or neonatologists, the most delicate and critical part of the job often comes before the patient—a critically ill infant—is even born. When a preterm birth is imminent, a neonatologist will talk with the parents about what to expect in the course of the next few hours or days as they become parents of a premature baby.

“Everyone thinks you just take care of babies,” says Gary Silverman, the newly arrived chief of neonatology at Magee-Womens Hospital and professor of pediatrics in the School of Medicine, “but I can tell you right now that taking care of the children is only a small component of what we do. I think the biggest part of our work is taking care of the families.”
The neonatologist’s ability to offer these parents encouraging news has increased exponentially in the 40-odd years since First Lady Jacqueline Kennedy gave birth almost six weeks early to a son. Patrick Kennedy weighed about four-and-a-half pounds and survived only two days. “Today, that kind of baby is really a bread-and-butter baby for us,” says Charles Bender, medical director of the neonatal intensive care unit (NICU) at Magee. “It’s a routine baby.” Even a baby born three months early and weighing a little more than a pound now stands a good chance of survival and, eventually, good health.

But when a baby is at the lower edge of this borderline of viability—born extremely early, with multiple complications, or weighing only a pound or so—Silverman will talk with the parents about expectations and possible outcomes.

For expectant parents, it is quite possibly the most heartrending experience of their lives. One day, they are six months into a normal pregnancy. The next, they learn that their baby will be born too early. Though the fetus is very much alive in the womb, the parents need time to grieve for the perfectly healthy newborn that they’d hoped to have. They’d anticipated this baby for so long, it’s as though they’d lived with the child since before conception. They may have given her a name already and have probably always thought of her as perfect and complete. If this is an extreme case, a birth at say, 24 weeks of gestation, they will become the parents of a baby so tiny and light she will rest in the hand like a cent skin as delicate as that of a ripe pear, eyes and lungs unprepared for the air she must breathe. For parents about to deliver a premature baby, the neonatologist describes the boundaries of hope.

Most of these expectant parents will take on a long and difficult struggle that ends in success. Some will witness the briefest of lives. And less commonly, some will become loving caretakers for a child who lives to adulthood and is never able to sit up or feed herself. “It doesn’t happen to all the children,” says Silverman. “I give them percentages, and I tell them that percentages don’t matter if your child falls into that group—it’s 100 percent for your child.”

It’s a slow day at Magee’s NICU—only 42 babies on hand—which means that Charles Bender has a few moments to talk. His brown hair is neatly combed and touched with gray. He wears a blue shirt and a bright red tie spotted with dogs, cats, raindrops, and umbrellas. Despite the perky attire, he seems a bit weary as he walks the wide hallway of this newly opened NICU, until he’s asked to describe what goes on here. “We save babies’ lives,” he says without hesitation. A smile lights up his face as the thought consumes him. “There can’t be any greater reward.”

All parents want the same thing, says Silverman. They want “everything” done for their baby. But what is everything? For some, it means weeks or months in the NICU and prayers for a long and healthy life. For others, whose babies don’t respond to treatment, it means providing relief from pain and discomfort, wrapping the baby in a blanket, and allowing the parents to cradle her until she ceases to breathe. For parents about to deliver a premature baby, the neonatologist describes the boundaries of hope.

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The new NICU is as colorful as a preschool. Its design incorporates lessons learned at Pitt and elsewhere that show a direct connection between the quality of the environment and the health of the baby. Patients get single rooms, each defined by three walls and a long curtain. As long as the baby is in the NICU, this room is the family’s turf, where they can feel a measure of privacy, where they can bond with their baby, speeding his development into a healthy infant that can go home. Magee’s NICU will be able to accommodate 48 newborns in this way by January (plus 15 in other ward beds). Bender describes the traditional model of the NICU, which is still in use in many hospitals, as “the television model.” There are lots of babies together in one room, each in its own incubator. There are bright lights, beepers and buzzers, and lots of commotion.

