develop our understanding of the science behind pulmonary surfactant to the extent we have. And, clearly, there's a good deal for the Buffalo medical community to be proud of regarding its contributions to surfactant therapy and research.

"But the surfactant story isn't over yet," he adds. "Even though it has already resulted in what would have to be considered one of the most dramatic breakthroughs in the past 50 years in terms of what neonatologists have in their repertoire for treating prematurely born infants, everyone involved believes there's much more to come."

## Discovering How the Lungs Work—or Don't

To get a sense of the fortitude Enhorning, Egan and others needed to bring exogenous surfactant to where it is today—and to appreciate the promise it holds for tomorrow—it's necessary to go back to 1929, when the "surfactant story" begins.

That year, a pulmonologist named Kurt von Neergaard, who was living in Switzerland at the time, first espoused the theory that in order for the lung to function, it needed an agent that would coat the inside of the airway, particularly the tiny air sacs called alveoli (of which an adult human lung has about three million). He surmised that this coating would prevent the alveoli from collapsing during expiration, when they become very small. Working from an understanding of the Law of LaPlace, he deduced correctly that this agent causes surface tension in the lung to change its value and that the agent is composed of a phospholipid or protein.

"He became so frustrated trying to get his work published, he gave up," explains Enhorning. Medical historians often cite von Neergaard's finding as a classic example of a "premature discovery," as nothing was done with his promising line of research until the early 1950s, when Richard Pattle in England and John Clements in the U.S. independently rediscovered the concept of an alveolar surface-active material that came to be known as "surfactant."

"John Clements was and probably still is the biggest name in surfactant research," explains Egan. Working at the University of California at San Francisco, Clements, in the 1950s, was shoring up his reputation as a giant in his field by focusing on the problem of surface tension in the lung and the role surfactant plays in alveolar stability. His research in those early years was primarily basic, which put his career in perfect synch with the pioneering phase the science of lung physiology was undergoing at that time.

"You have to understand that during that era—between 1940 and 1965—scientists were just beginning to gain a sophisticated understanding of how the lungs work and how we control breathing by mixing gas and air," says Egan. "And in the 1950s, these studies were being led by two or three great centers in the United





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States, one of which was at the University at Buffalo, where key contributions were being made by Hermann Rahn, Leon Farhi and many others in our Physiology Department."

A spin-off of the basic research going on at UB and elsewhere during this time was that scientists began to develop a more sophisticated understanding of lung diseases and their etiology, according to Egan.

With the stage thus set, a giant leap in surfactant research took place in the late 1950s, when a pediatrician named Mary Ellen Avery was invited to complete a fellowship in the laboratory of Jere Mead, a Harvard University physiologist. "Avery and Mead were thinking about the premature babies who had a progressively more difficult time breathing and then died. Their lungs were totally collapsed and looked like livers, and they had the idea that maybe these babies were missing this lung surfactant," explains Egan.

Following through on this idea, Avery and Mead completed a complex project in which they studied the lung material of infants who died of RDS (then called hyaline membrane disease), compared with the lung material found in babies with normal respiratory systems who died of other causes. In a now-famous paper published in 1959, the researchers "showed that surface tension was higher in infants dying from RDS than it was if you got the lung material from infants dying from other causes," says Enhorning.

Based on their findings, Avery and Mead put forth the idea that babies who have RDS are surfactant deficient, in the same way somebody with diabetes is insulin deficient.

"This idea really sparked enormous interest," Enhorning comments.

"This was very esoteric science," Egan emphasizes. "It wasn't anything the great majority of physicians around the country had any training in; they didn't understand it. There simply wasn't a good paradigm for it."

Soon after publication of the Avery and Mead paper, the scramble was on to concoct an exogenous surfactant material and get it into the lungs of babies born with RDS. Around the world, research groups moved into action, hoping to be the first to produce a lifesaving substance that would put a stop to a disease that killed approximately 10,000 babies each year in the U.S. alone.

At about this same time, in 1961, Goran Enhorning had just completed a PhD in physiology at Karolinska Institute's Medical School in Stockholm, Sweden, where

**Bruce Holm, PhD,** associate dean for research and graduate studies at UB's School of Medicine and Biomedical Sciences, came from the University of Rochester in 1988. That year, he teamed up with Sadis Matalon, then a UB physiologist, to show for the first time that high concentrations of oxygen can damage the cells in the lungs that produce surfactant. Today, the innovative studies conducted by Holm and his UB collaborators continue to help define the forward edge of surfactant research worldwide.

in 1952 he had earned his medical degree. Upon graduation he was awarded a Fulbright scholarship to study at the University of Utah, where he began research into surfactant. Normally, Fulbright scholars are limited to a one-year stay, but an exception was made for Enhorning and his visit was extended for another year. During this second year, Forest Adams, a well-known surfactant researcher from the University of California at Los Angeles (UCLA), came to the University of Utah to lecture, at which time he was introduced to Enhorning. As a result of their meeting, Adams

arranged for yet another year extension for Enhorning and made a place for him in his lab at UCLA.

