BREAKTHROUGH
Boston Children's Hospital

and the Bold Ideas that Change the World
For the children, families, healers and scientists of Boston Children’s Hospital.

Together, they break through the impossible to create healthier futures for all.
WITH GRATITUDE

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In 1869 a small group of Bostonians laid out a vision for a new children’s hospital. It would be a center for healing, yes. But it would also be a hub of discovery, dedicated to “the attainment and diffusion of knowledge regarding the diseases of children.”

With those words our founders shaped the future of both Boston Children’s and child health worldwide. They were the farsighted architects of a culture driven to find solutions, to do better by kids tomorrow than we can today. They set us on a path to improve health not for one child or a hundred but for all children. We have never wavered.

If our founders were here to celebrate our 150th anniversary with us, how proud they would be. Millions owe their lives to Boston Children’s Hospital. Premature babies who once struggled to breathe. Infants living despite having only half a heart. Children protected from polio. Anyone chemotherapy has saved.

Break Through: Boston Children's Hospital and the Bold Ideas that Change the World chronicles these achievements and more. It marks 150 years of delivering healthier futures for children and families. It proudly shares our history. But it also looks forward. Discovery and innovation are like a long, many-branched river. Each generation—no matter how brilliant—can navigate only so far. Then it’s left to the next one to pick up the oars and paddle on.

Will today’s big dreams be tomorrow’s headlines? We can’t predict the future. But we can guarantee that we will never, ever stop exploring. Our commitment is born of seeing children suffer. It compels us to take the tough cases, ask the tough questions and relentlessly pursue better ways to make children whole. It always has, and it always will—until our 200th anniversary and beyond.

Sandra L. Fenwick
Chief Executive Officer
Bad milk was an urgent medical concern. In the decades before pasteurization, conditions on farms were often unsanitary. Storage and transport—particularly in summer—turned milk bottles into microbe factories, and tubercular cows transmitted their disease. Children died at alarming rates. Nearly half of all deaths in 1870s Boston were children under five, and milk-borne illnesses were among the major causes.

In 1891, Rotch and chemist Gustavus A. Gordon established the world’s first milk lab. Their goal was to produce milk “freer from dirt, from bacteria, and thus from disease, than has ever before been accomplished.” Soon they were opening milk labs across the continent.

MILK AS MEDICINE
Rotch believed milk’s composition was as important as its cleanliness, and his milk lab was both research center and pharmacy, dispensing milk by prescription. He devised an elaborate “percentage” infant feeding method to adjust the proportions of fats, sugars and protein in cow’s milk to approximate human milk as closely as possible. And not just any human milk. Rotch altered proportions based on an individual infant’s illness and an analysis of the mother’s milk—an early foray into personalized medicine.

The Milk Man
Thomas Morgan Rotch devoted himself to child health at a time when fewer than 50 physicians nationwide treated childhood disorders. He was the nation’s first full professor of pediatrics and wrote the field’s first textbook, as well as the first American text on pediatric radiology. He presented the first paper on premature birth to the American Pediatric Society, designed an early incubator and, in the words of a contemporary, “raised pediatrics to the rank of genuine science.” Believing pediatricians should advocate on behalf of child health, he lobbied Congress to establish the Children’s Bureau. Little wonder he is considered one of the fathers of pediatrics.

MILK ALLERGIES
Today’s milk may be pure, but it can still endanger. Even a trace can send an allergic child to the ER. Desensitizing patients with tiny but increasing doses of allergen can help, but nearly all children react during treatment. Boston Children’s allergists led by Lynda Schneider may have the solution. They combine desensitization with a drug that quiets the immune system. Two pilot studies—one with milk, the other with peanuts—have shown promise.

Rotch published and taught his percentage method widely. Complex though it was (adherents used slide rules), Rotch’s method dominated infant feeding for three decades. It faded as pasteurization took hold and rigorous studies revealed the dubious assumptions on which percentage feeding was based. Rotch’s feeding system may have been more pseudoscience than science, but he was among the first to integrate lab and clinic and to personalize treatment—approaches that are the mother’s milk of medicine today.

The Purest Milk
1891
Death dispenses milk in a 19th-century cartoon.
Hunnewell building, supplied patients with germ-free milk.
Gridlock of an earlier era: the cows grazing on Longwood Avenue, in front of the hospital’s Hunnewell building.
The More Things Change...

Keeping squirmy children still for an X-ray required sedation until 1911, when the hospital bought a faster machine. Most imaging today can be done quickly, but some MRI sessions last 90 minutes or more and children may still require sedation. Pre-scan prep, advanced imaging techniques during and after the scan, and video goggles to distract patients have helped Boston Children's reduce sedation rates to 4 percent, compared to 30 to 45 percent at most children’s hospitals. Distraction is a time-tested technique. Stories did the trick in the 1950s (left).

A FEW HONEST PHYSICIANS

William Roentgen’s 1896 discovery of the X-ray galvanized the scientific world. According to one wry historian, Roentgen rays were soon being used by “physicists, engineers, photographers, some charlatans and a few honest physicians.”

“The Roentgen method is...in many cases proving expert physical examinations to be wrong.”

—THOMAS M. ROTCH

“A few” deserves emphasis. The medical community was slow to embrace what many viewed as mere shadows on paper. But Boston Children’s saw beyond the fuzzy contours of the earliest X-rays to a clear future of more precise diagnosis. The hospital brought on a radiologist, Percy E. Brown, in 1900 and founded the nation’s first radiology department in 1903—four years before Mass General and decades before most children’s hospitals.

NO OPERA, NO X-RAY!

The challenges early X-ray men such as Brown faced were many. Technical quality was poor and exposure time long. Antsy children required sedation. X-rays were made on huge glass plates, and moving them was “a back-breaking, hand-blistering job.”

X-ray burns led to amputations and worse.

At Boston Children’s, Brown faced a unique challenge: that wire run across the street to power the X-ray machine. “When there was no music there was no current,” he reported. “No opera, no X-rays!”

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X-ray burns led to amputations and worse.
In the early 1900s, a third of patients had tuberculosis of the bones. X-rays guided their treatment. The donkey’s bones were fine—he pulled a cart around the hospital’s convalescent home.

Early X-rays could not image internal organs. Today’s CT scans (kidney and ureter, top) reveal an organ’s architecture in exquisite detail, down to the blood vessels, while MRIs (heart, bottom) can even capture function. This one shows stresses on the heart muscle at work. Boston Children’s has led in developing pediatric urologic and cardiac imaging.

TO SEE THE UNSEEN
Dependent on arias though it was, the young department flourished. Boston Children’s was largely an orthopedic hospital back then, and bones were what early X-rays imaged best. The hospital’s 1903 annual report enthusiastically related the importance of “the newly equipped x-ray department... in determining with certainty the extent of the deformities to be treated.”

The department was both a research and diagnostic center. Boston Children’s made the first substantial US contribution to the literature (a differential diagnosis of a hip disorder) and published the first US textbook on pediatric radiology. From the days of Roentgen rays to today’s MRI sequences, it has pioneered tools and techniques to illuminate the inner topography of childhood disorders.

GROWTH CHART FOR THE BRAIN
First smile, first step, first word—we know when a child should reach each milestone. When she doesn’t, an MRI can reveal why. But discerning subtle deviations from normal in a child’s rapidly developing brain can challenge experienced pediatric radiologists, let alone novices.

The Boston Children’s Digital Health team partnered with GE Healthcare to address this challenge. They developed a cloud-based decision support tool that allows radiologists to view a patient’s scan and an age-matched normal control side by side. In a Boston Children’s study conducted by Sanjay Prabhu and colleagues, radiology trainees were 45 percent faster and twice as accurate when using these “normative references.” GE Healthcare is testing the tool with pediatric partners worldwide.

This decision support tool is just a first step. The ultimate goal is an AI system that moves diagnosis from qualitative interpretation to quantitative analysis. That project is underway.
Medical Maverick

James Gamble’s grandfather cofounded Proctor & Gamble and his father, a chemist, developed the formula for Ivory soap. Perhaps his father’s career inspired Gamble’s own decision to study disease “using the methods of chemistry.” This was so unusual that one mentor feared Gamble would become “lost in a ‘no man’s land’ between clinical medicine and fundamental science.” Rather than getting lost, Gamble blazed a trail for others.

DEHYDRATION

1923

Sitting on the porch of his beloved summer home in Maine, gazing at the ocean, James Gamble had an insight that would help save untold lives: perhaps our inner waters mirror the sea. After all, he mused, life began in an ancient ocean. Perhaps we have internalized the balance of water and salts (electrolytes) that nurtured earliest life.

OCEANIC CHALLENGE

Figuring out the composition of our inner waters was critical. When Gamble began his research just after World War I, diarrheal diseases filled hospital wards. They were particularly dangerous for infants. Diarrhea emptied tiny bodies of their liquid reserves, literally drying out babies too depleted to eat or drink. Doctors knew they needed to replace lost electrolytes as well as water but did not know which ones, at what concentrations. Despite their best efforts, 90 percent of severely dehydrated babies died.

Gamble attacked this problem with a then-radical approach: chemistry. He was one of a handful of pioneers applying biochemical analysis to human disease. Beginning at Johns Hopkins and continuing through his decades-long career at Boston Children’s, he precisely measured the electrolyte concentrations in different body fluids in health and disease.

“Before our extremely remote ancestors could come ashore to enjoy their Eocene Eden or their Paleozoic Palm Beach...[they needed] an enclosed fluid environment which would take the place of sea water.”

—JAMES L. GAMBLE

A “Gamblegram” may sound like an urgent wire from Vegas, but it conveys more serious gains and losses.

Gamblegrams illustrate electrolyte balance in health and disease and are still a useful tool today.
BALANCING ACT
Gamble’s seaside musings turned out to be right: the fluid in our blood and surrounding our cells is strikingly like seawater. Gamble further showed that all body fluids have the same concentration of electrolytes. Our kidneys and hormones keep that concentration steady: we thirst when the concentration of electrolytes gets too high and pee when it gets too low.

These findings formed the basis of fluid replacement therapy. Although others contributed, Gamble’s impact is regarded as “momentous.” Today, few babies in developed countries die of dehydration, and numbers elsewhere are diminishing.* Countless lives have been saved because an intrepid scientist spent a soft summer day gazing out to sea.

Another Replacement Therapy
Mark Puder remembers the call. His colleague was desperate. The treatment that sustained his patient’s life now threatened it: the child’s liver was failing, a well-known risk of long-term IV feeding. The colleague, a fellow surgeon, knew that Puder and pharmacist Kathleen Gura had discovered why the standard supplement caused liver damage. It was the fat, derived from plant oils. By swapping fish oil for plant oil they had eliminated liver damage in animal studies in Puder’s Vascular Biology Program lab. Could they give their formula to his patient? They did, with lifesaving results. Clinical trials followed, and the number of deaths and liver transplants dropped dramatically. The formula, Omegaven, is now FDA approved.

FANTASTIC VOYAGE 2.0
The child whips out her iPhone, loads the app, dons VR glasses and enters a cavernous world of long, snaky passages. The latest Oculus Rift fantasy game? Hardly. She’s a GI patient at Boston Children’s and is exploring her own intestines.

The dehydrating, diarrheal diseases of Gamble’s era may no longer be a threat, but this girl and tens of thousands like her endure the distress of inflammatory bowel disease. Symptoms can be embarrassing as well as painful, yet these children often rebel against treatment. Patient education is key to adherence, but materials to communicate effectively with patients and their families are lacking. Endoscopy reports meant for the medical record and small, static images are all most doctors have had.

That’s why Boston Children’s gastroenterologist Michael Docktor teamed up with Klick Health, a health marketing agency, to transform today’s most engaging technology into a patient education tool. Their app, HealthVoyager GI, offers patients an immersive, virtual tour of their own gastrointestinal tracts. The hope is that this personalized experience will help children understand their condition and motivate them to stick with treatment.

*Diarrhea remains a threat in poor countries. It kills more than 2,000 children a day—more than AIDS, measles and malaria combined.

The Weight of Water

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INFANTS 70% of body weight
ADULTS 60% of body weight
“Surgeons were scared to death of babies.”

This bald statement, from one-time Boston Children’s fellow and US Surgeon General C. Everett Koop, sums up the state of pediatric surgery a century ago. In the early twentieth century, not one US surgeon devoted his practice exclusively to children. General surgeons would remove a child’s appendix or drain fluid from the chest—the same operations performed on adults—but few attempted to correct congenital malformations.

Surgeons had good reason for fear. Anesthesia was rudimentary and blood transfusions unsafe. There were no antibiotics to control infection, and physicians did not yet appreciate children’s specific fluid and nutritional needs. They treated their young patients as “a fraction of an adult by weight,” said Koop. Any operation was risky, and infants born with a life-threatening anomaly invariably died.

“We were saving whole lifetimes that had never been saved before.”
—LADD RESIDENT H. WILLIAM CLATWORTHY, JR.

BIRTH OF A FIELD

Enter William E. Ladd. A Harvard-trained surgeon, Ladd began a career in general and gynecological surgery in 1908. He was in private practice but also volunteered to operate on “charity cases” at local hospitals. In 1910 Ladd added Boston Children’s to his roster. He was soon dismayed by how little his profession could offer children. Unwilling to accept that so many young patients were doomed, he devoted himself to unraveling the mysteries of their disorders.

“The autopsy table was his library,” recalled one of Ladd’s residents. When a patient died of an unknown cause, Ladd would make his way to the pathology room. He would examine the baby’s twisted intestine or malformed colon, partly formed esophagus or blocked bile duct, deciphering what was wrong and what might have been done to fix it. By focusing on accidents of birth, Ladd and a handful of other pioneering surgeons gave birth to a field.

GREAT LEAP FORWARD

Ladd became surgeon in chief at Boston Children’s in 1927, a post he held for 18 years. His tenure coincided with improvements in anesthesia and infection control that enabled longer operations and safer recoveries. Against this backdrop he established a culture of inquiry grounded in keen observation. He and his surgical staff spent hours not only at the autopsy table but also in the lab. Defects of the gut, the esophagus and, ultimately, the heart began yielding to their scalpels. They unflinchingly reported both failure and success. As success began to outweigh failure, Boston Children’s became a destination for both patients and aspiring pediatric surgeons.
William Ladd’s hands were so large he could cradle a preterm infant in one palm. His compassion was outsized, too. One observer noted that his successful care of his patients was due to his care for them. Numerous honors were his. In 1941 Harvard Medical School established the William E. Ladd Chair in Children’s Surgery, the first such professorship in the world. In 1954 the American Academy of Pediatrics inaugurated the William E. Ladd medal to recognize a pediatric surgeon who has made a singular contribution to the field.

Ladd’s lasting impact is equal reason for “just pride.” In 1997, 70 years after Ladd assumed leadership at Boston Children’s, a genealogy of pediatric surgery traced the lineage of 75 percent of all practicing pediatric surgeons in North America directly back to him. The authors described a “long golden cord” stretching from Ladd and binding the field together. It grows longer every year.

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A Healer’s Hands

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“...The type of operations performed are in greater and greater number on patients who a few years ago would have been considered beyond surgical help,” Ladd wrote in 1937. “That our mortality in these difficult and seemingly hopeless cases is low is a reason for just pride.”

Break Through: Pediatric Surgery

Once-fatal abdominal conditions cured by Boston Children’s surgeons exemplify the hospital’s impact.

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<td>Ladd procedure fixes twisted small intestines</td>
<td>Swenson pull-through cures megacolon, a disorder of the large intestine</td>
<td>Schuster method closes openings in the abdominal wall through which organs protrude</td>
<td>Kim STEP procedure lengthens short bowel</td>
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Surgical Sam, the world’s first breathing, bleeding pediatric trainer, brings unprecedented realism to surgical simulation. Developed by SIMPeds and the Chamberlain Group, it is now on the market, improving outcomes for children worldwide.

SIMULATION SAVES LIVES

A speeding car. A rain-slick road. A boy in the OR, clinging to life. Emergency surgery stems a hemorrhage, but the boy’s heart rate plummets. Pressure in the OR soars.

But it isn’t real. This is one of dozens of training scenarios offered by SIMPeds, the Boston Children’s Simulator Program. Established in 2003 by Jeffrey Burns and directed by Peter Weinstock, SIMPeds opened one of the first OR simulation suites in pediatrics in 2016. Within its walls, surgical teams operate on high-tech “trainers” that breathe and bleed as surgeons work through layers of skin and muscle that feel real. New surgeons and nurses safely get experience that would take years to build through real-life patient encounters.