“It makes a great television set,” he says, “but it makes a horrible place to be when you are sick.” About six years ago, the staff at Magee began to change the environment by dimming the lights, cutting down on unnecessary noise like the radio, and simply lowering their voices. Within a month, Bender says, they cut the use of sedation drugs by more than 50 percent, because the babies showed fewer adverse reactions that required sedation. Babies came off the respirators sooner, ate more readily, gained more weight, went home earlier, and began to show age-appropriate interest in their environment rather than hostility toward it.

Silverman arrives at Pitt as the School of Medicine’s new chief of the Division of Neonatology and Developmental Biology, having witnessed this evolution of NICU design in the past 20 years or so in NICUs at Washington University (St. Louis Children’s Hospital) and Harvard University (Children’s Hospital Boston). Insights learned in the NICU have made his work at the laboratory bench stand out.

“Gary is one of a rare breed of pediatric scientists,” says David Perlmutter, chief physician and chief scientist at Children’s Hospital of Pittsburgh and chair of pediatrics in the School of Medicine. “He is an MD/PhD who is both superb as a clinician and competitive as a scientist at the NIH [National Institutes of Health]. There are very few academic pediatricians who are competing successfully at the NIH while still involved in the clinical enterprise.” In neonatology, he says, there are even fewer prominent physician-scientists than in most pediatric subspecialties, perhaps because the field has flowered relatively recently.

Sessions “Sesh” Cole, the neonatologist who was Silverman’s clinical mentor at Washington University, puts the number at “fewer than six people around the country like Gary.” (Cole counts himself among that handful of scientists who are also clinical neonatologists.) “One of the only ways that we’re going to be able to care for babies better five years from now . . . is by bringing fundamental discovery research to the bedside. And Gary is one of the few people around the country who is genuinely able to do that.”

As a freshman at Washington & Jefferson College, Silverman appears to have been equal parts science prodigy and typical adolescent. The Youngstown native chose the
Small college in Washington, Pa., over others for one reason: They told him he wasn't too small (about 5-foot-9) to make the football team. For a kid who'd figured his football career ended with high school, that was the clincher.

That first year, he showed up unannounced at the office of Dennis Trelka, head of the biology department, to ask him to be his adviser. This would have been an unmitigated indication of Silverman's maturity if the discussion hadn't quickly turned into an argument. The freshman wanted to do an honors project in biology. Trelka said that wasn't possible. No student had ever done that before the junior year. Silverman was insistent, and Trelka finally suggested he might want to come back at another time, when he was ready to discuss this in a more effective manner, because he was not going to win this case. Furthermore, maybe he should consider asking someone else to be his adviser, because the two of them didn't seem to be hitting it off.

Silverman did come back another time, still wanting the head of biology to be his adviser. (He liked the fact that Trelka looked him in the eye and laid down the rules.) The eventual compromise was that Silverman would do his honors project as a sophomore. Throughout the next few years, Trelka would occasionally visit Silverman at Hahnemann Medical College (now Drexel) in Philadelphia, where Silverman had arranged to do summer research. The two have been close friends ever since.

Silverman was quite an athlete, admits Trelka. He was quick and coordinated, a four-year starter at corner-back and a track athlete who broke the college's pole-vault record. "But he was a better student than a football player," Trelka says with a hearty laugh. "And I would say that even if he were in the room."

As an undergrad, Silverman didn't know much about being an MD, except that it was a way to get into the sort of science he wanted to do—he was interested in immunology and cancer. He applied to a highly competitive physician-scientist program at the University of Chicago Pritzker School of Medicine. Eight applicants were accepted, he learned, and he was number nine. When one of those eight opted to go elsewhere, Silverman squeaked in. At Chicago, he worked in the lab of Richard Rothberg, head of pulmonary medicine at the pediatric hospital. Occasionally, Silverman would have to track him down in the cystic fibrosis clinic to discuss lab results. "I'd find him on the wards," Silverman recalls, "and I would watch him interact with families and patients. ... I don't think I've ever seen anybody as gentle with patients and families as he was. I think that had a pretty big influence on me."