In Adams's lab, Enhorning continued work he had begun in Utah on an ingenious apparatus he called a bubble surfactometer, which he readily admits took him more than 15 years to fully develop. In the decades that followed, however, the bubble surfactometer would greatly enhance scientists' ability to run physical tests on surfactant preparations in order to assess their surface tension-lowering properties prior to *in vivo* studies.

Adams's lab also provided the setting for Enhorning to work alongside another young scholar, Tetsuro Fujiwara of Japan, who, like Enhorning, would go on to devote his career to the elusive goal of developing a surfactant-replacement product.

One of the requirements of Fulbright scholars is that they return to their country of origin for a minimum of seven years upon completion of their studies abroad. As a result, in 1964 Enhorning left Los Angeles to return to Sweden, but that was not the last he and Fujiwara would see of one another.

## The Rush to Find a Cure

During the years that Enhorning and Fujiwara were studying in the U.S., the race had intensified among scientists who hoped to be the first to determine the active components of lung surfactant and to discover a replacement substance.

Foremost among the scientists exploring this problem was Clements in San Francisco, who, in collaboration with M. H. Klaus, was studying the biochemistry of surfactant. Using the limited testing technology they had available to them at the time, they concluded that the surface tension-lowering component of the material resided in its phospholipid, most specifically a biologically rare molecule called dipalmitoylphosphatidylcholine, or DPPC.

Convinced that DPPC was the active surface tension-lowering substance in surfactant, the San Francisco group then decided to take a step that remains controversial to this day.

"They took this DPPC material, which they had only tested in physical systems, not biologic systems," says Egan. "It looked like surfactant. Best of all, it was easy to make, easy to work with, and they were really convinced they had the 'guts' of it, so their next thought was, 'Let's test it in babies.'" Additional motivation to push ahead with testing had come in 1964, when a Canadian group, which had rapidly followed up on Clements's findings, published a paper reporting that they had found some improvement in babies with RDS who had been treated with a DPPC mist.

In 1965, therefore, with their new DPPC solution in hand, the Clements team boarded a plane for Singapore, where they had access to a large population of babies and could complete their studies quickly.

"They took aerosolized forms of DPPC and fogged it into the babies," recounts Holm. "And remember, these are the days before mechanical ventilation. The babies were in these plastic hoods, and they just put this mist of DPPC in the hood and that was the concept of ventilation. Looking back on it, most of the DPPC probably stuck on their hair and face. I'm sure almost none of it got in their lungs. If it had, it probably would have had some positive benefit. But they hadn't done any animal studies so, among other things, they didn't know how to deliver it correctly."

Upon returning, the group published a landmark 60-page paper in *Pediatrics* in 1967, concluding that exogenous surfactant was *not* efficacious for the treatment of infants with RDS.

"So here you have the biggest names in surfactant research saying that surfactant therapy doesn't work," says Egan. "And not only that, but concluding that surfactant deficiency was a *result* of RDS rather than the *cause* of it."

Once the paper was published, interest in surfactant-replacement research for RDS, in large measure, came to a sudden halt. "Clements's conviction alone and his stature in the academic community were such that the publication of this paper turned the entire field of surfactant research in the wrong direction for more than 10 years," Egan explains. Pausing, he adds, ". . . with the exception of one kind of idiosyncratic, brilliant intellectual who lived in Sweden and was an obstetrician by training."

## "This Has Been Tried Before and Does Not Work"

Back in Sweden, with his bubble surfactometer in tow, Goran Enhorning was running some tests of his own. "DPPC was inexpensive, it was sterile, it didn't have any antigenic proteins, so it was appealing. If you could use DPPC, it would have been wonderful. But you couldn't. It was hopeless. I found that out with the bubble surfactometer," he recalls.

At this point, Enhorning turned to a pathologist named Bengt Robertson for help, and together the scientists experimented with various surfactant preparations, which they began early testing of on rabbit neonates. "What they found," Egan explains, "is that the rabbits lived longer and breathed better. But because the medical establishment was by now convinced that surfactant deficiency was *not* the cause of RDS, they had trouble getting their work published.