Experienced professionals plan and practice the most daunting operations. Teams iron out kinks in their choreography before moving into the OR.

SIMPeds continually develops new scenarios, preparing surgeons in ways William Ladd could never have imagined. It is making surgery safer not just at Boston Children’s but around the world: the program has partnered with 16 hospitals in 13 countries to introduce simulation training.
She asked for ice cream. Everyone cried.

One moment she lay unconscious, her skin tinged blue, her chest muscles paralyzed, her diaphragm too weak to sustain a breath. The next she was inside an 800-pound metal tank outfitted with pumps, pressure valves and a rubber collar. Doctors sealed the collar around her neck, and the tank became air-tight. Then they started the pumps. Air flowed out, in, out, in. The child inhaled, exhaled, inhaled, exhaled. Her skin turned pink. She woke up. Asked for ice cream.

This Boston Children’s patient, an eight-year-old identified only as B.R., had polio and was the first person in the world treated with an iron lung. The joyful tears accompanying her recovery weren’t for her alone. They were for the thousands of polio patients who could now be saved from dying of respiratory failure.

SUMMER SCOURGE
Polio was a cruel and capricious visitor. It struck mainly in summer, felling privileged kids canoeing at summer camps and poor ones splashing in city pools. It swept through neighborhoods, sickening children on one block but leaving those on another unscathed. Some children were back at play the next week; others, paralyzed for life. Some years the outbreak was mild but in others it overwhelmed hospital wards and staff. In 1955, during the last and worst polio epidemic in Boston, carloads of anxious parents and feverish children jammed Longwood Avenue. Medical residents ran from car to car, checking for children whose labored breathing signaled a need for immediate care. The flood of patients was so great that the hospital ran out of cribs—and nurses. Other hospitals loaned both.

MUSCULAR RESPONSE
Boston Children’s had long experience responding to such crises. Robert W. Lovett, orthopedic surgeon in chief from 1912 to 1922, was an ardent student of the disease. He had defined its three stages—acute, convalescent and chronic—and advocated intense muscle training during convalescence to rebuild strength and maximize mobility. Lovett devised methods to test muscle strength and a rehab strategy that combined exercise with massage, heat and hydrotherapy. In 1914 he launched a course to train nurses and others in the techniques.

Iron Lung
Philip Drinker, an engineer at the Harvard School of Public Health (HSPH), invented the iron lung. He built the prototype on the roof of what was then HSPH and later became the Wolbach building at Boston Children’s. He was the first to test his new machine. Look closely and you can see his head resting on two pillows.
Ping-pong, stairs, bicycles and even a replica of a bus helped patients learn how to reengage in normal life despite paralysis.

Flexi-mitts promise to turn child’s play into a powerful diagnostic tool.

The Long and Short of It

For nearly 30 years, Boston Children’s orthopedist William T. Green and his associate Margaret Anderson meticulously recorded leg lengths in normal and paralyzed children.1 Their growth charts were adopted worldwide and are still used to predict—and correct—leg-length discrepancies, which were a significant cause of disability for polio survivors. Green also pioneered operations to improve mobility for polio patients. These, too, remain in use. Since polio is all but eradicated, the patients are children with cerebral palsy and other congenital bone or muscle disorders.

Their training came none too soon. Polio ravaged the country in 1916. Boston Children’s was ready not only to treat its own but also to help others. Hospitals from as far as Minnesota and Montana sent nurses for polio rehab training, while Lovett organized care for patients throughout Massachusetts and Vermont.

The 1916 epidemic was so bad that Massachusetts established a permanent commission to coordinate diagnosis and care for the state’s polio victims. It was housed at Boston Children’s and ran by a Boston Children’s orthopedist until 1961. By that time, new cases of polio were becoming rare, thanks to another chapter in the history of polio— and Boston Children’s (see page 42).

A SOLUTION IN HAND

A simple system for measuring muscle strength was among Robert Lovett’s great contributions. With it, any physician treating polio patients could more accurately diagnose remaining capability and determine which muscles were most promising for treatment.

Today, a different group of patients urgently needs early and accurate diagnosis of brain-muscle communication: premature infants. The tiniest of the tiny—those weighing less than 1,000 grams at birth—are at grave risk of neuromotor and other disabilities. But physicians can’t predict which babies will develop problems. This is heartbreaking because early treatment could save children from a lifetime of limitation.

A solution may be at hand: flexi-mitts. The brain-child of Boston Children’s psychologist Eugene Goldfield, flexi-mitts are soft, wearable sensors that affix to a toddler’s hands. They measure the amount of force a child exerts and the angle of the joints during play. These measures indicate how well the child can plan and execute a motion. At-risk toddlers who diverge from healthy peers could be candidates for treatment. Goldfield is developing the mitts with colleagues at the Wyss Institute for Biologically Inspired Engineering and Beth Israel Deaconess Medical Center. A study begun in 2017 is informing design and providing data on normal development.
1932 Rh DISEASE

The first two babies piqued little interest. Siblings born 18 months apart, each had life-threatening anemia; each received blood transfusions and recovered. But then their little sister came along.

She, too, was grievously ill at birth. She had jaundice, bruising and an enlarged liver and spleen. Her symptoms subsided with treatment, but at 18 days she showed signs of anemia identical to those of her siblings. This strange occurrence sent Louis K. Diamond on a quest that would culminate in a life saving treatment for thousands of babies.

ONE DISEASE OR MANY?
Diamond was a pediatric hematologist, a specialist in blood disorders. He’d become hooked on the field as a resident, when he recognized that a child diagnosed with Hodgkin’s disease actually had mononucleosis, one of the first cases reported.

Diamond’s diagnostic sleuthing came into play again with the three siblings. He combed the literature for similar cases and studied the hospital’s own patients. Once again, he overturned a diagnosis—actually, hundreds of diagnoses. Diamond had found that four diseases long thought to be distinct were actually one, which he called erythroblastosis fetalis (EF). This insight was “a cornerstone, on which five decades of medical progress were to be built.”

When a mother who is Rh- has an Rh+ baby, her body may produce antibodies against the Rh factor. Her first child will be fine, but a second Rh+ baby is at risk.

In its first 10 years, the Blood Grouping Laboratory received more than 190,000 blood samples from near and far. It performed more than a million tests. (Louis Diamond is at right.)

TESTS AND A CURE
Progress on EF began in earnest in 1939, when researchers in London discovered its cause: the newly identified Rh factor, a blood protein. The presence of Rh in a baby whose mother didn’t have it could trigger a ferocious immune attack, destroying the infant’s red blood cells.

Louis Diamond and the Red Cross
During World War II, the military turned to the Red Cross to collect blood. After the war, the Red Cross turned to Louis Diamond to transform its wartime effort into a permanent National Blood Program. As the program’s first technical director, Diamond established 35 blood banks across America.
Researchers worldwide rushed to develop a test to determine mother and infant Rh status and a treatment to save the babies.

In Boston, hospitals banded together to support a new Blood Grouping Laboratory at Boston Children’s. “This work was so new and perplexing that it could not be performed by the regular laboratories and so important that it could not be neglected or delayed,” Diamond explained. The lab soon developed the first definitive test for Rh sensitization (earlier tests missed 50 percent) and a practical method of exchange transfusion (the total replacement of a baby’s blood), which cured the disease. Diamond’s method became the world standard. It saved more than 200,000 babies in just the US before a serum to prevent Rh disease became available. That serum is so effective that few babies are born with Rh disease today.

WHAT’S YOUR TYPE? The International Society of Blood Transfusion recognizes 36 blood group systems, not just ABO and Rh. Some 600,000 different combinations of blood antigens are distinguishable in human blood!

Break Through: Rh Disease

1932
Erythroblastosis fetalis (Rh disease) identified

1942
Blood Grouping Laboratory opened

1945
Test detects Rh sensitization in all women

1946
Exchange transfusion cures babies

ANOTHER BLOOD DISORDER SOLVED

A decades-long hunt for the cause of a rare blood disorder ended in 2018. The disease is Diamond Blackfan Anemia (DBA), named for Louis Diamond and his Boston Children’s colleague Kenneth Blackfan, who identified it in 1938. DBA patients don’t make enough red blood cells, and Boston Children’s researchers have figured out why.

The first clue came in 1978, when David Nathan discovered that patients’ red blood cells form but fail to mature. Vijay Sankaran has now found the reason: the cells can’t make a vital protein because they have too few ribosomes, which are needed to assemble proteins. Gene therapy may one day supply the missing protein and a cure. Meanwhile, a drug Leonard Zon and George Q. Daley discovered promises to boost red blood cell counts for DBA patients and is due to enter clinical trials.
The babies fell asleep to Betty Lank humming. They awoke to her softly singing hymns. In between, their every breath was in her hands.

Lank was a nurse anesthetist. During her 34 years at Boston Children’s, her soothing soprano calmed some 16,000 children, from hours-old babies to teens. But her impact reached further. “We loved those little babies,” she reminisced at age 95, and that love motivated innovations that improved anesthesia care for children everywhere.

Ether was introduced in 1846. It was initially perceived as so easy to give that anyone handy was roped into service—orderlies, medical students, even stretcher-bearers during World War I. No matter that they weren’t trained. As Robert Smith observed, “The vomiting, convulsions, and occasional fires and deaths that were introduced along with ether were overlooked.” The field became increasingly professionalized during the 20th century as nurses and physicians established training programs.

FIELD-SHAPING PARTNERSHIP

Lank oversaw anesthesia at Boston Children’s until 1946, when Robert M. Smith became the hospital’s first full-time physician anesthesiologist in chief. Before then, anesthesiology had been largely a nursing specialty. But World War II presented an urgent need for battlefield anesthetists, and many enlisted physicians stepped up. Smith himself had directed anesthesia for General Patton’s army in Europe.

At Boston Children’s, Lank and Smith formed a formidable team. They improved patient monitoring: Lank adapted techniques for measuring arterial blood pressure to children, while Smith introduced continuous monitoring. This was a revolutionary idea and set a new standard. Smith also demonstrated the benefits of using breathing tubes and muscle relaxants in children.

These advances, plus safer anesthetics and improved technology, enabled Lank, Smith and their peers to keep children safely anesthetized for increasing lengths of time. This in turn allowed surgeons to undertake more complex operations. By 1969, when Lank retired, many once-fatal conditions were routinely corrected and pediatric anesthesia was an established specialty.

Newborn Pain

Both pain and the medications to treat it can be unhealthy, particularly for a newborn’s brain. We don’t know how much analgesic is enough or too much for a baby; we can’t predict the long-term effects. To find out, Christos Papadelis and colleagues are developing the first system to integrate objective measures of an infant’s pain. A mobile unit placed by the baby’s bed tracks brain waves and physiological changes such as sweat. The goal is to inform pain management for NICU patients, potentially saving infants from brain damage and their parents from added distress.
Pain fibers are activated when cellular “gates” called ion channels open. Many analgesics work by blocking these channels. But what if, instead of blocking ion channels, a drug used them to infiltrate the cell and silence its activity once inside? Neurobiologist Clifford Woolf and colleagues have created compounds that do just that. What’s more, they’ve engineered the compounds to enter only channels that are unique to pain fibers. The compounds should thus have high selectivity and no unwanted effects. A startup formed in 2018 is developing this Trojan horse of a drug.

Anesthesiologists Charles Berde and Daniel Kohane, along with Chilean colleagues, have turned a nerve-numbing toxin into a safe local anesthetic. The toxin, NeoSTX, is produced by algae like those that cause red tide. Researchers long recognized its medical potential but didn’t know how to give it safely. The Boston Children’s team solved this problem by combining NeoSTX with other drugs. Their new anesthetic appears to block pain without affecting the heart or brain, as other anesthetics do, and a single injection provides days of relief. A German pharmaceutical company licensed the drug and began clinical trials in 2018.

In another novel approach, Kohane is using light or ultrasound to release a pain blocker just where and when it’s needed. He and colleagues bundle the drug into minuscule sacs called liposomes, which can be delivered to nerves at the site of injury. The liposomes consist of lipids (fats) and light- or ultrasound-activated sensors. When the sensors are triggered, the liposomes release their cargo. This system may one day provide patients with safe, on-demand pain control at the push of a button.
1938

The operation could have ended his career. But Robert Gross did it anyway.

His patient, seven-year-old Lorraine Sweeney, experienced life through the living room window, watching friends play hopscotch and jump rope when she could not. She was thin, tired and weak, her heart failing.

Sweeney had a patent ductus arteriosus (PDA), an open channel connecting the heart’s two major blood vessels. The ductus is a normal part of an unborn baby’s circulation but should close shortly after birth. When it doesn’t, excess blood surges into the lungs and the heart’s left side must work much harder. The heart enlarges and ultimately fails.

On an August morning in 1938, Gross opened Sweeney’s chest to reveal her PDA. He rested a finger on her beating heart and felt a massive tremor. Through the stethoscope it sounded like rushing steam, almost deafening. But then Gross tightened a silk suture around the offending channel. Sweeney’s heart quieted. The roar was gone. The tremor was gone. Gross tied a knot and permanently closed the PDA.

HEARTENING PROGRESS

When Gross tied off that vessel, he opened a new field of surgery. Before then few surgeons had dared breach “the sanctity of the human heart,” and none had succeeded. Once Gross showed it could be done, progress was swift. In Stockholm surgeons repaired a narrowed aorta. In Baltimore they relieved symptoms of “blue baby” syndrome. In Minneapolis they performed the first open-heart surgery (on an adult).

Back at Boston Children’s, Gross and his successors continued to make field-defining contributions: The first aortic graft, a major milestone in vascular surgery. The first permanent pacemaker implanted in a child. The first operation to correct what was then a uniformly lethal condition, hypoplastic left heart syndrome. The first repair of a newborn baby’s heart.

1960

Robert Gross implants the first permanent pacemaker in a child

1983

William Norwood corrects hypoplastic left heart syndrome

2004

Pedro del Nido converts a one-ventricle heart to normal circulation

NEWBORN HOPE

For decades following the first open-heart operation, surgeons repaired children’s, but not infants’, hearts. Newborns were seen as too fragile to survive. Years of research in the laboratory convinced the cardiac team at Boston Children’s otherwise. On January 2, 1983, they corrected transposition of the great arteries in a four-day-old baby.

Aldo Castañeda, chief of cardiac surgery at the time, reflected that “this event initiated the era of neonatal open heart surgery.” Around the world, neonates destined to die lived. Others who would have been saved as children were spared years of living with failing hearts.

Robert Gross received the Lasker Award twice, one of only two physicians ever to be doubly honored.

Heart Healthy Mom

Lorraine Sweeney was sitting up and playing with a doll two days after her famous operation. By 1983, the 25th anniversary of her surgery, she was Lorraine Sweeney Nicoli, mother of two and appearing on the Today Show as the American Heart Association’s Heart Mother of the Year. By the 80th anniversary, in 2018, Sweeney Nicoli was a grandmother, great-grandmother and the world’s longest-lived survivor of congenital heart disease surgery.
SURGERY MEETS SCIENCE

The research leading up to that first neonatal heart repair is another measure of Robert Gross’ enduring impact. “Gross had this concept that you really need to understand why an idea would work, or if it didn’t work, why it didn’t work,” said Chief of Cardiac Surgery Pedro del Nido. “He established the tradition that new things get tested in a laboratory before you take them into children.” 3

Gross had repeatedly practiced the PDA procedure in the lab before entering the OR that August morning in 1938. Years later, he jokingly told Sweeney that he would have ended up a chicken farmer in Vermont had she not survived. He was only 33 and the chief surgical resident when he performed her operation—an operation his boss, William Ladd, opposed.

Gross had waited until Ladd was on vacation, halfway to Europe, to schedule the PDA repair. Ladd learned of his protégé’s audacity from newspaper headlines. The relationship between the two was never the same. But neither was the world.

Virtual Surgery

Successive generations of imaging technologies—from catheter-guided cameras to echocardiograms to CT and MRI scans—have provided ever-finer views of the inner workings of the heart. They have made diagnosis more precise and surgical planning more reliable. But they are nothing compared to what Tal Geva, chief of cardiology, envisions. Geva and colleagues are developing dynamic computer models of the heart by fusing images from multiple sources. The resulting multidimensional view would enable surgeons to model and test specific interventions.