Rothberg pushed Silverman into pediatrics simply through his example. He also told him, without explanation, that he needed to spend part of his career at Children's Hospital Boston, so Silverman applied for a pediatric residency there. He planned to pursue a fellowship there as well, in hematology-oncology. But in his third year of residency, he ran into a dilemma. He was in the fellowship director's office, being offered the hematology fellowship, but he couldn't sign the papers. Somewhere in his pediatric residency, he'd become intrigued by the incredible complexity of taking care of newborns. It was a critical care subspecialty, but it included this fascinating element of developmental disease. "Here," says Silverman, "you had this rapidly developing organism, and the diseases you were seeing were related to disorders of development, either acquired, because the child was born prematurely, or constitutional—there was some genetic component to it. And that's when I finally made my break with immunology, because I saw that and thought, This is really fascinating!"

Silverman went to see the director of the neonatology fellowship, Sesh Cole, and told him that he couldn't sign the hematology fellowship papers. That's good, Cole replied, because you really need to go into neonatology. In part, Cole wanted to recruit this promising scientist to his own field, but he had also watched the young resident in the NICU, and he saw the spark of interest. Silverman knew he was right. Neonatology was "one of the last frontiers of pediatrics," he says.

Cole soon relocated to Washington University in St. Louis, where he continued to mentor Silverman as a clinician. There, Silverman joined the laboratory of Stan Korsmeyer, whom Perlmutter refers to as "one of the best physician-scientists in the world." Korsmeyer had discovered the BCL-2 gene was mutated in certain types of cancer, and realized that the gene was fundamentally important to the control of apoptosis, or programmed cell death. This was the beginning of the modern era of apoptosis cancer research, which continues to this day.

From 1988 to 1991, Korsmeyer had Silverman build a map of the long arm of chromosome 18, which is where BCL-2 is. To do this, Silverman worked with genetics pioneer Maynard Olson in what was really the forerunner of the human genome project. Olson manipulated yeast to replicate DNA, creating the first maps of mapping human chromosomes. In the course of investigating chromosome 18, Silverman stumbled upon several genes for a class of proteins whose function was a mystery. Today, these proteins are the focus of the laboratory that he brings with him to Pittsburgh. They appear to be keys that will open up a whole new understanding of basic cellular functions and possibly lead to new lifesaving treatments for the tiniest of patients.

Silverman’s lab has zeroed in on a group of proteins known as serpins. They are protease-inhibitors, so they stop the action of specific enzymes. Many serpins are well studied and their functions understood. Silverman’s new boss, Perlmutter, for example, studies a serpin that, when inherited in a mutant form, causes a type of liver disease in children. One member of this serpin family inhibits an enzyme that attacks the lung. Others inhibit the clotting pathway. These proteins circulate in the blood-
Silverman’s serpins look similar, but they have at least one major tantalizing difference—they are not secreted into the bloodstream at all. For some reason, they are inside our cells. Silverman’s lab has already published evidence that one group of these serpins inhibits intracellular proteases, which he likens to molecular scissors that can injure cells. Programmed cell death is triggered by these scissors.

By knocking out individual serpin genes in the nematode worm Caenorhabditis elegans (see “Family Portrait,” below), Silverman is discovering that the proteins play important roles in basic cellular functions—he says that biologists never dreamed that serpins were involved in these processes. For example, when a cell is exposed to high salt concentrations, it shrinks, and before the cell gets damaged, it corrects itself and takes up water to return to its normal shape. Conversely, if the salt concentration outside the cell drops, the cell takes on water and swells. Normally, the cell controls the swelling before it ruptures. In worms with certain serpins knocked out, the cells are unable to adjust to these changing conditions and they die. Silverman thinks that these serpins inhibit intracellular proteases that kill off the cell when conditions change. Adjusting to changing salinity is one of the most basic cellular functions that all living things must perform. A lot of diseases are associated with changes in cellular volume, says Silverman. Diarrhea kills countless children worldwide through dehydration. In diabetic ketoacidosis, dehydration leads to cellular injury and death. In congestive heart failure, cells take on too much water. Serpins may be key to controlling these processes and mitigating the damage.