"I think people in the field ignored Goran's early work because he was producing evidence that was contrary to conventional wisdom, because he was up in





**Edmund "Ted" Egan II, MD,** UB professor of pediatrics and physiology and founder, president and CEO of ONY, Inc., holding a vial of the company's exogenous surfactant product, Infasurf. In the early 1980s—building on Goran Enhorning's seminal contributions—Egan worked with Robert Notter at the University of Rochester to develop the drug. Their efforts fueled a race among scientists around the world working toward this same goal.

**"In the 1950s, these studies were being led by two or three great centers in the United States, one of which was at the University at Buffalo, where key contributions were being made by Hermann Rahn, Leon Farhi and many others in our Physiology Department."**

**— EDMUND "TED" EGAN II**

Sweden and because he had very distinguished people openly pooh-poohing his work."

After years of having his work essentially blackballed by the scientific community, Enhorning finally met with temporary success in 1972. "The editor of *Pediatrics* who accepted the paper Robertson and I coauthored was an exception," recalls Enhorning, "and he invited me to follow up with an editorial on our work." Despite publication of this paper, however, Enhorning and Robertson again found their work ignored; between 1972 and 1976, few journals accepted their papers. "Papers we submitted were rejected with one line: 'This has been tried before and does not work,'" recalls Enhorning.

A year before publication of the paper in *Pediatrics*, Enhorning had moved to Canada to take a position at the University of Toronto. There, he continued collaborating with Robertson, who still lived in Sweden but made extended visits to Canada. "In 1973 and 1974, I did a study with Robertson I consider very important," says Enhorning. "We deposited surfactant in the pharynx of premature rabbit neonates, who inhaled it with their first breath, and X rays showed how it opened up their lungs. We published this study in 1975, and it was at that point that we started thinking about seriously testing it in babies." Toward this goal—and with publishing no longer an insurmountable hurdle—Enhorning and Robertson submitted a steady stream of papers on animal studies they conducted throughout the latter half of the 1970s.

It was during this time, in 1977, that Enhorning first published a paper describing, in depth, his bubble surfactometer, which has since become a staple tool used by scientists studying surfactant.

Based on the work Enhorning and Robertson were doing in the 1970s, researchers began revisiting the idea of creating a synthetic surfactant material. Some were once again testing the DPPC substance that Clements had unsuccessfully experimented with in the mid-1960s.

For example, in 1976 Fujiwara was back at UCLA and was working with Adams in an attempt to duplicate the Enhorning and Robertson studies by depositing DPPC in the upper airways of sheep. Frustrated with their results, they concluded that surfactant therapy didn't work.

"During a trip to Los Angeles that year, Robertson visited Adams's lab and was told about the frustrating results of the experiments. He told them that what they needed to use was natural surfactant from adult animals, not a synthetic material like DPPC. So they changed their techniques and then could confirm our studies," explains Enhorning.

Shortly thereafter, Robertson returned to Sweden permanently and Enhorning began collaborating with Fred Possmayer, a biochemist who worked in London, Ontario, at the University of Western Ontario. Their goal was to develop a surfactant material that would be safe to test in babies. "One of the big problems we had was that the raw material—the natural surfactant—was very difficult to get," Enhorning recounts.

To overcome this problem, Enhorning paid a visit to a local slaughterhouse in Toronto. "I got really lucky because one of the investigators working in research at the slaughterhouse had just had a baby who developed RDS, so

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**Biochemist Fred Possmayer, PhD,** of the University of Western Ontario in London, Ontario, collaborated with Goran Enhorning in the late 1970s to prepare a sterile and active exogenous surfactant product using material obtained from the lungs of large calves. It was this product that Ted Egan and Robert Notter used as a basis for developing Infasurf for treatment of neonates with respiratory distress syndrome.

he arranged for me to get lung lavage from large calves."

The surfactant material that Possmayer made using raw material obtained at the slaughterhouse was extremely active in terms of its surface tension-lowering properties; however, when they attempted to sterilize it with gamma rays or by autoclaving, this crucial activity was lost. "We felt this was due to its high protein content," says Enhorning, who by this time understood, as did all researchers in the field, that surfactant was a complex mixture composed of 90 percent lipids and 10 percent proteins. "In an attempt to rid the material of these proteins, we extracted the surfactant lipids and resuspended them in saline solution, and the material we obtained could then be autoclaved and sterilized without it losing its surface activity," he explains.