S-T-R-E-T-C-H

Surgeons today routinely return young hearts and vessels to health by replacing a valve or a narrowed segment of aorta. However, artificial valves and grafts don’t grow with the child, so they must be replaced. Two innovations promise to eliminate these repeat operations. Pedro del Nido and colleagues at Brigham and Women’s Hospital are designing a valve with a braided outer rim inspired by Chinese finger puzzles. 4 It would elongate as the child grows. Heung Bae Kim’s inspiration comes from nature. Abnormal pressure (from a tumor, for example) can cause a blood vessel to stretch. Kim is using tissue expanders (see photo) to replicate this process in patients and create enough natural tissue to repair a narrowed abdominal aorta. 5

Cellular power packs called mitochondria are jolting dying heart cells back to life. Harvested from a patient’s healthy muscle cells, the mitochondria are injected into the heart toward the end of bypass surgery. This ingenious procedure, devised by researcher James McCully, is saving kids like Avery Gagnon (left).
Millie was drowning in her mother’s milk. Even a single sip triggered a spasm of vomiting and coughing that turned her blue. She was rushed to Boston Children’s on her first day of life.

Millie had been born with a gap in her esophagus and a connection between it and her windpipe where none should be. No baby with this condition had ever lived. But Millie did—and made medical history as one of the first two children in the world to survive it.

**BAD CONNECTIONS**

The condition was as difficult to correct as its name is daunting to pronounce: esophageal atresia (EA) with tracheoesophageal fistula (TEF). EA is a gap in the tube connecting the mouth and stomach. It is relatively rare, affecting one in 3,000 live births. Most often, babies who have EA also have TEF, an opening between the trachea (windpipe) and esophagus that allows food to pass into the lungs.

Decades of bold but failed attempts to treat the disorder had preceded Millie’s arrival at Boston Children’s. Most entailed efforts to feed babies directly through the stomach. This was futile for an infant with TEF because the contents still sloshed into the trachea. In 1929 Boston Children’s radiologist Edward Vogt published the first X-ray-based classification of EA to discriminate among those with and without TEF and different types of the latter. Even as he offered this guide, however, Vogt lamented that the condition was “apparently hopeless.”

“Since the majority of these infants are entirely normal in other respects,” he wrote, “it is hoped that some ingenious surgeon will eventually devise a cure.”

**BRIDGING THE GAP**

That “ingenious surgeon” turned out to be Vogt’s own colleague William Ladd. Ladd and a peer in Minneapolis simultaneously, though independently, devised a three-step procedure to close the fistula, place a feeding tube and then create a new esophagus with a tube formed from skin.

Other advances followed. Surgeons learned to directly close short-gap EAs and to bridge long gaps with a piece of colon rather than a skin tube. Within a decade the hopeless turned hopeful. Millie, we know, thrived. She ate normally, played, went to school, married. Ladd danced at her wedding.

**NEW METHOD GAINS TRACTION**

An implantable robot may one day give children with long-gap EA a natural esophagus. At Boston Children’s, these patients already benefit from a grow-your-own technique. Hospital surgeons exert small amounts of tension on the two disconnected ends of the esophagus to stimulate growth. The segments are usually long enough to join in just two to three weeks.

John Foker developed this procedure while at the University of Minnesota. In 2009 he began working exclusively with Boston Children’s surgeon Russell Jennings to fine-tune the technique. Jennings and team have since developed it further, and Boston Children’s is the world center for the Foker process.

Initially, infants were in a medically induced coma during the Foker process so surgeons could safely increase tension. Now, surgeons use tiny telescopes to grow the esophagus together, often without needing to induce a coma. Tomorrow, an implanted robot may do the job, freeing babies to kick, wiggle and squirm while the esophagus grows.

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**Everly, Ever Strong**

Everly Birren twirls through the house in her princess dress, runs over to hug her sister and then scoots out to help feed the neighbor’s donkey. This five-year-old’s blissfully normal whirl belies her precarious beginnings. Everly was diagnosed in utero with long-gap EA and born six weeks premature. She spent her first four months at Boston Children’s, first growing big enough to undergo the Foker process (see Fast-Forward), then in a medically induced coma while her esophagus grew and was repaired, and, finally, undergoing repeat dilations to keep her esophagus wide enough for food. She was fed through a “g-tube” throughout. Today, Everly snacks on popcorn, pancakes and mint chocolate chip ice cream and dreams of being a farm girl. Or maybe a ballerina.

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**Fast-Forward**

The bright white in this X-ray should extend straight down to the baby’s stomach. Instead, it ends where the top part of the esophagus ends.
William Lennox lay in bed, debilitated by the first of the strokes that would take his life. But even then, he puzzled over epilepsy. “What is it, this peculiar ‘psychomotor seizure’?” he asked a visiting colleague. Lennox had identified the syndrome. He had named it. And yet he was not satisfied. He felt his characterization was imprecise, and imprecision, he knew, could maroon a patient.

Lennox had come to Boston Children’s Hospital in 1944 to establish the world’s first pediatric seizure unit. At the time, 16 states barred people with epilepsy from marrying. Job discrimination was rife and the stigma of epilepsy enormous. Lennox noted, “In some families a murder could not be more carefully hidden.”

Against this backdrop Lennox conceived an epilepsy center that would meet all of a child’s—and family’s—needs. From the start, he included social workers and psychologists in treatment teams. He dedicated the new unit to advocacy as well as treatment, training and research. His motivation was strong: Lennox had been a medical missionary in China when his younger daughter began having seizures. Upon returning to the States, he focused his missionary zeal on solving her disease.

CARRYING THE TORCH

The Seizure Unit propelled Lennox’s research and advocacy as never before. It drew patients from around the world, and nearly every patient participated in a study. Earlier in his career Lennox had characterized three main types of seizures. Now he defined more precise syndromes. One, Lennox-Gastaut, bears his name. Earlier, he had spearheaded clinical use of electroencephalography (EEG). Now he used EEG to probe the heritability of epilepsy, studying twins and patients’ families. He laid the foundation for today’s understanding of how genes and environment interact to trigger the disease.

Above all, the Seizure Unit became a model for the world. Nearly 50 years after the unit’s founding, Cesare Lombroso, its second director, reflected that he met alumni in “practically every country…ably carrying the torch for epilepsy.”

Lennox received the Lasker Award—America’s Nobel—for his contributions. Although he ran out of time to answer his own question about “this peculiar psychomotor seizure,” he wrote a textbook to guide those carrying forward the torch of epilepsy—among them his coauthor and noted epileptologist Margaret Lennox-Buchthal, the daughter whose illness motivated his career.

Epilepsy is the second most common neurological disorder (after stroke) and the most common in childhood. One in 200 children will develop seizures.

First for Neurology

The Seizure Unit was far from the hospital’s first significant contribution to pediatric neurology. In 1929 Boston Children’s opened the nation’s first pediatric neurology and neurosurgery units. The Neurology Service was also the first multidisciplinary program in the country. Its founder, Bronson Crothers, recognized that children with complex neurological problems required emotional and social, as well as medical, support.
Boston Children’s researchers have devised an ingenious way to record seizures in zebrafish. They gently anchor a fish in a recording chamber, position its head beneath a grid of tiny electrodes and fill the chamber with liquid. By adding chemicals to the liquid, they can induce seizures and test drugs to stop them.

Zebrafish make excellent models of human disease. They’re cheap and easy to raise, and they share many genes with people. Plus, their embryos are transparent. Researchers can peer through their skin to watch the miracle of development unfold. At five days, the brain and spinal cord are visible.

Boston Children’s Annapurna Poduri and Alexander Rotenberg are using zebrafish models to study genetic forms of epilepsy, including epilepsy related to the gene PCDH19. This disorder causes clusters of seizures and affects only girls. Anti-seizure medications help a minority of patients, and even then only partially. The hope is that the fish will reveal new treatments—first for PCDH19-related epilepsy and then for others.
Farber and clinical colleagues at Boston Children’s and what is now Brigham and Women’s Hospital gave folate to 90 terminally ill patients ranging in age from under three to over 71, with 27 different cancer diagnoses among them. At least 11 of the children had leukemia. The results were disastrous. Folate stoked leukemia like oxygen stokes fire, and the children’s white blood cell counts soared. Farber halted the trial. But within this failure he saw the possibility of future success: if folate so dramatically intensified leukemia, might an anti-folate stop it?

The first great advance against cancer began with a horrifying failure.

Sidney Farber was chief of pathology at Boston Children’s. Through his microscope he witnessed the decimation of a young child’s blood as immature white blood cells furiously divided and divided again, colonizing the bone marrow and crowding out normal blood cells. His diagnosis: acute lymphoblastic leukemia (ALL). It was, he knew, a death sentence. No treatments halted, let alone cured, ALL. The family would most likely be burying this child within weeks.

The fury of ALL kindled an equal fury in Farber. He would do more than diagnose this hopeless disease: he would find a treatment. And he had an idea of where to start.

**COULD A VITAMIN SOLVE CANCER?**

Farber knew that folate, a B vitamin, was essential for blood cell formation. Individuals deficient in folate developed a severe anemia that reversed when they took the nutrient. What’s more, two enticing studies reported that folate had inhibited tumor growth in animals. Might it halt human cancers, too?

Sidney Farber received the Lasker Award and many other honors. The treatment he initiated took a great leap forward in the 1970s when David Nathan, then chief of hematology and oncology, brought multidrug protocols developed for adults at the NIH to children at Boston Children’s. This innovation became a mainstay of therapy for childhood leukemia and led to the high cure rates we see today. Nathan went on to serve as chief of medicine at Boston Children’s and president of Dana-Farber.

Folate, a B vitamin, takes its name from the Latin for leaf, and leafy greens have lots of it. Cells can’t divide without folate, making it both essential for normal growth and a treatment target in fast-growing cancer.

**Masked Identities**

Scott Pomeroy, chief of neurology, puzzled over a common clinical occurrence. Two children whose tumors looked identical under the microscope would have radically different responses to treatment. Why? In a landmark 2002 paper, Pomeroy and colleagues from Dana-Farber, MIT and the Hematology-Oncology Division at Boston Children’s answered that question: medulloblastoma, the most common childhood brain cancer, is not one disease but several, distinguishable by the expression of specific molecules and unique genetic mutations. The differences don’t end there, either. Pomeroy and another set of colleagues have since shown that even genetically related tumors can produce different proteins, changing a cell’s behavior. Treatments that target one such protein could make hard-to-treat medulloblastomas more vulnerable to radiation. The image shows different gene expression patterns among medulloblastoma subtypes.
Farber turned to a chemist and friend, Yella Subbarow, who was developing antifolates for a pharmaceutical company. In the fall of 1947, Subbarow sent Farber a small quantity of one antifolate. It did little good. But the next worked a miracle. First one child, then another, regained energy and appetite. Their white blood cell counts plummeted. They returned to school. Laughter reentered their lives.

Farber treated 16 children from November 1947 through April 1948, 10 of whom responded to the drug. Their remissions lasted only a few short months, but those precious months of normalcy were a gift to families—and to humanity. They were the first proof that a drug could treat cancer.

Farber concluded the New England Journal of Medicine article reporting this success with what has proved to be the understatement of understatements: “A promising direction for further research concerning the nature and treatment of acute leukemia in children appears to have been established by the observations reported.”

That “promising direction” spawned the field of chemotherapy, not just for acute lymphoblastic leukemia but for all cancers. Today, 80 to 90 percent of all children with leukemia are cured.

Five-year survival rates for children with ALL

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<tr>
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<td>2005</td>
<td>59%</td>
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Cancer, Visible

A see-through adult zebrafish has opened a window onto cancer. Stem cell scientist and hematologist Leonard Zon and team created casper and have used the fish to plot melanoma’s evolution from the first mutated cell through metastasis, revealing new targets for treatment. They have also devised a gene editing system to turn the diminutive zebrafish into a mighty model for any cancer that arises in organs that zebrafish and people have in common. The system models the genome of a given tumor in its tissue of origin—melanocytes for melanoma, for example. This streamlined approach saves months, making it feasible to recreate and compare the unique mutational landscapes of multiple tumors.

NO CHILD LEFT BEHIND

The extraordinary progress in curing leukemia has left one group behind. These patients harbor a mutation so pernicious that it alone can trigger their disease, in contrast to the multiple mutations necessary to activate most cancers.

The mutation impairs the mixed lineage leukemia (MLL) gene. Normal MLL helps regulate blood formation, both before and after birth. But in MLL-rearranged leukemia, the MLL gene fuses with one of more than 60 possible partners to produce new, cancer-causing genes. Like Bonnie and Clyde on a crime spree, MLL-fusion genes unleash widespread destruction. They do this by destabilizing the epigenome, which controls which genes are on or off. A virulent leukemia results. Tragically, this is the most common leukemia in infants. Half still die.

But oncologist Scott Armstrong has found a smoking gun: many MLL-fusion genes need an accomplice, the protein DOT1L. Armstrong has already brought one DOT1L inhibitor to trial (in adults). It proved safe, and clinical development continues.
Thomas Weller set 20 glass flasks on the laboratory benchtop. Into each he added bits of human skin and muscle, plus a solution of salts and ox blood to nourish the cells. This was the culture in which he hoped to grow varicella, the chickenpox virus.

No one had done it, but Weller was optimistic. He was a junior associate of famed virologist John Enders, and together they had devised a simple system for growing viruses in human tissue. The theory was that culturing varicella with the cells it ordinarily infected—skin and muscle—would encourage its growth.

Weller had collected varicella from the throat of an ill child. As it turned out, he had enough for only 16 flasks. But in Enders’ lab, nothing went to waste. The boss was as notorious for his frugality as he was respected for his science. So Weller opened the nearby storage cabinet and pulled out some poliovirus. He had little hope it would grow in his skin and muscle cell cultures; every attempt to cultivate poliovirus outside of the nervous system tissues it naturally infected had failed. But Weller mixed the poliovirus into the remaining flasks anyway.

Twenty days later, the results were in. The varicella was a bust. But the poliovirus? It grew.

**SUBDUING A SCOURGE**

The implications were stunning. The polio epidemics that thundered across the country had made developing a vaccine a top public health priority. But to succeed, researchers would need vast amounts of dead or weakened virus, and no one could produce it. The cultivation methods of the time were cumbersome, costly and, by today’s standards, cruel: the virus was grown in the spinal cords and brains of monkeys. Quantities were limited. But more, virus grown in nerve cells could cause fatal allergic reactions. It could be used to study disease but not for a vaccine.

But now, the Boston Children’s team had grown poliovirus in non-neural tissue. Enders and Weller doubled down on refining their technique. A pediatric research fellow, Frederick Robbins, joined them, and in short order the trio perfected their culture methods and developed tests to both detect the presence of poliovirus in the culture and determine its type (there are three strains of poliovirus). They showed that they could weaken the virus over time and that the weakened virus could induce immunity. The ground was set for a vaccine. Jonas Salk produced the first one, using killed poliovirus, in 1955; Albert Sabin followed with a live attenuated (weakened) polio vaccine in 1961, using viral cultures established in Enders’ lab.

Enders was “a true honest scientist,” said one colleague. “He had no tremendous aspirations in terms of academic stature. He had great aspirations for moving the field of virology ahead.”

**IN THE US TODAY:**

- Polio: eradicated
- Measles: eradicated*
- Hib: down 99.7 percent

* Travelers can still bring measles into the US, sparking outbreaks.
Enders, Weller and Robbins received the 1954 Nobel Prize in Physiology or Medicine for “their discovery of the ability of poliomyelitis viruses to grow in cultures of various types of tissue.” But what they had accomplished went far beyond the victory over polio. By giving the scientific community a simple recipe for growing large quantities of virus in a test tube, they had “launched a new epoch in the history of virus research.”

An explosion of vaccine development followed, and one by one, the dreaded, familiar viral diseases of childhood became memories. Measles. Mumps. Rubella. Chickenpox.*

**Second Triumph**

Few vaccines have saved more lives than the one for measles, another Enders triumph. With a new crop of young associates, Enders not only cultured the virus but also developed the first vaccine. His vaccine was licensed in the United States in 1963, and 19 million doses were administered before an even better version came along. The new vaccine used the same strain of measles virus but in a weaker form. Its developer dubbed it Moraten, for “more attenuated Enders.” It eliminated side effects that Enders’ original vaccine sometimes caused.

Before Enders’ measles vaccine, more than 90 percent of US children developed the disease. An estimated 3 to 4 million people in the US were infected each year. Although most US patients recovered fully, the same was not true globally. Major epidemics killed an estimated 2.6 million people annually, mainly children.