Other serpin genes appear to play a role in responding to bacterial infection. Many infectious organisms use proteases to either gain access to the cell or gain access to the body. They break through barriers to get into cells. They use their own proteases or they activate proteases of the host to survive and evade immune surveillance.

Silverman thinks that physician-scientists could learn to manipulate serpins to enhance protection against infection, possibly even in newborn patients. Some preliminary data suggest that serpins protect the lungs against protease-mediated injury. It looks like much of the chronic lung inflammation that premature babies suffer could be due to proteases. The serpins he is studying are highly expressed in the lungs but are not turned on yet in premature infants. Silverman can imagine a therapy that turns on the genes so that the body produces the serpins or another that actually provides such proteins to premature infants, delivered via the bloodstream or as an aerosol directly into the lungs—custom-made serpins for what ails you.

Silverman’s erstwhile mentor, Cole, predicts that these discoveries will lead to dramatic changes in treatment—perhaps providing therapy in fetal life, through the mother. Though he knows that Silverman entered medicine for the science, Cole remembers him for the way he has embraced both roles of the physician-scientist. One night in particular, amid the worst ice- and snowstorm of a Missouri winter, Silverman took a transport call in the NICU. A physician at a suburban hospital had an infant in serious trouble. He needed his patient to be transported to St. Louis, a two-hour trip, where more specialized care was available. Silverman worried for the safety of the ambulance crew and the infant should anything go wrong on those icy roads. He made a few telephone calls and arranged for a state trooper and a snowplow to escort the ambulance to St. Louis. Somehow, he was able to convince the powers that be that, though the plow driver and the trooper were probably busy this night, shepherding this baby to the hospital was the most important thing they could do. So, for the next few hours, the plow cut through the snow, and flashing lights pressed on through the stormy darkness, slowly pushing back the boundaries of hope.

FAMILY PORTRAIT

Most people don’t feel much kinship with worms, but medical researchers often look at life from a different perspective.

Gary Silverman, Pitt’s new chief of neonatology and developmental biology, spends a lot of time thinking about the tiny nematode worm, Caenorhabditis elegans. He’ll point out that at the cellular level, we’re a lot like C. elegans. There are certain processes in humans that can’t be studied in the worm, but Silverman is interested in how cells react to various stresses—for that, the 1-millimeter worm is ideal. It reproduces quickly and has a hermaphroditic form that permits self-fertilization—producing worms with the same genetic makeup. The fate of each cell from the zygote to the adult animal is known. The neurological pathways are completely mapped out. To top it off, the worm is transparent, so changes in development are easily observed.

Silverman has found genes for the proteins he studies in creatures as divergent as worms, humans, and even jellyfish, meaning these proteins were probably present in the primitive multicellular creature that was ancestor to us all. Through millions of years of evolution, the ability to produce these proteins has been conserved, presumably because they serve basic and vital cellular functions.

When Silverman started mapping human chromosomes 15 years ago, it took years to identify such shared genes. Now, he says, it takes about 15 minutes. “That’s why work that we do on something as fundamental as C. elegans can have immediate clinical import to a 700-gram baby that’s sitting in the NICU at Magee,” he says. “You can discover a biochemical pathway in a very simple organism and then sit at your computer and determine whether or not any of those proteins exist in humans.

“You’re going to find enough clues there to be able to ask pretty relevant questions in mammalian or human systems pretty quickly.” —CS

In a close-up of the worm C. elegans, a newly discovered protein glows green where it is expressed. Worms overexpressing this protein experienced developmental abnormalities (white arrow), suggesting a critical role for such proteins in development—perhaps of humans as well as worms.