However, unbeknownst to Enhorning and Possmayer at the time, a few tiny apoproteins slipped through and made it into their experimental material. It wasn't until the mid-1980s that scientists made the critical discovery that these apoproteins of pulmonary surfactant, which have since been named SP-B and SP-C, are essential for an immediate expression of surface activity.

"Possmayer and I extracted the phospholipids from the material. By doing that, we thought we would get rid of the proteins, which we felt might be dangerous and which interfered with our attempts to sterilize the material," says Enhorning. "We thought we had removed all the proteins but, serendipitously, we hadn't. Later we found out that about 2 percent of the extract was made up of proteins that had slipped by when we analyzed its properties."

Once Enhorning and Possmayer discovered how to produce their sterile, active substance, they wrote about it extensively in journal publications.

## Coming Around to Goran Enhorning's Idea

"By the late 1970s, everyone had come around to Goran Enhorning's idea of 10 years earlier: that it probably is surfactant deficiency that causes RDS," Egan explains. "The obvious next step, then, was determining what kind of surfactant-replacement therapy you're going to give. Basically, you have two options—synthetic and natural."

Egan, himself, entered the field of surfactant research at about this time. In 1977 he moved to Buffalo, where he had accepted a joint appointment as chief of neonatology at Children's Hospital of Buffalo and professor of pediatrics and physiology at the University at Buffalo's School of Medicine and Biomedical Sciences.

"Ted Egan was a physiologist who had some world renown for his work in lung-water clearance," explains Holm, referring to the process in which, at birth, a baby absorbs the liquid that fills its lungs and establishes breathing. "And as a neonatologist and chief of neonatology at Children's, he obviously was interested in developments with surfactant therapy."

Once in Buffalo, Egan set up his lab, where he conducted ongoing studies on sheep related to his research. Soon he met Robert Notter, a scientist who earlier in his career had given up a faculty position in chemical engineering at Pennsylvania State University in order to go to medical school, which he felt would better prepare him to pursue a consuming interest he had in lung surfactant. After he completed medical school at the University of Rochester, he stayed on as a faculty member, dedicating himself to his research.



"By 1980, Bob Notter had a synthetic mixture of surfactant that we both thought would work, and we decided that the best way to find out was to test it in my sheep," recalls Egan.

Egan and Notter were encouraged by a paper that had just been published in Cambridge, England, which reported that surfactant had been tested on babies with very good results. Based on the Cambridge study and others, they were acutely aware that groups around the world were hard at work in the ongoing race to develop their own surfactant products. They knew, for example, that Fujiwara had returned to Japan and was working there; that Clements was working in San Francisco; that Robertson had returned to Sweden, where he was continuing his research; that a group in San Diego was approaching the problem by extracting surfactant from amniotic fluids; and that Enhorning and Possmayer continued their work in Toronto.

It was with great anticipation, therefore, that Egan and Notter began their experiments in 1981. Notter had extensively tested his surfactant preparation in physical systems and had found it very promising. "We took this synthetic product and put it in preemie lambs that were surfactant deficient, and the results were disastrous," Egan recalls.

Frustrated with their lack of progress, Egan and Notter decided they needed to pull back and reassess their methodology because, as Notter pointed out, everything was looking good on his physical systems, so perhaps they needed to look at whether Egan's "experimental setup" was flawed. "In other words, he was saying to me, If we have good stuff, would we even recognize it?" Egan says. Thinking there was only one sure way to determine this, the scientists decided they would put their synthetic mixture aside and instead test a dose of whole surfactant taken directly from the lungs of an animal.

"We were simply looking for a positive control," Egan says. However, what occurred that day in March of 1981, when they tested the new surfactant mixture, was something Egan says he will never forget.

"It was stunning. It was probably as exciting a lab event as I've ever participated in. Surfactant-deficient sheep are pretty doleful animals, let me tell you. But when we gave them the surfactant Bob provided, they were acting like mature fetal sheep getting ready to be born. It was fantastic."

But the biggest surprise was yet to come. "I thought what we had used was whole lung surfactant as we had planned," Egan says. "But when it worked so well, I said, 'This whole surfactant is great!'" It was at this point that Notter informed Egan that what they were testing was an extract he had prepared based on the published works of Enhorning and Possmayer, an extract that he had slightly modified to his own specifications.

"There's no doubt that Enhorning and Possmayer were much farther down the road with their natural extract in 1981 than we were with our synthetic product. Until we ran this test, Bob was primarily interested in a synthetic product. But once this new extract looked so good and once I found out that there was almost no protein in it, I thought, 'We're home,'" Egan recalls.