Today, the vaccine revolution that began with four extra flasks of skin cells, salts and ox blood has eradicated polio from all but three countries. Measles is not far behind.

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**Quiet Success**

**Haemophilus influenzae type b (Hib)** may not have grabbed as many headlines as polio, but it was as common, deadly and disabling. It was once the leading cause of bacterial meningitis and postnatal intellectual disability in young children. Nearly all those affected were younger than five. In 1968, while at Boston Children’s Hospital, David Smith, Porter Anderson and colleagues began work on a Hib vaccine. Their success, accomplished after the team had moved to the University of Rochester, is credited with saving upwards of 800,000 lives.

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*Weller succeeded in isolating varicella in 1952, the first person to do so. The key was the source of the virus. Throat swabbiages didn’t work, but virus recovered from chickenpox blisters did.
Cancer vaccines teach the immune system to recognize a part of cancer cells as dangerous, initiating a seek-and-destroy mission to rid the body of its deadly burden. Most such vaccines target a protein that is unique to cancer cells but not essential for their growth. If some cells in the tumor don’t make the protein, they can evade detection and continue to thrive and divide. Roberto Chiarle has developed a cancer vaccine with a better target, a protein essential to the tumor’s growth. By combining his vaccine with drugs that also attack this target, he has delivered long-lasting remissions to animals with both lymphoma and lung cancer. A clinical trial in lung cancer is set to open in 2019 at the Dana-Farber Cancer Institute.

A new, modular vaccine technology promises to deliver more effective, less expensive vaccines to conquer a wide range of infections that threaten health worldwide. Fan Zhang, Yingjie Lu and Richard Malley developed the Multiple Antigen Presenting System (MAPS) to enhance immune response while reducing the time, complexity and cost of vaccine production. Their proof-of-concept vaccine against pneumococcus proved so successful in preclinical trials that a company, Affinivax, was formed in 2014 with support from the Bill and Melinda Gates Foundation. Affinivax is further developing the pneumococcal vaccine and applying the MAPS platform to other pathogens.

Newborns and the elderly are at greatest risk of infection, yet their unique immune systems often don’t respond sufficiently to vaccines. Ofer Levy launched the Precision Vaccines Program in 2016 to study and model age-specific immunity and develop vaccines that trigger a protective immune response in vulnerable populations. The program unites academia, government and industry in targeted vaccine development, bringing precision medicine to immunization. It has already developed unique vaccine testing platforms outside the body, using immune cells from different populations, and has discovered new adjuvants, molecules that boost vaccine responses.

**INJECTING HOPE**

Vaccines stand alongside antibiotics as one of the greatest medical triumphs of the 20th century. The World Health Organization estimates they prevent 2.5 million deaths a year. As the 21st century races along, genomic technologies and a deeper understanding of the immune system are expanding vaccine applications beyond prevention to treatment, while enabling more cost-effective, potent and customized products. Three efforts at Boston Children’s Hospital offer a shot of hope for a healthier future.

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In the early 1950s, doctors at Boston Children’s were perplexed by a rare and puzzling condition: a small handful of patients suffered from a relentless wave of fevers and infections. Antibiotics, having just become widely available, were vital for treating these children, who otherwise would have succumbed to their first bout of infection.

Although Boston Children’s physicians didn’t know it at the time, others across the country were witnessing the illness, too. Charles A. Janeway, physician in chief at Boston Children’s, was among a vanguard of trailblazing physician-scientists who recognized this disease, dissected its biological and molecular roots, and discovered powerful therapies to treat it.

Walter Reed Hospital in Washington, DC, Janeway completed the first characterization of this mysterious disease, now known as X-linked agammaglobulinemia (XLA). Patients with this condition lack an important class of blood proteins called gamma globulins. These missing proteins include antibodies that enable the immune system to recognize and destroy pathogens. Without them, the body is vulnerable to a barrage of infections.

EXPERIMENT OF NATURE

Janeway described his pioneering discoveries in a scientific paper published in 1953. His work helped revolutionize the understanding and treatment of XLA, the first human immunodeficiency to be described.

Indeed, XLA offered a crucial experiment of nature—an inherited disorder that Janeway and his colleagues could observe in their own patients and dissect in the laboratory before returning to the clinic with insights to help improve patients’ lives. This bedside-to-bench-and-back cycle not only propelled the understanding of XLA but also helped illuminate poorly understood aspects of the intricate human immune system.

In addition, it gave birth to immunology as a medical subspecialty.

PAYING IT FORWARD

Today, this legacy lives on in an unparalleled approach to pediatric immune disorders at Boston Children’s. “We have a tradition of extremely rigorous science—of tracing the origins of patients’ problems and following them as deep as the science will allow,” said Raif Geha, chief of the division of immunology at Boston Children’s. “Very few places have that.”

This tradition flows from Janeway’s vision and dedication to helping patients. He recruited passionate, creative clinicians to join Boston Children’s and inspired a multitude of young physicians and researchers. This commitment to training is reflected not only in the hospital’s continued leadership but also in the impressive number of today’s pediatric immunologists who launched their careers at Boston Children’s.

Gene Hunt

Humans carry some 20,000 different genes. About half are expressed in the immune system. That means there are 10,000 possible ways the immune system can fail. Yet only about 350 different forms of primary, or inherited, immunodeficiency have been described, representing less than 1 percent of all immune-related genes. To identify more, immunologists led by Raif Geha and Janet Chou are pursuing a broad, international effort to comb the DNA of patients with unknown forms of primary immunodeficiency. They are cracking open the biology of these mysterious disorders—just as Charles Janeway did with XLA nearly seven decades earlier. At left: a white blood cell.
Shwachman immediately saw the implications for diagnosis. At the time, CF testing involved snaking a nasogastric tube into the intestines of a fasting, hospitalized child. If physicians could use something as simple as sweat instead, the chances of identifying and treating patients early would improve. Within two years Shwachman had the first practical sweat test for CF. It used a plastic bag to encase the child’s body and keep sweat from evaporating. The “sweat bag” was the primary CF test until the end of the decade, when a former Shwachman intern developed an easier method that remains in use today.

WORK TO DO

When Shwachman began his career, nearly all children with CF died before their second birthday. He sat with family after bereaved family. “I’ve had to cry with them. I can’t help it,” Shwachman recollected. “But, that doesn’t solve the problem. You’ve got work to do and you’ve got to keep on going.” Shwachman kept going through 30 years of building the largest CF clinic in the world, devising new diagnostic methods and setting treatment standards. When he retired in 1976, his oldest patient was 54.

INSIGHTS FROM OUTLIERS

Two rare groups of CF patients may reveal new approaches to treatment. They are outliers: patients whose disease progresses much more rapidly or slowly than is typical despite the same mutation. A Boston Children’s team scoured the genomes of five outliers in search of genes that might modify the effects of the CF mutation and thus explain these differences. They found several and are creating patient-specific stem cell models to further study the interactions of the modifier and CF genes. The team—physician-scientist Ruobing Wang, stem cell scientists Carla Kim and George Q. Daley, and geneticist Pankaj Agrawal—hopes that insights from outliers will lead to new treatments for CF patients who do not benefit from today’s drugs.

“I wondered why we couldn’t diagnose it [CF] before these children died, so that perhaps we could do something for them.”

—HARRY SHWACHMAN

Blood, Sweat and Genes

All 50 states now screen newborns for CF. A blood test for pancreatic enzymes comes first, followed by a sweat test if CF is suspected. Genetic testing is also available. Nearly 2,000 mutations in the CF gene have been identified, and drugs that correct the most common ones are helping 95 percent of CF patients breathe easy for the first time. Boston Children’s participated in the clinical trials.
If President John F. Kennedy’s son Patrick had been born today, he almost certainly would have lived. But when the premature baby was rushed from Cape Cod to Boston Children’s Hospital in 1963, medicine had little to offer him. Patrick had been born five and a half weeks early, and his lungs were perilously underdeveloped. He had what was then called hyaline membrane disease, more commonly known today as respiratory distress syndrome (RDS). The tiny air sacs in his lungs collapsed with each breath, and with each collapse damaged cells accumulated in his airways. They formed a mucousy membrane that made it even harder to breathe. Just 39 hours and 12 minutes after his birth, Patrick Kennedy died.

It would be decades before a treatment for Patrick’s disease became available. But even as he struggled for breath, the key discovery had been made—by a young pediatrician who would dedicate her career to saving infants just like him.

**MARY ELLEN AVERY**

**Breath of Air**

Mary Ellen Avery arrived in Boston in 1957 primed to investigate why premature infants’ lungs failed. She had never forgotten the first preemie she’d seen, when she was just 12 years old. Her interest in lungs was more recent: diagnosed with tuberculosis shortly after medical school, she’d become fascinated with the mechanics of breathing. Now, having completed her training, she’d accepted a dream fellowship at Boston Children’s Hospital and the Harvard School of Public Health. She’d work with renowned neonatologist Clement Smith and study lung biology in the Harvard lab of Jeremiah Mead.

Mead tasked the budding physician-scientist with investigating pulmonary edema, a buildup of fluid in the lungs. People with this condition can literally foam at the mouth. Avery realized that preemies had the opposite problem: their lungs, at autopsy, showed no bubbly substance at all.* She soon figured out why. In 1959 she and Mead reported that preemies’ immature lungs lacked surfactant, a foamy material that lowers the surface tension of the lungs’ air sacs, enabling them to inflate again after exhaling.†

**Playing with Bubbles**

The reaction was underwhelming. “Everyone had their own theory,” Avery recalled many years later. “People couldn’t see why it [surfactant] mattered.” Avery was dismissed as “playing with soap bubbles.” Unperturbed, she continued to build the case for surfactant. Over a 30-year career at three world-leading medical centers (the last 10 as chief of medicine at Boston Children’s), Avery helped identify the components of surfactant, the cells that produce it and when it develops in the fetal lung. She also inspired the research that turned her discovery into a treatment.

**They Breathe**

In 1970 Avery gave a talk in San Francisco. Tetsuro Fujiwara, a pediatrician visiting from Japan, listened intently. Inspired, he spent the next 10 years replicating and expanding on Avery’s research. In 1980 Fujiwara published definitive proof that a lack of surfactant caused RDS. A rush to develop synthetic surfactant followed, and in 1990 the FDA approved the first one. Premature babies born today receive surfactant minutes after birth. Their lungs frothy with bubbles, they breathe.

* The more premature a baby, the greater the risk of respiratory distress syndrome. Those born before 29 weeks’ gestation face a 60 percent chance of developing the condition; by 35 weeks most make enough surfactant to protect their lungs.

**Another Cure Bubbling**

Surfactant saves premature babies’ lives, but it doesn’t necessarily save their lungs. These infants are at risk of bronchopulmonary dysplasia because of the ventilator support they need to breathe. However, hope for prevention is bubbling up in the form of exosomes, tiny orbs that carry growth factors, genes and other biological instructions from one cell to another. Stella Kourembanas, chief of newborn medicine, and Alex Mitsialis discovered that exosomes from mesenchymal stem cells, which can give rise to a variety of adult tissues, can repair bronchopulmonary dysplasia. An industry partner is transforming these exosomes into a therapy. A clinical trial is set for 2019.
ROP progresses in two stages. The first is a response to oxygen levels, which are twice as high outside the womb as within and higher still for babies who need supplemental oxygen to breathe. This dramatic increase in oxygen causes a decrease in VEGF. Normal blood vessel growth stops, and healthy vessels retreat, leaving patches of the retina without a blood supply. In phase two, the blood-deprived retina, now hungry for oxygen, overcompensates. VEGF surges, but the vessels that form are weak, leaky and too abundant. They can break, scarring the retina and leading to blindness.

Just like their lungs, the eyes of very premature babies (<32 weeks’ gestational age) are not ready for the world. The blood vessels that nourish the retina haven’t finished growing, leaving the infants at risk for retinopathy of prematurity (ROP). This disorder, in which wayward, leaky blood vessels grow in place of normal ones, is the most frequent cause of childhood blindness in developed countries.

In the mid-1990s ophthalmologist and biochemist Lois Smith found the cause of those leaky vessels: vascular endothelial growth factor (VEGF). Her discovery led to the first drug treatment for ROP, but the drugs, VEGF-blockers, have a drawback. They may seep from the eye into the circulation and impede essential blood vessel growth elsewhere. The long-term consequences are unknown.

Smith is part of an international consortium assessing the safety of VEGF blockers. At the same time, she is seeking factors that modulate rather than block VEGF. She has found one that appears to affect only aberrant VEGF production, making it a promising target for a future therapy to save premature infants’ imperiled sight.
Serving at the US National Naval Medical Center in the early 1960s, Judah Folkman noticed something odd about tumors. When he placed a bit of tumor in an isolated but blood-infused rabbit thyroid, it would grow to the size of a pinhead and then stop. But that same tumor, transplanted into a living mouse, expanded wildly.

Looking at slices of those tumors under the microscope, Folkman could see why: growing tumors teemed with blood vessels; dormant ones did not. This jibed with observations Folkman, a surgeon, had made in the operating room. The large tumors he removed were red, hot and bloody; others were just tiny white nodules. What, he wondered, turned those nodules into vicious cancers?

UPENDING DOGMA
Folkman presented his answer to that question in a 1971 *New England Journal of Medicine* paper that revolutionized understanding of cancer and launched a new field of medicine.

By that time Folkman was chief of surgery at Boston Children’s and had a small lab in which he pursued tumor blood vessel research. His studies convinced him that angiogenesis, the growth of new blood vessels, is the pivotal event that turns cancer from dormant and harmless to potentially lethal. Without a dedicated blood supply, tumors can’t grow larger than a pinhead. With it, they receive nutrients to grow and have escape routes through which to spread. They lay waste to organs and lives.

This is the theory Folkman laid out in the *New England Journal*. He further proposed that tumors made factors that stimulated or inhibited angiogenesis. If researchers could identify the inhibitors, they could develop therapies to shrink tumor blood vessels and halt cancer’s lethal course.

PERSISTENCE DESPITE DERISION
His ideas met with derision. Everyone “knew” that tumor blood vessels resulted from inflammation. And the notion that tumors made substances that encouraged and stopped blood vessel growth? Preposterous.

But Folkman and his team persisted. He was driven by insatiable intellectual curiosity and profound compassion. This was a man who, as a teen, had asked for a microscope instead of the offered jeep as a gift; the son of a rabbi, he never veered from his father’s precept to be a rabbi-like doctor. Once Folkman envisioned the possibility of saving patients by starving their tumors, no amount of criticism could derail him.

FOLKMAN’S LEGACY
Through decades of painstaking research, Folkman and his team proved that cancer’s growth did indeed rely on angiogenesis. They isolated the first angiogenesis stimulators and inhibitors, developed life-extending treatments and paved the way for the hundreds of labs worldwide that pursue angiogenesis research today.

Angiogenesis is now recognized as a fundamental biological process implicated in more than 60 diseases. In some, blood vessels grow where they shouldn’t. They infiltrate joints in rheumatoid arthritis or bleed into the retina in macular degeneration. In others, new blood vessels that could stimulate healing don’t form. Wounds fester. Heart muscle starved for oxygen dies. Angiogenesis research promises to prolong life and prevent disability from many of these disorders. Blinding eye diseases are already a case in point.

CANCER

1971

“Folkman developed an entirely new field. Like many spectacular advances, it drew derisive commentary and skepticism.”

—HARDY HENDREN, FOLKMAN’S SUCCESSOR AS CHIEF OF SURGERY

Maestro
Judah Folkman often said that great research is conducted like a great symphony orchestra. The combined talents of the players produce far greater works than even the finest virtuoso working alone. He recruited and mentored researchers who shared his passion for discovery and his commitment to science that would improve human health. The lab he started with just one assistant is today the 100-scientist-strong Vascular Biology Program (VBP).

Under the direction of Marsha A. Moses, the VBP is the largest program of its kind in the world.
In the 1990s Folkman and colleagues Tony Adamis, Robert D’Amato and Pat D’Amore identified the factor that stimulates blood vessel growth in age-related macular degeneration, the major cause of late-life vision loss. The same stimulator, vascular endothelial growth factor (VEGF), is at play in two other rapidly blinding conditions as well. One affects people with diabetes, the other premature babies (see page 54). VEGF-blockers can help them all. Three are now available. They inhibit blood vessels from invading the retina and are the first drugs to prevent blindness.

A Urine Test for Cancer?