It was from this point onward that Egan and Notter abandoned their quest for a synthetic surfactant and focused their efforts on refining a natural extract.

## Which Way to Go?

All the scientists working on surfactant worldwide had come to this difficult junction in their research. Obviously a synthetic product was attractive: It would be easier to mass-produce, would be available in limitless quantities, could be more easily controlled for quality and could be patented and sold as a brand-name product, something that was sure to attract the needed support of pharmaceutical companies.

Natural products, on the other hand, while holding exceptional promise, posed very formidable challenges. "In 1980 we knew that natural surfactant was about 10 percent proteins and that one of these proteins was very large. Like the proteins in your blood, it clots, coagulates and you can't sterilize it; it has all kinds of problems," Egan explains. "So we were faced with two issues: if we were going to develop a natural replacement product, it had to be one that wouldn't hurt the patient, yet was hardy."

In 1983, despite these complications, the Buffalo-Rochester team of Egan and Notter and the Toronto team of Enhorning and Possmayer had each begun small, prospective placebo-controlled trials of natural surfactant extract to prevent RDS in preemies—at last marking the start of full-fledged efforts on the part of the two groups to test the drug in babies.

Two years later, both the Buffalo-Rochester group—now joined by clinicians Melinda Kwong and Donald Shapiro—and the Toronto group had completed larger randomized clinical trials, which they each reported on in the August 1985 issue of *Pediatrics*. Using what were similar extracts, they demonstrated that calf-lung

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surfactant extract did prevent lung disease in premature babies and could significantly reduce the severity of respiratory disease.

"After seeing the results of these clinical studies, all of which were so compelling for this particular material, Ted took it on as a crusade to go out and see that it became widely available," recounts Holm. "Early on, he had offered the calf-lung surfactant, pretty much free, to pharmaceutical companies, but they had already committed to marketing products developed by other groups. Also, another reason why they weren't interested in the material was that it had been reported on in professional journals to such an extent it was considered to be in the 'public domain,' so it couldn't be patented.

"So this really was the genesis of the idea 'Let's go out and make and market our own product.'" In hindsight, Holm adds, "Remember, these were academic physicians with no background in commercializing a drug, and so they were too naive to know that they couldn't go through the FDA process without any financial backing."

What they did have, according to Holm, was "the best of intentions and a belief that what they were doing was for the greater good."

Determined to provide a parent company for his orphan drug—which has since been dubbed "Infasurf"—Egan founded ONY, Inc. (Ontario New York), in 1985 and set up offices in the Baird Research Center located near the University at Buffalo campus.

## A Boost from Basic Research

While surfactant was entering its clinical-trial phase, other equally momentous developments were again taking place on the basic-science side of surfactant research.

Much of it centered on Bruce Holm, who in 1981 came to work in Notter's lab at the University of Rochester while pursing a doctorate in toxicology. Over the next seven years, Holm gained considerable recognition for a series of contributions he made to the field of surfactant.

In the mid-1980s, it was Holm and Jeffrey Whitsett, a researcher at the University of Cincinnati, who conducted a study that finally identified apoproteins as the mystery component in surfactant that enables it to be efficiently adsorbed by the lungs. In their paper, which was published in *Pediatric Research* in 1986, they were the first to show the functionality of the apoproteins SP-B and SP-C.

From the start, Holm was primarily interested in studying adult respiratory distress syndrome (ARDS) and its potential connection to surfactant. "No one had ever really wanted to study surfactant in adults," he explains. "Initial attempts to do so went nowhere because the dogma at the time was that surfactant deficiency was related to a quantitative deficiency—as in the case of premature babies—but not to a qualitative deficiency; therefore, the accepted belief was, 'It can't be part of the issue.'"

By the late 1980s Holm, who had admired Enhorning for many years, began to collaborate with the senior scientist and others on studies demonstrating a mechanism by which plasma proteins were shown to inhibit surfactant function. These findings, published in 1988 in the *Journal of Applied Physiology*, helped introduce the concept that surfactant-replacement therapy could be of benefit to a much wider range of lung conditions than just RDS.

"While we were off doing clinical studies, Holm was working with researchers throughout this area—in Buffalo, Rochester, Toronto and London, Ontario—to find out that you can inhibit lung surfactant, which was a brand new concept," explains Egan. "They were showing that surfactant plays a role in lung diseases, not just when it is missing, but when it becomes deactivated by things seeping into the lungs that don't belong there and which start tearing up the surfactant, making it terribly difficult for people to breathe. We began to see it as being similar to autoimmune diseases, where the body turns on itself."

In 1988 Holm also teamed up with Sadis Matalon, who was then a physiologist at the University at Buffalo, and others to publish a study that showed for the first time that high concentrations of oxygen can cause changes in Type II pneumocytes, the cells that produce surfactant.

"Obviously, this was really very important because we use oxygen as an essential therapy for treating lung diseases," explains Egan, who notes that, today, the 40-year-old Holm is recognized as "one of the world's leading experts on oxygen toxicity."

"Not only did Holm and Matalon document that oxygen can damage cells in the lungs that make surfactant, but they also showed that if you give an animal surfactant, it will speed its recovery, diminish the injury or even prevent it," he adds.

While studying oxygen toxicities, Holm also refined a technique for isolating the Type II pneumocytes. This was a very important development, as well, according to Enhorning, because "more and more, physiologists are studying disease at the cellular and molecular level."

## Critical Mass Converges in Buffalo

As the years passed, it became increasingly clear that, philosophically, the Buffalo-Rochester group had much in common with the Toronto group and that, together, they stood apart from other groups worldwide. Most important, they shared the philosophy that *both* lipids and proteins must be included in surfactant preparations if they were to produce optimal results. Furthermore, they felt strongly that both SP-B and SP-C must be present because their research had shown that the two apoproteins work synergistically.

In contrast, in the late-1980s Clements's group in San Francisco, which had by then partnered with Burroughs Wellcome, was developing a synthetic preparation called Exosurf that was composed primarily of DPPC and contained no protein. In turn, Fujiwara's group in Japan, which had partnered with Abbott Labs, was testing a patented product called Survanta, manufactured from a mince of whole cow lung, supplemented with synthetic phospholipids and neutral lipids, but containing only trace amounts of the SP-B apoprotein.

Given the long years of collaboration between the Buffalo-Rochester-Toronto researchers, it came as no surprise when Egan successfully recruited Enhorning to Buffalo in 1986, followed in 1988 by Holm, who came from the University of Rochester to complete a postdoctoral fellowship at UB, during which time he worked with Enhorning and others to continue his novel work on surfactant inhibition.

## There's So Much at Stake

Once the randomized clinical trials were completed on Infasurf in 1985, Egan initiated the process whereby he hoped to win Food and Drug Administration (FDA) approval for the drug. Immediately, he was told by the FDA that in order for Infasurf to be considered for approval, controlled studies of it had to be completed. "This meant some of the babies would get surfactant and some of the babies would get nothing," recalls Egan. "So I said, 'I can't do that.'" Egan's appeals to the FDA to make an exception to their rule did not meet with success. As a result, he decided to delay controlled clinical trials until other surfactant drugs came on the market, at which time he could compare one surfactant to another.

In 1990, his wait ended when Exosurf was approved by the FDA and debuted as the first surfactant drug available in the U.S., followed closely by Survanta in 1991.

In the intervening years, while waiting for Exosurf to come on the market, Egan made Infasurf available to all babies in Buffalo who needed it, something he was able to do while Infasurf was classified as an "investigational new drug." This strategy was given a boost in 1989, when the FDA gave Egan's company, ONY, Inc., permission to charge for Infasurf so that costs for its development could begin to be recouped. However, the FDA gave the company permission to do this with the stipulation that it upgrade its manufacturing facilities to meet the requirements for a commercial venture. The only way to get the needed equipment in a timely manner was for the owners of the company to guarantee a loan, which Egan did personally after buying out the other owners.

"I was placed in a position where I felt we had developed something that was really a super therapy but which, because it wasn't a mainstream commercial venture, was about to be abandoned," Egan says. "I thought about my own motivation up to this point—why I went into this in

**Robert Notter, MD,** gave up a faculty position in chemical engineering at Pennsylvania State University to earn a medical degree, which he felt would better prepare him to pursue a consuming interest he had in lung surfactant. In the 1980s, as a faculty member at the University of Rochester, he collaborated with Ted Egan at the University at Buffalo to develop the surfactant drug Infasurf.

## The Surfactant Story

**"It's this cell-biology aspect that will take us to the next level. The philosophy shouldn't just be 'Okay, we can keep them alive.' That, of course, is very important for the physician, but, for a scientist, you always want to go one step farther; you want to see if you can prevent this from happening in the first place."**

**— BRUCE HOLM**