VBP Director Marsha A. Moses was first in the world to identify and validate cancer biomarkers in urine, opening the possibility of simple and inexpensive urine tests to detect disease, signal recurrence at its earliest and monitor treatment. Two studies demonstrate the potential. Moses has identified proteins in urine that signal pancreatic cancer,3 and, while a fellow in her lab, neurosurgeon Edward Smith had similar findings in brain cancer.4 In 2017 Smith completed a multicenter trial that successfully distinguished benign tumors from a particularly lethal pediatric brain tumor, something only a risky brainstem biopsy can do now.

THE PAYOFF: LIVES SAVED

In 2004 the FDA approved Avastin, the first drug to fight cancer by blocking blood vessel growth. More than a dozen antiangiogenic drugs have followed. They are in use around the world, and some of the most potent have come from the Vascular Biology Program.

In the early 1990s VBP researcher Robert D’Amato searched the scientific literature for drugs whose side effects could be due to a lack of angiogenesis. He found a pariah: thalidomide. D’Amato recognized that the heartrending defects of thalidomide babies may have occurred, at least in part, because blood vessels never grew to feed their developing limbs. Research proved him right,5 and the FDA approved thalidomide for cancer in 2006. Thalidomide and two related drugs discovered in the D’Amato lab are now frontline treatments for multiple myeloma. Another VBP drug entered clinical trials in 2017. Developed by Randolph Watnick, it significantly shrunk primary and metastatic tumors and eliminated new metastases in laboratory studies of numerous cancers.6 Hope is high that it will do the same in people.
Her name is lost to history, but generations of scoliosis patients owe her a debt of gratitude. She was a patient at Boston Children’s Hospital in the early 1970s, a young teen with the sideways curve of scoliosis deforming her spine. Her curve wasn’t large enough to require surgery. Nor was it small enough for watchful waiting. The best treatment, said her doctors, was a brace.

**UNWELCOME CURVES**
Efforts to nonsurgically correct scoliosis dated back centuries. Hippocrates used ropes and winches to stretch the spine. The 1500s brought iron corsets; the 1800s, leather, or plaster of Paris so thick it took days to dry. Plaster jackets dominated when Boston Children’s opened its scoliosis clinic in the 1890s. Back then, rickets and tuberculosis of the bones caused most scoliosis. The jacket’s rigid embrace stabilized the spine from pelvis to armpit—and, sometimes, chin—while bones healed.

By the time our young patient got her scoliosis diagnosis in 1972, both cause and bracing had changed. Rickets and tuberculosis were rare. But adolescent idiopathic scoliosis, a curvature of unknown origin, still brought patients to the clinic.
When a Brace Is Not Enough

Severe scoliosis requires surgery to straighten the spine and stop the curve from progressing. Surgeons realign and fuse the curved bones, then insert metal rods to stabilize the spine as it heals. Affixing these rods is a delicate business, and early techniques limited the degree of correction surgeons could attempt. In the 1970s John Hall devised an approach that produced greater curve correction and faster healing. He also dared operate on patients few others would: those with congenital scoliosis, which can deform the lungs and chest and lead to early death. His innovations helped generations of scoliosis patients stand tall.

BOSTON BRACE

Bracing for these patients is designed to keep the curve from progressing and causing back pain and breathing difficulties later in life. In 1972 the most common brace combined a girdle, metal rods and a neck ring. Straps and pads attached to the rods exerted corrective pressure on the spine; the neck ring and a chin pad immobilized the head. Patients wore the brace 23 hours a day. Our patient refused.

Fortunately for her, she had a compassionate physician, Chief of Orthopedics John E. Hall, and Hall had an inventive orthotist, Bill Miller. Inspired by their rebellious patient, Hall and Miller devised a low-profile brace made of light plastic. It used strategically placed openings and internal padding to straighten the spine, and it eliminated the unsightly metal rods and chin support.

This, the Boston Brace, was not only more acceptable to patients—it was more effective. It quickly became, and remains, the global standard. Patients worldwide benefit from the stubbornness of one long-ago teen.

NEXT-GEN BOSTON BRACE

A bad brace can’t correct a spine, and making a good one takes skill. To reduce error, the original Boston Brace used prefabricated molds. John Hall and Bill Miller traveled the world, teaching orthopedic teams how to customize the molds for individual patients. Soon, computers will do the customizing. They will calculate corrective forces, determine where to apply them and 3D-print the brace.

The orthopedist need only upload X-rays and measurements. Boston Brace manufacturer Boston Orthotics & Prosthetics is developing the system in consultation with Boston Children’s orthopedists.
Rock-a-bye Baby
When lullabies, rocking and cuddling all fail, many a glassy-eyed parent turns to Richard Ferber’s Solve Your Child’s Sleep Problems for advice. Ferber’s prescriptions have restored sleep and sanity for so many that his name is a verb. Ferber started the Boston Children’s Sleep Center, the first in pediatrics, in 1978. Today the center treats more than 4,000 children a year, newborns to adolescents, for problems from apnea to insomnia to sleepwalking.

Brazelton not only became a pediatrician—he became America’s pediatrician. Through an Emmy Award–winning TV show, 24 books and a syndicated column, he helped generations of parents bond with their babies and discover both their own and their children’s competence. His popular works rested on a foundation of academic research carried out at Boston Children’s.

THE LANGUAGE OF BEHAVIOR
Brazelton’s great contribution was recognizing that babies teach parents as much as parents teach them. He entered practice at a time when infants were seen as little more than clay to be molded: prevailing wisdom held that newborns couldn’t even hear, see or feel pain.

Brazelton was among a cadre of researchers who recognized that babies were sentient from the start. But more, he showed that they communicated from day one, too. Behavior was their language. In babies’ reaction to noise or light, in their responses to being held in their mothers’ arms or by a stranger, they taught adults what they needed to thrive. One just had to look and listen.

“As a clinician, I was used to complexity, but the complexity of the newborn’s behavior was a brand-new, exciting wonder.”
—T. BERRY BRAZELTON

T. Berry Brazelton cross-trained in pediatrics and psychiatry and pioneered what is now called developmental-behavioral pediatrics, a holistic approach that addresses all aspects of a child’s well-being: emotional, cognitive, behavioral and physical.

Lessons from Romania
If Brazelton illuminated babies’ competencies, Charles Nelson and colleagues have shown how neglect can demolish them. In 2000 they launched the Bucharest Early Intervention Project, a study of Romania’s abandoned children. Languishing in institutions, these children had lower IQs, blunted language and more mental illness than children in the community. The researchers randomly assigned 68 of them to high-quality foster care. Their ongoing study demonstrates the benefits of a stimulating, nurturing environment and the consequences of its absence. The foster children, particularly if placed before age two, are increasingly like their community peers. But neglect is etched into the biology of those still in institutions. They have smaller brains, more rapidly aging cells and more mental illness, a heartbreaking warning about the impact of neglect.
The children had a virus that caused dozens of small tumors to grow and regrow on the larynx and in their bronchial tubes. The result was a dangerous narrowing of the airway that could restrict voice, breath, and life. Surgery to open the passage was tricky: it could scar the larynx and make the condition even worse. Yet these children needed surgery often. Their disease was relentless.

Gerald Healy, newly arrived at Boston Children’s in 1976, had a solution. He had been part of the first team to use a carbon dioxide laser to correct airway disorders in adults. The laser, he realized, would be particularly beneficial for kids. It was astonishing. A single, concentrated beam of light delivered through an endoscope vaporized scar tissue. It annihilated tumors and coagulated nearby blood vessels but left normal tissue intact. As a result, patients experienced less swelling and scarring. These side effects were particularly dangerous for children and often necessitated a breathing tube. Limiting the side effects would mean faster recoveries and fewer complications.

**CLEARING THE AIRWAY**
Healy was eager to make laser surgery available to his young patients, but there was a hitch: no one made endoscopes small enough for children’s airways. The pediatric market was so small that manufacturers were reluctant to develop tools for kids.

Healy knew of a possible exception, though. The Pilling Company, an endoscope manufacturer founded in the early 20th century, was more interested in the patients than the market. It would handcraft endoscopes to a surgeon’s specifications. Healy worked with the company’s engineers to design the child-sized tools he needed.

In late 1976 Healy performed the world’s first laser surgery at a pediatric hospital. Within a decade he and his team had performed more than 1,500 laser procedures on children from around the world. Today laser surgery is one of a number of endoscopic approaches to airway disorders. Children who once had major, open operations, breathing tubes, and weeks-long recuperations are in and out of the hospital in a day, often with little more than a sore throat to show for their surgery.

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**Lasers and Beyond**

The carbon dioxide laser was an innovation twofer: the endoscope used to deliver the laser was as pioneering as the laser itself. A long, illuminated tube inserted through the nose or mouth, an endoscope offers clear views of the child’s airways. It can also deliver balloons to open a narrowed windpipe and microtools to remove tumors or cysts. Under the direction of Reza Rahbar (left) and Francis Fynn-Thompson (right), the Boston Children’s Center for Airway Disorders is a world referral center for endoscopic procedures, as well as complex surgery when endoscopy isn’t enough.

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**Giving Voice**

Throat surgery, autism, cerebral palsy, muscle wasting disorders—all can rob a child of speech. But they need not end communication. Augmentative communication gives voice to the voiceless. Howard Shane and John Costello pioneered the field at Boston Children’s. Their many innovations include the EZ Board, which allows people to converse by pointing to pictures and is now available in 20 languages; Puddingstone Place, a visual learning system for children with autism; and message banking so patients who know they will lose their voice can still call the dog, ask for water or say, “I love you.”
That same year they demonstrated the existence of angiogenesis inhibitors. They created a polymer containing an extract from cartilage and implanted the capsule near a blood-engorged tumor. As the bead slowly and steadily released its cargo, the blood vessels retreated. The tumor shrank. Fourteen years later, Marsha A. Moses, now director of the Vascular Biology Program (VBP), and colleagues purified the responsible agent, the first innate angiogenesis inhibitor. Many millions of people worldwide have benefited from slow-release implants, and Folkman and Langer’s heirs in the VBP, as well as others in the Boston Children’s community, continue to develop new drugs—and new ways to deliver them.

IMAGINARY INHIBITORS?
The notion that such inhibitors existed was controversial. Decades later Folkman would delight in quoting an early grant reviewer who wrote that “the so-called existence of angiogenesis inhibitors is only in the mind of the principal investigator.” To prove that what was in Folkman’s mind was also in the human body, Langer, a chemical engineer, set out to develop a slow-release polymer that wouldn’t cause inflammation and could deliver macromolecules—proteins and other large molecules with therapeutic potential, including angiogenesis inhibitors. No one had done it; few even believed that slow release of macromolecules was possible. But skepticism never stopped Folkman or anyone in his lab.

Langer mixed and matched polymers and solvents and experimented with ways to shape and dry the solutions until he developed a matrix that trapped macromolecules. By altering factors such as the shape of the implant, the type of polymer or the amount and particle size of the macromolecule powder, he could control the rate of release. Folkman and Langer published this success in 1976.

Robert Langer began his career in Judah Folkman’s lab. Now one of only 10 institute professors at MIT, he’s been dubbed the Edison of medicine. He has developed and patented hundreds of drug delivery materials and devices.

Folkman and Langer created a polymer infused with cartilage extract to prove the existence of angiogenesis inhibitors.

Special Delivery
Two Vascular Biology Program scientists are developing nanoscale carrying cases for new classes of cancer-fighting molecules. Marsha Moses and colleagues at the City College of New York are using minute, targeted nontoxic spheres called liposomes to ferry gene-silencing technologies, while Bruce Zetter and partners at Brigham and Women’s Hospital have created a hybrid self-assembling lipid polymer to deliver gene-modifying therapies right to the heart of a cell. Proof-of-concept studies of both raise hopes for future therapies that infiltrate and destroy tumors. At left: nanolipogel. 
Drug delivery systems that control where a drug is released promise more effective treatment with less medication and fewer side effects. These two take precise aim at their targets: blood clots and middle-ear infections.

**BUSTED: BLOOD CLOTS**

When blood pushes through a narrowed vessel, the increased force causes platelets to stick to the blood vessel wall and clot. This sets the stage for heart attacks, pulmonary embolisms and strokes. But now, researchers Donald Ingber, Denisa Wagner and colleagues have harnessed that force—called shear stress—for healing. They are using it to activate nanoparticles coated with a clot-busting drug. Clusters of the nanoparticles (blue) break apart when they encounter a narrowed blood vessel. The individual particles then adhere to the clot and degrade it. This future therapy is a collaboration between Boston Children’s and the Wyss Institute for Biologically Inspired Engineering, which Ingber founded.

**EARACHE RELIEF GELS**

An antibiotic gel inserted directly into the ear canal promises a fast-acting, targeted treatment for the most common childhood malady: middle ear infections. More than 90 percent of all US kids get them, and most must take antibiotics. The antibiotics can cause side effects and, too often, are left unfinished, spawning drug-resistant bacteria.

Daniel Kohane, Rong Yang and colleagues developed the new gel. It starts as a liquid, hardens upon contact with the warm eardrum and then releases its healing cargo over time. In animal studies, the gel cleared infection within 24 hours. The NIH named it one of the most promising medical advances of 2016, and a pharmaceutical giant has licensed it.
No Excuse
Fifty thousand US children are still treated for lead poisoning each year, and 500,000 still have blood lead levels above the Centers for Disease Control's threshold. There is no excuse. As Boston Children's epidemiologist and lead poisoning expert David C. Bellinger wrote in a 2016 *New England Journal of Medicine* commentary on the lead contamination crisis in Flint, Michigan, “We know where the lead is, how people are exposed and how it damages health. What we lack is the political will to do what should be done.”3

**“THE MIND GIVES WAY”**
Lead wreaks havoc on the nervous system. Even the ancient Greeks recognized that “the mind gives way” when exposed to lead, and the outsized hazards for children were reported as early as 1904. But just how severe this hazard was took decades to establish.

Physicians assumed children recovered completely once an episode of lead poisoning resolved and exposure to the lead stopped. But Elizabeth Lord, a psychologist at Boston Children’s, suspected otherwise.

In the late 1930s she began following children admitted to the hospital for lead poisoning and chronicling their development. In 1943 she and Randolph Byers published a landmark study exposing the lingering devastation of lead poisoning: A nine-year-old still reading only primers. An eight-year-old so unruly he could not make friends. A six-year-old expelled from school for setting fires. Of 20 children treated for lead poisoning as infants and considered cured, only one was developing normally.2 Here was proof that lead poisoning caused permanent harm. But how much lead was too much? It would take another 35 years, a second Boston Children’s team and the schoolchildren of Chelsea and Somerville to supply the answer.

**THE TOOTH STUDY**
When the tooth study began, prevailing wisdom held that lead had to cause obvious poisoning to harm a child’s brain. The teeth told a different story. →
SUGAR: THE NEW LEAD?

Childhood obesity is one of today’s most urgent public health crises, and sugary sodas play a supersized role. A 2001 study by Boston Children’s endocrinologist David Ludwig was first to document this link, setting off a flood of research.7 Public policy initiatives soon followed. Federal regulations now prohibit the sale of sugary drinks in US schools, and countries across the globe are taking aim. Indeed, the World Health Organization urges a tax on sugar-sweetened beverages. This is a sweet step on the long road to healthier diets—and weights—for our youth.

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**Break Through: Lead Poisoning**

None of the study participants had ever had lead poisoning. Yet the children whose teeth had the highest lead levels lagged far behind those with the lowest on a wide range of measures, from IQ to motor coordination to attentiveness in class. Lead damaged young brains at levels lower than ever suspected.

Over the next decades, evidence accumulated as inexorably as lead itself: no amount of lead is safe for a child’s developing brain.4 Today, both paint and gasoline—the historically biggest sources of childhood lead exposure—are lead free, and most states either mandate or recommend childhood lead screening.

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Claudia De Pass knew she shouldn’t go in the ocean. The cold could trigger her sickle cell disease. But, as she put it, “It’s hard to tame a kid who wants to be exactly like her friends.”

So De Pass waded in. Pain hit with the speed and ferocity of a shark attack. “It’s like there’s blood in the water and the next thing you know, you’ve got sharks all over you, swarming.”

DEADLY ROADBLOCK
De Pass was no stranger to sickle cell crises. Her disease is caused by a mutation in hemoglobin, the oxygen-carrying component of red blood cells. When emptied of oxygen, mutated hemoglobin molecules clump together and cause red blood cells to sickle. The sickled cells clog small blood vessels, starving tissues and leading to overwhelming pain. If blockages affect major organs, sickle cell disease can be deadly.

When De Pass’ father rushed her from the beach to Boston Children’s Hospital, there was no effective treatment. Narcotics controlled pain. Penicillin protected against pneumonia. Transfusions helped combat anemia. But the sickled cells persisted. Throughout her childhood and teens, De Pass was hospitalized six to ten times a year. Each stay lasted weeks. “My future looked horrible, horrible,” she said. She feared she would “not have a life, not have any dreams.”

Then De Pass became the first sickle cell patient in the world to take hydroxyurea.

SLAYING THE SHARKS
Hydroxyurea had long been used to treat blood cancers when Chief of Hematology and Oncology David Nathan advocated trying it for sickle cell disease. He believed it might boost fetal hemoglobin, a form that doesn’t sickle but turns off at birth. Nathan teamed with De Pass’ hematologist, Orah Platt, to test his theory. The results in animal studies were spectacular, and Platt invited De Pass to participate in the first trial.

For De Pass, the decision was easy. At 17 she was spending more time in the hospital than at school. She told her mom, “It can’t be any worse than this. I’m missing life.”

That first trial in 1983 led to others, culminating in 1995 when the National Heart, Lung, and Blood Institute stopped a 21-center randomized control trial and made hydroxyurea available to all. Hydroxyurea remains the primary treatment for sickle cell disease.

1983

SICKLE CELL DISEASE

For 30 years researchers sought the gene that switches fetal globin off and adult globin on. A therapy to flip this switch could potentially deliver a cure. If successful, it would boost levels of non-sickling fetal hemoglobin enough to provide a permanent fix.

In 2008 Vijay Sankaran and Stuart Orkin found the gene. A team led by David Williams then developed a gene therapy to flip the hemoglobin switch and opened a trial in 2018. It’s too soon to claim victory, but six months after treatment the first patient was symptom free.

Every Day Extraordinary

Hydroxyurea isn’t a cure, but it controls symptoms well enough for most sickle cell patients to live a normal life. Thirty-five years after she first received hydroxyurea, Claudia De Pass still has sickle cell crises but they are less frequent. The child who feared she would have no dreams is an adult who has lived them: travel, work, marriage—ordinary blessings that she is grateful for every day.

Sickle cell disease is the most common inherited blood disorder, bringing debilitating pain, organ failure and early death to millions worldwide, mostly of African descent. Hydroxyurea extends life. Even then, the average sickle cell patient lives only 46 years. Below: sickled (purple) and normal red blood cells and David Nathan, one of the physicians who introduced hydroxyurea.
The surprises just kept coming. David Williams had been recruited to Boston Children’s as a hematology research fellow, but the researcher with whom he was supposed to work departed before he arrived. The lab he was assigned to instead wasn’t at Boston Children’s but at MIT’s Cancer Center. The project involved gene therapy, not the biology of infection-fighting white blood cells, his interest at the time. But the biggest surprise? Not a single paper had been published on the project Williams was undertaking.

That project: insert a foreign gene into the cells of a living animal. Success would show that gene therapy could work.

VIRAL TECH

The idea of gene therapy—adding healthy genes to faulty cells to treat disease—had ignited the scientific imagination in the 1960s and 1970s, a time of dramatic advances in our understanding of DNA and the link between genes and disease. By the early 1980s technology was catching up with imagination. Scientists could cut, paste and copy genes. They had learned to make vectors, viruses stripped of their own disease-causing capabilities but still able to invade cells and reproduce. They’d turned those viral vectors into carrying cases for foreign genes. When the virus reproduced, it churned out copies of the alien gene.

1984

A viral vector carries a corrective gene into a defective cell.

David Williams devised the original methods for inserting genes into cells.

The process worked in cultured cells. The next step was to shrink the distance between petri dish and patient by transferring genes into a living animal.

ELUSIVE TARGET

Richard Mulligan, the MIT scientist in whose lab Williams was now working, and David Nathan, chief of hematology at Boston Children’s, had joined forces to tackle this challenge. Mulligan had recently developed a new vector. It used a retrovirus, which is particularly adept at burrowing into a cell’s DNA. Rather than killing host cells and moving on, retroviruses stay put, reproducing every time the cell divides. Mulligan’s vector thus promised express delivery to the right address with no forwarding possible, exactly what would be needed for gene therapy.

The “right address” was a rare cell that forms all the components of blood, the blood stem cell. Blood stem cells are what reconstitute a patient’s blood and immune system after a bone marrow transplant. Genetically corrected, they could potentially treat dozens of disabling, often fatal, genetic blood disorders.

PERSISTENCE PAYS

Williams got to work, with mentorship from Nathan. They had no published studies to guide them. Indeed, little was known about blood stem cells, how to manipulate them or even how to identify them. But through experiment after experiment, Williams worked out the culture conditions and methods to infuse blood stem cells with foreign genes that functioned when transplanted into an animal. His success, in mice, paved the way for gene therapy.¹

¹The first major gene therapy trials took place in Paris and London from 1999 to 2002. They cured a lethal immune deficiency, but six of 20 children developed leukemia. The vectors landed near and inadvertently activated cancer-causing genes.
Inspiring Patients

The Gene Therapy Program’s first patient, Agustín Cáceres, arrived from South America in 2010 with a mouth bristling with ulcers and no working immune system. He had bubble boy disease, the same disorder that had killed his older brother. Five years later, Agustín was healthy and inspiring others. His story convinced Kala Looks that gene therapy was the solution for her son Levi (top, with gene therapist Sung-Yun Pai), born in 2015. Thanks to newborn testing for bubble boy disease and early gene therapy, Levi has never been seriously ill.

The same can’t be said of Brenden Whittaker (bottom). For most of his life, Brenden was unable to plan more than a day ahead. Chronic granulomatous disease (CGD), an immune disorder, had cost him part of his liver, part of a lung and his hopes of ever finishing college or having a career. But in 2015 Brenden became the first patient in the hospital’s CGD gene therapy trial. Three years later he was bartending, completing an associate’s degree at a community college and planning the next steps toward fulfilling his dream of becoming a physician.

When Williams returned to Boston Children’s in 2007, he quickly helped assemble a team to develop new technologies for obtaining better control over the side effects of vectors and how vigorously they are expressed. The Gene Therapy Program he launched, part of a multinational consortium and the first in the Harvard system, treated its first patient in 2010. Now under the direction of Alessandra Biffi, it has corrected many life-threatening blood disorders, with no severe side effects to date.

HAVE YOU HEARD?
The mouse startled at sound as soft as a whisper. Most mice would. But this mouse had been deaf. It had the same genetic mutation as children with Usher syndrome, an inherited disorder that destroys hearing and sight.

The Usher mouse was the second model of hereditary deafness that Jeffrey Holt, Gwenaëlle Gébéoc and colleagues successfully treated with gene therapy. A corrective gene delivered into the mouse’s inner ear had infiltrated the specialized cells responsible for hearing and restored their function. Much work lies ahead, but the team is moving toward clinical trials for hereditary hearing loss.

What’s more, Holt and collaborators at Harvard Medical School have discovered the gene that controls whether sound becomes hearing. Their findings end a 40-year search for hearing’s gatekeeper protein. Gene therapy to correct mutations in this gene and others could benefit millions.
Imagine this. You land in Massachusetts on a mission to find a family named Jones. All you know is that they live somewhere on the Cape, north of the elbow. You don’t know whether they’re butchers, bakers or candlestick makers. Nor do you know if they live in a one-room bungalow or a mansion by the sea. How do you ever find them?

The task geneticist Louis Kunkel faced in finding the Duchenne muscular dystrophy (DMD) gene was akin to finding the family Jones. Because DMD almost exclusively affects boys, scientists knew the gene was on the X chromosome. Colleagues at the University of Oxford, England, had further traced it to the chromosome’s short arm. But that was it.

The methods Kunkel devised to ultimately find the exact address involved hamsters, chickens and a boy dubbed B.B. They revolutionized how scientists hunt disease genes.

**NO TRAIL**

DMD progressively destroys muscles. Since the cause of this relentless muscle loss was unknown, traditional gene-finding methods wouldn’t work. Those methods follow the trail of biochemical breadcrumbs from the protein a gene produces back to the gene itself. But some 10,000 proteins orchestrate how muscles form and function, and Kunkel had no clue which one failed in DMD. He would have to find the gene based on location alone, something that had never been done in humans.

Kunkel may not have had the protein, but he did have a starting point: DNA from a boy born with three genetic disorders, including DMD. The boy, B.B., was missing a chunk of his X chromosome that almost certainly contained the disease genes. Kunkel’s inspired idea was to compare B.B.’s X chromosome to X chromosomes from a healthy individual and remove the DNA they had in common. He hoped the remaining healthy DNA would harbor at least part of the DMD gene.

**IN THE NEIGHBORHOOD**
The subtraction experiment yielded the hoped-for DNA fragments. Through months of exacting work, Kunkel and his graduate student, Anthony Monaco, tested one fragment after another. The last was the charm: it was missing from five unrelated Duchenne patients in addition to B.B. Further research brought Kunkel and Monaco to the neighborhood of the DMD gene. A DNA menagerie got them to the right door.

**Staircase Science**

Two flights up from Louis Kunkel’s lab, hematologist Stuart Orkin was hunting genes for blood disorders. He had already found all the mutations for thalassemia, the first full genetic characterization of a disease. When Kunkel published his report on the DNA probes developed from B.B.’s cells, Orkin saw a golden opportunity. B.B. had a blood disorder, chronic granulomatous disease (CGD), in addition to DMD. The two genes had to be near each other, so Orkin proposed using Kunkel’s probes to fish out the CGD gene. “We would go up and down the stairs and exchange reagents and discuss findings,” recalled Orkin. His team nabbed the CGD gene even before Kunkel found DMD. It was the first disease gene identified solely by location.

Duchenne muscular dystrophy decimates muscles. A preschooler with the disease will begin to stumble. By junior high he will be wheelchair bound; in high school he will struggle to breathe. At the time Louis Kunkel started his search for the gene, few patients survived their 20s. Today, better symptom control helps many live into their 30s, and treatments that correct underlying mutations are on their way. The first gained approval in 2016.

The Duchenne muscular dystrophy gene is the largest of our 20,000 genes. It occupies one one-thousandth of the human genome.
Exons, the protein-making parts of a gene, are spread along a chromosome like pearls separated by gold chain. Kunkel and Monaco couldn’t be sure that their DNA snippets contained the “pearls,” not the material in between. They turned to animals for confirmation. The exons of some genes are the same from species to species, conserved over eons of evolution. Kunkel speculated that a gene as critical as the one damaged in DMD would be among them. He and Monaco tested their human DNA fragments against DNA from hamsters, monkeys, chickens and mice. Two matched in all species. They had found the DMD gene.1

**NEW ERA**
Kunkel’s lab went on to identify the DMD protein, which they named dystrophin.6 With it, scientists were finally able to dissect the biology of DMD. Further, Kunkel’s methods opened a new era of disease gene finding. They were “an important landmark in the history of genetics,”7 used worldwide until the advent of faster, more efficient technologies.

**A Sizeable Challenge**
How tall or heavy a child grows is determined mostly by genetics—not one genetic variant alone, though, but thousands that act together. The GIANT (Genetic Investigation of ANthropometric Traits) Consortium, a large international team led by Boston Children’s endocrinologist Joel Hirschhorn, has unearthed more than 3,000 genetic variants linked to height and many others linked to obesity.8 Their discoveries are helping to unravel the biological causes of pediatric growth disorders and excess weight gain while also teaching scientists how to use powerful genomic sequencing technologies to understand diseases controlled by many genes, including diabetes and heart disease. Meanwhile, the GIANT team is combing the genomes of more than 3 million people to identify even more height- and obesity-related genes.8

**WOULD YOU WANT TO KNOW?**
We can now sequence all of a baby’s genes at birth. But should we? Boston Children’s geneticist Alan Beggs and colleagues at Brigham and Women’s Hospital are answering that question through BabySeq, a federally funded project exploring the medical and ethical implications of newborn genetic screening.8

**PRECISION MEDICINE FOR KIDNEY DISEASE**
New genetic technologies are uncovering increasingly subtle genetic causes of disease. They’ve shown, for example, that many childhood kidney diseases (CKD) thought to arise spontaneously are actually recessive genetic disorders. This is good news. Each recessive gene mutation is like a “you are here” sign: it points unequivocally to the malfunctioning gene, enabling researchers to zero in on treatment targets.

Friedhelm Hildebrandt, chief of nephrology, was among the first to uncover the genetic nature of CKD.10 He has amassed the world’s largest databank of DNA samples from children with these diseases (10,000+) and discovered more than 90 novel mutations to date. These findings make possible precision medicine for CKD. For the first time, researchers can target specific genes to block their destructive effects. Hildebrandt and his team have already identified two potential new treatments for incurable forms of the disease.11

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Wolfe enlisted psychologist Joanna Breyer and nurses Janet Duncan and Michael Comeau to help bring the specialty to children. Social worker Marsha Joselow soon joined.

BEGIN WITH THE CHILD
PACT launched in October 1997, one of the nation’s first two pediatric palliative care programs. What began as a consultative service in oncology focused on end of life is now a hospital-wide program available to any family with a seriously ill child, at any stage of illness, no matter what the outcome.

PACT works with patients, families and care teams to alleviate symptoms, facilitate communication and promote healing and comfort. It supports treatment of the underlying illness while simultaneously striving for quality of life.

Conversations begin with the child: What brings her joy? What does he love to do? What are the family’s hopes for treatment? Through these conversations, PACT helps families make care decisions that align with their deepest beliefs. It helps them find meaning in the midst of uncertainty and loss.

Joanne Wolfe recalls her “physician, heal thyself” moment.

Hannah was a cheerful, winning six-year-old when Wolfe successfully treated her for leukemia. She graduated from elementary school. Middle school. High school. Wolfe never expected to see her again. But during college Hannah’s cancer returned. A bone marrow transplant produced another remission, but three years later Hannah was back in the hospital, dying.

Wolfe was not only Hannah’s oncologist. She was also founder and director of the Pediatric Advanced Care Team (PACT), the hospital service that helps patients like Hannah, their families and care teams to have difficult discussions about end-of-life wishes. It was time for Hannah and her family to begin. But Wolfe wasn’t ready.

“As physicians we grow to love our patients,” she said. “It’s hard for us to say goodbye, too.”

It took a PACT colleague’s gentle urging for Wolfe to start the conversation and help give Hannah a final gift: a good death.

CHILDREN SUFFERED
For Wolfe, Hannah’s story is a touchstone, a reminder of why she started PACT. As an oncology fellow in the Boston Children’s and Dana-Farber joint pediatric oncology program in the late 1990s, Wolfe conducted the first large study of symptoms and suffering in young cancer patients’ last days. She interviewed bereaved parents of 103 children who had died between 1990 and 1997. The stories she heard pierced her heart. The children endured overwhelming pain and fatigue. They struggled to breathe. They suffered. Suffering was less likely, however, if physicians actively participated in end-of-life care.

Wolfe became convinced that children at the end of life needed care explicitly designed to help them live as well as possible for as long as possible. Such palliative care was becoming standard in adult hospitals but had yet to take root in pediatrics.

Deadly Duo
Cancer and poverty are a lethal combination. More poor children with leukemia die than wealthier ones, and the strains of poverty, not treatment differences, may be to blame: a Dana-Farber/Boston Children’s study led by Kira Bona found that poorer children had a higher risk of relapse than wealthier ones even when treatment was uniform. Bona is now investigating whether alleviating material hardships such as food insecurity can shrink this troubling gap.
The needle pierced Jennifer Miller’s pregnant belly. It breached the uterus and the placenta and passed through amniotic fluid, through the fetal chest wall and into her unborn baby’s pulsating heart.

Just weeks earlier, Miller and her husband, Henry, had received terrifying news: their son would almost certainly be born with hypoplastic left heart syndrome (HLHS). A pinched aortic valve was constricting blood flow to his left ventricle, the heart’s main pumping chamber. The ventricle would fail to develop. Their son would need three open-heart surgeries before his fourth birthday, the first within days of birth. Risk of failure was high—30 percent—and even if the operations saved their baby’s life, his heart would never be normal. It would have one pumping chamber instead of two. Their son would have half a heart and a lifetime of limitations.

RISK WORTH TAKING
Seeking a better solution, the Millers contacted Wayne Tworetzky, director of the Fetal Cardiology Program at Boston Children’s. Tworetzky had an audacious proposition: open the valve in utero. He believed Miller was early enough in her pregnancy for the baby’s heart to develop normally with blood flow restored. The only catch: no one had ever succeeded in preventing HLHS.

Only 12 fetal heart interventions had been reported worldwide. Of these, just two had successfully opened a valve. One baby still needed the postnatal operations, and the other was unlikely to have ever developed HLHS, as the valve was expanded late in the pregnancy and the heart was already sufficiently large. The Boston Children’s team and their obstetrics partners at Brigham and Women’s Hospital had themselves attempted to open a fetal heart valve the year before but had failed.

Undaunted, the Millers said yes. The chance that their son could have a normal heart was enough.

HAPPY BIRTHDAY, BABY!
In the OR two weeks later, Boston Children’s cardiologist Audrey Marshall threaded a slender wire through the needle in Miller’s abdomen and up into her baby’s grape-sized heart. With ultrasound as their guide, Marshall and team eased the wire into the tiny aortic valve. They slid a balloon-tipped catheter over the wire, inflated the balloon and stretched the valve. Then they withdrew the catheter and watched. Blood flowed through the aortic arch. Would it be enough? The only way to know was to wait until the baby emerged from the watery cocoon of his mother’s womb.

Jack Miller was born on November 21, 2001, pink, wailing and with a small but fully functioning left ventricle. As The New York Times announced to the world, his was the first successful in utero correction of HLHS. Today, the Boston Children’s Fetal Cardiology Program is the largest and most successful in the world.

FETAL HEART

No Need Unmet
In 2008 cardiologist Jane Newburger teamed with psychologist Janice Ware to address one of the most worrisome consequences of congenital heart disease and its treatment: learning and behavioral problems. The Cardiac Neurodevelopmental Program they launched has helped set national standards for evaluating and treating young heart patients with developmental challenges. It sponsored the nation’s first conference on the topic, which in turn inspired an ongoing, multicenter collaborative committed to maximizing patients’ quality of life, for life. Since not all patients experience developmental difficulties, program research aims to identify those at greatest risk as early as possible and to develop targeted treatments so that every child can participate in the full range of life’s opportunities.
The Boston Children’s fetal imaging team has, for the first time, detected irregular brain folding in congenital heart disease babies. The brain’s folds separate functional areas and pack in the neurons, increasing cognitive ability, so irregular folding could be a harbinger of developmental problems ahead. The image shows the development of a normal brain from 23 to 30 weeks gestation (above the lines) compared to that of a fetus with heart disease. Differences in folding are obvious at 29 weeks.

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HEARTS AND MINDS

Fetal imaging can reveal the irregular anatomy of congenital heart disease. Soon, it may also capture telltale signs that the brain, as well as the heart, is veering off course.

More than half of all children with severe heart disease will experience developmental difficulties. For some the risk starts after birth, a consequence of factors such as low blood pressure, infection or the side effects of life-saving procedures. But for others, trouble starts in the womb because faulty genes or low oxygen levels impede normal brain maturation. If researchers could develop an imaging signature to identify those babies most at risk, treatment could begin as early as possible, when the brain is most malleable. One day, it might even begin before birth.

The Boston Children’s fetal heart team has joined forces with neuroimaging experts Ellen Grant and Kiho Im and neurologist Caitlin Rollins to build a picture of brains at risk. Earlier studies from Boston Children’s and elsewhere have shown slower brain growth in fetuses with congenital heart disease compared to those with normal hearts. Now Grant, Im and their team are developing imaging techniques to identify more subtle changes. Their insights will distinguish those children at greatest risk and enable researchers to link symptoms to underlying biology and, ultimately, specific treatments. The goal is a future in which genetics and imaging guide prenatal treatment.
A treatment designed to help children in rural Africa is changing practice in the United States, offering an innovative, cost-effective approach to hydrocephalus, or "water on the brain."

In 2001 neurosurgeon Benjamin Warf and his family moved to a remote, rural town in Uganda. It had no reliable electricity or running water, no dependable police force or phone. But it did have a new pediatric hospital—the first in the country devoted to neurological disease—and Warf was to direct it.

The hospital had been built by CURE International, a Christian nonprofit, and the directorship fulfilled Warf's long-held dream of being a medical missionary. He opened the hospital doors to what he described as "a river of children." A shocking number had hydrocephalus.

**SHUNTLESS SOLUTION**

In the United States, hydrocephalus is most often a complication of either premature birth or a congenital disorder such as spina bifida. It is relatively rare and quickly treated with a shunt to divert the excess fluid to the abdomen, where it is absorbed.

The picture in Uganda was entirely different. As Warf first reported, most of the infants' hydrocephalus was caused by infection and often went untreated because medical care was scarce. More than half of the children were expected to die by age two.

Shunts were not a viable solution. The devices are expensive and frequently fail, bringing patients back to the hospital for emergency surgery. Such return visits were not possible for most children in rural Uganda. For many, a shunt malfunction would be fatal.

Warf combed the literature for an alternative approach to treating infant hydrocephalus. He found two, both abandoned in the 1950s. One creates an opening to allow trapped fluid to escape; the other cauterizes some of the tissue that makes cerebrospinal fluid and thus limits the amount produced. Neither had been successful on its own, but in an inspired move, Warf combined them. The result? Long-term success rates better than those of shunts, and at less cost.

When Warf came to Boston Children's in 2009, he brought his shuntless hydrocephalus technique with him. The hospital now routinely uses the procedure for select patients, and research continues to support its effectiveness. A study conducted in Uganda and completed in 2017 showed that cognitive outcomes and brain development were equally good for children treated with the Warf procedure and with a shunt. A solution designed to help children where help is hard to reach is now saving lives in Boston, and CURE Hydrocephalus, a consortium Warf founded, is training surgeons in developing countries.

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**WHO CAN BE HELPED?**

The buildup of fluid in hydrocephalus compresses the brain. Sometimes the brain expands again once pressure is relieved, but sometimes it does not. Warf has partnered with neuroimaging expert Ellen Grant and engineers Ivy Lin and Jason Sutin to determine why. They have brought a powerful brain-imaging technology called near-infrared spectroscopy (NIRS) to the bedside of Ugandan hydrocephalus patients. Because NIRS doesn’t produce radiation, it can be used safely over time. The researchers’ goals are to develop a brain imaging profile that can predict whether a child’s brain is likely to bounce back, as well as to use NIRS to monitor progress and, ultimately, guide treatment decisions.

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**Sustainable Solutions**

Every child everywhere is entitled to good health. Yet each year, 6 million children worldwide do not live to see their fifth birthday. Under the direction of Michelle Niescierenko, the Boston Children’s Global Health Program partners with local colleagues in more than 30 countries to develop creative, sustainable programs that address problems ranging from heart defects to Ebola to infant mortality and child development. The emphasis from the start is on building local capacity so partners can address their own needs and the Boston team can move on to tackle the next problem in child health.
Police rushed the limp infant into the ER. The baby’s mother and her grandmother ran beside them. Hannah Kinney, a resident and the lone doctor on duty that predawn morning, felt for the infant’s pulse. Nothing. She listened for a heartbeat. Nothing. She compressed the baby’s tiny chest again and again. Nothing. As she declared the infant’s death, the cop next to her told her flatly, “They did it, Doc.”

Kinney never forgot those words. She also never forgot the mother’s raw wail of grief. Her own certainty matched the cop’s: they didn’t do it. She would spend her career unlocking the biology of the disorder that did: sudden infant death syndrome (SIDS). Her findings would point an accusing finger not at parents but at the biochemistry of an immature brain.

INVISIBLE DISEASE
SIDS claims more babies in their first year of life than any other cause of death. Seemingly healthy infants put down for sleep never wake. Most are less than six months old. Their disorder is the largest subset of sudden unexplained death in pediatrics (SUDP), a catchall diagnosis for infant, child or teen deaths that remain a mystery even after autopsy.

Kinney began her research at Boston Children’s in the late 1980s. At the same time, studies from around the world began linking sleep position, heavy bedding and other sleep-related risks to SIDS. “Safe to sleep” campaigns alerted the public, parents began placing their infants on their backs to sleep and rates of SIDS dropped by more than half. Small though their numbers were, however, babies still died.

TRIPLE RISK
Kinney’s painstaking studies began to reveal why. She focused on the brainstem, which controls breathing and the brain’s sleep alarm. This “alarm”—mediated by the brain chemical serotonin—is triggered when oxygen levels get too low or carbon dioxide too high, as can happen when an infant rebreathes exhaled air while sleeping facedown. Healthy babies shift position in response. But Kinney discovered that the alarm never sounds for 40 percent of infants who die of SIDS. Their brainstems make too little serotonin. Here was clear evidence that in SIDS, age, biological vulnerability and an environmental risk converge to turn a family’s dreams into a nightmare.

The team Kinney built at Boston Children’s continues to pursue scientific answers that will assure parents that they didn’t “do it” and, ultimately, save infants’ lives. In 2017 they found elevated serotonin levels in the blood of SIDS babies. If further research confirms a relationship between low brain-stem serotonin and high blood levels, a simple heel prick could one day alert caregivers to take extra preventive measures.

A fascination with the brain, a desire to alleviate suffering and a fierce sense of social justice drove neuropathologist Hannah Kinney to study SIDS. Having faced an accusation, she spent a 30-year career seeking scientific evidence to exonerate others.

Robert’s Program
In 2012 Hannah Kinney and pediatrician Richard Goldstein founded Robert’s Program to further research while evaluating and directly supporting families facing incomprehensible loss. Parents who lose a child to SUDP feel they’ve violated their “sacred obligation” to protect their child. Their guilt is crushing, and the lack of answers can make acceptance nearly impossible. “Even in the face of uncertainty, we must help,” says Goldstein. Robert’s Program provides genetic testing, autopsy analysis and bereavement counseling to help families find a path forward.
John Brownstein began graduate study as a field biologist, painstakingly collecting mosquitoes and ticks in pursuit of his PhD. To keep his mosquitoes alive, he fed them. On his arm. Brownstein figured there had to be an easier way to collect data. Besides, one case of Lyme disease was enough! The solution became clear when Brownstein realized he could mine the wealth of data on the Web for public health purposes.

Brownstein put that insight into action in 2006. He had by then abandoned mosquitoes, earned his PhD in epidemiology and built the Computational Epidemiology Group at Boston Children’s Hospital. He'd watched social networking sites, blogs, chat rooms, online news aggregators and crowdsourcing platforms proliferate. He was more convinced than ever that Internet chatter could fast-track disease surveillance and, ultimately, save lives.

**HEADS UP ON HOT SPOTS**

Brownstein enlisted his colleague Clark Freifeld, a computer scientist, to help develop a tool that would trawl the ever-growing bounty of online data for warnings of disease outbreaks and then aggregate, filter and display the results with at-a-glance clarity. The result was HealthMap. The website monitors news reports, eyewitness accounts and official sources such as the Centers for Disease Control and the World Health Organization for references to more than 200 infectious diseases. First algorithms, and then human analysts, filter the data, discarding questionable reports before results are displayed. The HealthMap display is a world map searchable by place, disease and information source. Pins of deepening color signal the severity of health alerts. HealthMap operates around the clock to provide real-time updates so health officials can stay ahead of emerging crises. And not just officials. HealthMap is available to all.

In 2009 the team released Outbreaks Near Me—a free, GPS-guided mobile app that shows the latest health alerts in a user’s vicinity. Whether jogging around town or trekking through Machu Picchu, users can search for outbreaks, submit disease reports and create customized maps for quick viewing. The app offers a simple way for individuals to stay out of an outbreak’s path and, through their self-reports, contribute to public health surveillance.

**WISDOM OF THE CROWD**

For Brownstein, who is now chief innovation officer at Boston Children’s, HealthMap was just the beginning. His Computational Epidemiology team has launched multiple projects mining Twitter, Yelp, Facebook and other social media to detect public health threats. Their studies show that crowdsourced data not only track with official alerts but can also signal trouble weeks in advance. In 2018 the Department of Homeland Security awarded the group the grand prize in its Hidden Signals challenge. The team will integrate all of its data sources into a single dashboard called Pandemic Pulse to spot biothreat signals and stop outbreaks before they start.

Digital Health

**2006**

**Outpacing Outbreaks**

Early detection is vital to stop a virulent, fast-moving disease such as Ebola from engulfing nations. So, too, is knowing where and how fast the virus is likely to spread. This crucial information offers the best hope for deploying resources where most needed and halting contagion. HealthMap detected the 2014 Ebola outbreak nine days before the World Health Organization (WHO) issued its first alert. The team has since analyzed publically available WHO data to reveal the pattern and speed of disease spread across three countries, demonstrating a powerful new tool for planning outbreak response.

**The shrimp that kept you up all night? And your Yelp review, blasting the restaurant? They may help your local public health agency track foodborne illness.**

**The HealthMap Foodborne Dashboard**

scours Yelp restaurant reviews and Twitter posts for reports of gastric misery and allows public health officials to view complaints in their area in real time.

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John Brownstein’s HealthMap tracks outbreaks real and imagined—it had a cameo in the movie Contagion. In real life it monitors flu, fever, food poisoning and more.
MEXICO: Improved resident training

ARGENTINA: Connected the sole pediatric intensive care team in Tierra del Fuego, the furthest point on the continent, to the rest of the medical world

ZAMBIA: Helped physicians who had no adequate resources and no intensive care colleagues become adept at caring for the critically ill child

ROMANIA: Increased competence in caring for children with a serious heart defect

TURKEY: Reduced infection from central lines, leading to earlier patient discharges

ISRAEL: Saved a child’s life when a resident remembered a simulation and fixed a ventilator valve setting

RUSSIA: Changed burn management at a Moscow hospital

OPENPediatrics is improving practice across the globe.

Jeffrey Burns and Traci Wolbrink continually enhance OPENPeds. Next up: exploring AI to power smart simulators. The simulators would integrate data from users worldwide to support clinical decision making.

Jeffrey Burns and Traci Wolbrink

When Chief of Critical Care Jeffrey Burns realized that his son could collaborate more easily with other online gamers than he himself could with a distant physician desperate for guidance to save a child’s life, he determined to change the status quo for medical knowledge sharing. His colleague Traci Wolbrink was equally committed. In Cambodia, she’d seen a locally created breathing device save children with pneumonia. In Malawi shortly after, Wolbrink helped doctors build something similar. She wondered how many more children in how many more countries could benefit from this alternative to an expensive, high-tech device. And how could the idea be shared without the serendipity that brought her from Cambodia to Malawi?

These experiences sparked OPEN-Pediatrics, a free online platform that promotes the exchange of knowledge between pediatric physicians and nurses around the world. Created in partnership with IBM Interactive, OPENPeds allows practitioners anywhere to download courses, view videos, perform simulations, test themselves and communicate with one another. Its on-demand, peer-reviewed content draws 300,000 visitors a month. OPENPeds has been accessed from every country and territory on the planet and has created a global community of learners. As Burns observed, “Nothing crosses borders like a willingness to collaborate on the care of a critically ill child.”
Ask its founders if starting the first US clinic for transgender children took courage and they’ll say no. It was simply the right thing to do.

Endocrinologist Norman Spack had been seeing transgender patients in private practice for nearly a decade when he joined the Department of Endocrinology at Boston Children’s. His patients suffered intolerably from the mismatch between their gender and genitalia. Many were certain they were in the wrong body as young as age three. By adolescence, their bodies felt like a betrayal.

“Boston Children’s has a long tradition of bold breakthroughs, of being willing to take risks and of doing the right thing for patients.”

—DAVID DIAMOND

Spack began inviting his patients and their families to medical rounds so his new colleagues could learn about the struggles they endured and the risks they faced. Transgender youth are two to three times more likely than their peers to experience depression or anxiety, intentionally hurt themselves or have suicidal thoughts. Forty percent attempt suicide.

The decision to help these children was easy. In 2007 Spack and urologist David Diamond launched the Gender Management Service (GeMS). The clinic initially served both transgender patients and those with sex-related anatomical anomalies. But as calls poured in from parents desperate to help their gender-nonconforming children, GeMS shifted focus exclusively to them.

Spack imported a model of care developed in Holland. Under the “Dutch protocol,” patients receive counseling in the years before medical intervention is appropriate, followed by a stepwise approach to transition that combines psychological support and medical treatment.

Treatment begins with reversible puberty blockers. These both suppress distressing physical changes and provide a developmental pause during which young teens can reaffirm their decision or change their minds. This approach, which GeMS pioneered in the United States, is now endorsed by the American Pediatric Association and codified in international guidelines. It has been adopted by 60 institutions nationwide.

The vast majority of patients continue their transition. At around 14, they begin hormone therapy to develop the deep voice or curvy hips of their identified gender; at 18 or older they may opt for gender-affirmation surgery. They enter adulthood feeling no longer like a mismatched puzzle, but whole.

Bully-Proofed

A staggering 83 percent of transgender youth report being bullied. They and other vulnerable children may face a 24/7 cycle of abuse as bullies turn social media into a forum for cruelty. Boston Children’s founded the first hospital-based clinic to help these children and their parents. Led by pediatric neurologist Peter Raffalli, the Bullying and Cyberbullying Prevention and Advocacy Collaborative (BACPAC) arms children with strategies to build resilience and to develop strong, protective peer and adult support groups. It teaches parents how to advocate for their child.
“I thought I didn’t deserve to see the sun.”

The boy who spoke those words is among the 3 million US teens who struggle with depression each year. Fortunately for him, he is also among the thousands who have benefited from Break Free from Depression, a high school curriculum that brings depression itself into the sunlight to help teens and their families recognize the illness and seek support.

Now available worldwide, Break Free from Depression was born in Boston’s underserved neighborhoods. It was developed by Boston Children’s Hospital Neighborhood Partnerships (BCHNP), a program that brings behavioral health services to children and adolescents where they live and learn. BCHNP places social workers and psychologists in schools to provide direct services to youth and empower teachers to spot and respond to social, emotional and behavioral health concerns.

Depression is a big one, and school personnel are often unsure how to best support students grappling with the disease. BCHNP director Sheila Dennery and her team recognized an urgent need for a brief, easy-to-implement depression awareness curriculum.

BREAK FREE BREAKS THROUGH

The BCHNP team began piloting Break Free from Depression in Boston high schools in 2008. The comprehensive program includes parent and staff development workshops and a four-lesson curriculum.

The cornerstone of the curriculum is a moving documentary in which real teens honestly and openly share their struggles with depression and suicide and the ways they have learned to find help, healing and purpose. Presentations, interactive activities and group discussions built around the video develop students’ depression awareness.

It works. Participating students have consistently demonstrated increased understanding of depression, decreased stigmatizing attitudes about depression and enhanced confidence in their ability to find help for themselves or a friend.

The local success of Break Free from Depression led to presentations, webinars and train-the-trainer workshops at national conferences. Soon, schools in 38 states were using the curriculum. Break Free from Depression reaches tens of thousands of students a year.

In 2017 Break Free from Depression went global. Videos of the train-the-trainer workshops and all materials are now available through OPENPediatrics, the hospital’s free, online learning platform (see page 98). Those on the frontlines of teenage depression anywhere in the world can take the training, download the curriculum and help teens break free from depression.

Mighty Awesome

One million downloads would be a brag-worthy milestone for any video game site. But it is especially so for Mightier, whose games reward emotional control rather than shoot-'em-up prowess. Mightier ties gaming success to emotional regulation through a heart rate monitor that controls game difficulty. Games get harder as a player’s heart rate rises, easier as it slows. On-screen feedback and deep breathing tips promote self-control. As kids learn that mastering frustration and anger is a winning strategy, they begin to apply the lesson in real life: studies show fewer emotional outbursts and less oppositional behavior after 12 weeks of play.2 Mightier was conceived and developed by Joseph Gonzalez-Heydrich and Jason Kahn at Boston Children’s Hospital and is now available online from Neuromotion Labs.
On Wednesday evenings, after the pizza’s served and the soft drinks poured, the slides begin. The images come from around the world but are far from a travelogue. One shows a lower leg as broad as the man’s torso; another, an infant with a vascular tumor that extends from chest to thigh. Yet a third captures the heartbreaking weight of a growth so big it pulls a child’s cheek to his shoulder.

These disorders are all vascular anomalies, and the men and women brushing pizza crumbs off their fingers are the world’s leading experts on their treatment. They are members of the Boston Children’s Vascular Anomalies Center (VAC), the first program of its kind in the world and for decades, the only one. On Wednesday evenings they lend their expertise to stumped colleagues and parents desperate for answers.

But one Wednesday a decade ago, the images flashing across the screen weren’t from afar but from VAC’s database. And the presenter wasn’t stumped. He was one of VAC’s own, radiologist Ahmad Alomari, and he was sharing the results of a months-long immersion in the medical records, scans and photos of patients with PUVA: provisionally unique vascular anomalies.

“—that’s a fancy way of saying we don’t know,” quipped VAC codirector Steven Fishman.

But one Wednesday a decade ago, the images flashing across the screen weren’t from afar but from VAC’s database. And the presenter wasn’t stumped. He was one of VAC’s own, radiologist Ahmad Alomari, and he was sharing the results of a months-long immersion in the medical records, scans and photos of patients with PUVA: provisionally unique vascular anomalies.

“—STEVEN FISHMAN

Vascular anomalies occur when the body’s conduits—the vessels that carry blood or lymph—go awry. Blood vessels may snarl or proliferate madly; lymphatics may leak, causing tissues to swell. The resulting vascular tumors and malformations can affect any organ, cluster in syndromes and cause parts of the body to overgrow.

While some vascular anomalies, such as port wine stains, are relatively common, many are among the rarest disorders. There may be fewer than a dozen known cases worldwide. If the VAC team can’t provide a diagnosis, chances are no one can. The hundreds of PUVAs among the thousands of cases in the VAC database weigh heavily. Each represents a child living with uncertainty as well as disability and pain.

That’s why the team gathered for Alomari’s presentation sat rapt. Alomari presented one PUVA case after another, all identical. He had found a new syndrome. Along with colleagues at the National Institutes of Health, he named it CLOVES, an acronym for its origin (congenital) and major physical signs.

Alomari published his description of CLOVES in 2009. Geneticist Matthew Warman and team then reached into VAC’s freezers for tissue samples from CLOVES patients, extracted DNA and searched for the gene. They found it in 2012. Scientists could now follow the thread of disease from its genetic start through the labyrinth of molecular changes that lead to symptoms, seeking opportunities to intervene. One drug has already shown promise for treating a disease that just a decade ago had no name.

He Wrote the Book

When plastic surgeon John Mulliken began treating patients with lymph and blood vessel abnormalities in the late 1970s, this medical and surgical field didn’t even have a name. Working with Juliane Glowacki in Judah Folkman’s lab, he proposed the first cell-based classification system, lifting “a cloud of terminological confusion.” Mulliken coined the term vascular anomalies, cofounded the field’s professional society, coauthored its first textbook and started the Vascular Anomalies Center at Boston Children’s.
DEFEATING TANGLES IN THE BRAIN

Neurosurgeon Edward Smith describes his collaboration with radiologist Darren Orbach as the equivalent of Burger King and McDonald’s teaming up to sell fries. Their specialties typically take separate approaches, but they have united to more successfully treat arteriovenous malformations (AVMs), potentially deadly tangles of blood vessels found primarily in the brain.

Surgeons cut AVMs out. Interventional radiologists close them off with glue or coils. Smith and Orbach combine the two procedures during one operation, first sealing blood vessels feeding the AVM to reduce bleeding, and then dissecting and removing the AVM itself. Their procedure results in fewer complications and higher cure rates. Codirectors of the Boston Children’s Cerebrovascular Surgery and Interventions Center, the two have demonstrated the benefits of tag-teaming to treat other vascular conditions as well.

MRIIs transformed into 3D-printed models of an individual patient’s AVM aid in surgical planning and reduce OR time. Shown here: a vein of Galen malformation. This is a particularly dangerous AVM because the vein of Galen carries blood back to the heart. Normally, capillaries would slow the rush of blood from arteries into the vein. But here, as in all AVMs, arteries and vein connect directly. The high-pressure blood flow forces the heart to work overtime, posing a grave risk of congestive heart failure. Boston Children’s is one of the few places in the world that specializes in treating vein of Galen malformations.
A marvel of the young brain is its plasticity, a capacity on vivid display when a child learns to play the piano or speak a new language. But what underlies this extraordinary capability? The answer could make it possible to hit rewind, to reactivate this youthful plasticity in older brains. Such a capacity could revolutionize the treatment of a range of neurological conditions in children as well as adults.

Boston Children’s Hospital neuroscientist Takao Hensch was the first to reveal, in a landmark 1998 study, that such a feat is possible. Since then, Hensch and his colleagues have pioneered studies of the brain’s plasticity. Their primary focus is to understand—and even manipulate—special windows of heightened activity in the developing brain. These windows, called “critical periods,” open and close early in life and enable the brain to acquire new skills. “But these windows of opportunity are also windows of vulnerability,” said Hensch, “and it’s becoming clear that many neurological conditions, from autism to schizophrenia, can begin during these crucial times.”

THE DEVELOPING BRAIN

During critical periods, the brain soaks up and integrates information from its surroundings to establish the proper connections. When these periods end, so do the windows of developmental opportunity. If these critical periods are disrupted, the brain’s circuits may not properly form. Just as a faulty electrical circuit cannot switch on a light, damaged circuits in the brain can lead to a host of problems, from difficulties seeing and hearing to impaired social, emotional and cognitive abilities.

One of the best-studied critical periods affects vision. Children develop high-acuity vision because the brain learns how to combine the visual inputs from the left and right eyes. When this process is disrupted—for example, if the brain is slow to read the signals from one eye (a condition known as amblyopia)—visual problems, even blindness, can result. That’s because the neurons ferrying information from the “lazy” eye fail to wire up during their critical period; when the period ends, they’ve lost the opportunity to do so.

Windows of brain development that close early in life may not seal shut. Takao Hensch has shown they can be reopened in mice, raising hope of extending the period during which conditions such as amblyopia (lazy eye) can be reversed.

“Critical periods define who we are—it’s how a brain that looks basically the same from one person to the next can be shaped and sculpted to make each one of us unique.”

—TAKAO HENSCH

¿Hablas Español?
The rolled “s” of Spanish or tonal nuances of Mandarin can defeat even the most dogged late-life language learner. Auditory critical periods, like their visual cousins, close early: we become deaf to tones we did not hear during the critical period. But Takao Hensch has discovered that Lynx1, a molecule that locks down the visual system, does the same for hearing. Further, his findings suggest that a drug that overrides Lynx1 might be able to reopen the auditory critical period. The implications are extraordinarias!
**RELEASING THE BRAKE**

In a groundbreaking study published in 2010, Hensch and his team unearthed one of the molecular “brakes” that helps bring an end to this critical period. It works by blocking acetylcholine, an important chemical that sends messages within the brain. Notably, mice that lack this brake can spontaneously recover from amblyopia, even into adulthood.

Even more exciting, the researchers could achieve a similar recovery using a drug that boosts acetylcholine. The team’s findings suggest that reopening critical periods could reverse visual disorders, particularly amblyopia, the most common cause of visual impairment in children. Could other critical periods be reopened, too? Hensch is looking at hearing next.

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**Bye-Bye, Lazy Eye**

Amblyopia can be a vexing challenge for clinicians. About half of kids with the disorder have no obvious signs. That means the disease can go undiagnosed until it is too late, stealing their chances for normal vision.

David Hunter is determined to create a world where no cases of amblyopia are missed. Through dogged effort, he developed a pediatric retinal scanner called the Rebion blinq™. Designed to be used by medical assistants in a pediatric practice, the noninvasive device is more than 95 percent accurate at detecting amblyopia or other eye problems in children. “After more than 20 years of research and development, we have finally completed the journey from bench to bedside,” Hunter said.

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**REVERSING AMBLYOPIA**

If caught early, amblyopia is fairly easy to treat. But once a child reaches eight or 10 years old, it is often too late to restore normal function; the critical period has passed.

That picture could change. Spurred by his lab’s discovery that acetylcholine-boosting drugs can increase visual plasticity, Takao Hensch and an ophthalmology team led by Carolyn Wu have launched a clinical trial of one such drug, donepezil, which is already FDA approved.

They are enrolling children age 10 and older whose amblyopia can no longer be successfully treated with the standard methods.

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**Here’s an eye-opener:**

amblyopia affects 2 to 3 out of every 100 children.

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Ask your doctor for a copy of your health records, and chances are you’ll receive an armload of printed pages in return. This is true even if your records are electronic, as an increasing number of patients’ health records now are. How can this old-fashioned approach persist in an era of high-tech health care?

The answer lies in the ways health data are stored, accessed and shared. Despite the widespread use of electronic health records, most patient information remains squirreled away in disparate digital systems that are rigid, incompatible and inaccessible. Insights that could improve individual and public health remain locked up with the data.

But this picture is changing. A team of researchers from the Boston Children’s Computational Health Informatics Program and Harvard Medical School is transforming how health information is accessed and shared. Led by Ken Mandl and Isaac Kohane, they are creating an app store for health as diverse and accessible as the one on your phone.

SMART SOLUTION

Mandl and Kohane first proposed a smartphone-like approach to electronic health records in an influential 2009 New England Journal of Medicine editorial. President Obama had just signed an economic stimulus package that included $48 billion for health information technology. This investment opened an unprecedented opportunity to design a flexible, uniform system for tapping data in electronic health records to improve health care, wellness, public health and research.

Mandl and Kohane envisioned health IT employing a single, open-standards interface any app developer could use to access and securely share electronic health record data. The resulting platform would “provide a universal application programming interface’ to connect apps to the electronic health record in the same way you connect apps to your phone,” explained Mandl. It would support a limitless array of tools for patients, clinicians and the broader healthcare community. Consumers would download, preview and then either keep or reject an app, fostering innovation and spawning a competitive market for health apps.

A year later, backed by a $15 million government grant, Mandl and Kohane turned vision into reality. They launched SMART (Substitutable Medical Apps, Reusable Technology), a groundbreaking, open-source health information technology platform that quickly became the industry standard.

TIPPING POINT

Adoption reached a tipping point in 2019. The Veterans Administration now uses SMART to power mobile health apps, and all the electronic health record giants have built SMART support into their systems. So have Apple, Microsoft and Google. What’s more, through Mandl’s efforts, the 21st Century Cures Act requires that health IT use a common interface to provide access to all of a patient’s health data. SMART will be that interface. Its approach to an app-based health information economy will effectively be the law of the land for healthcare IT.

Hacking Pediatrics

What happens when you bring together the greatest minds and organizations in pediatric medicine, business and technology for one day? You get a unique, collaborative effort, led by Boston Children’s, called Hacking Pediatrics. Directed by Michael Docktor, Hacking Pediatrics is the only hackathon in New England dedicated to solving the big challenges in child healthcare.

"ALEXA..."

Your son breaks out in an itchy rash. Your daughter spikes a sudden fever. What should you do? Ask Alexa. In 2016 a pioneering team of Boston Children’s inventors, led by Nitin Gujral, released KidsMD, the first healthcare app (or “skill”) for Amazon’s Alexa. It provides information on a host of common childhood illnesses and can help parents determine if their child needs a doctor.

More recently, the team, together with experts from Seattle Children’s Hospital, created a new Alexa skill, known as Flu Doctor, to help inform kids and their families about the flu and flu vaccines.
John Meara keeps a sheet of paper under his desktop blotter. It’s a 37-item checklist he sent to his surgical team two weeks before they were to give Dominic Gundrum a new face. The list covers every item the team would need in the operating room. One word appears time and again: backup.

Meara, chief of plastic surgery at Boston Children’s, wanted extra units of blood. Extra drains. Extra drills. Extra everything. He was leaving nothing to chance.

Meara and Mark Proctor, chief of neurosurgery, had been preparing for weeks for what would be one of the most challenging operations of their careers. And they were no strangers to challenge. As codirectors of the hospital’s Craniofacial Program, they operated on patients few others could help, referred from around the world. But Dominic was one in a million—actually, one in about 50 million. Meara estimated that a baby with his combination of anomalies would be born only once every five to ten years in all of North America.

“I’VE SEEN THIS”

Each of Dominic’s conditions was so rare that few centers ever saw them individually, let alone together.

The first was a triangle-shaped cleft that ran from the baby’s brow to his upper lip, splaying his face. The second was a protrusion of brain tissue called an encephalocele. Dominic’s cleft was so large that part of his brain had pushed outwards, forming a ball beneath the skin between the two halves of his nose.

The encephalocele had been diagnosed in utero, and doctors had told Dominic’s parents, Mary and Mark Gundrum, that their baby might not live. If he did, they warned, he might be severely disabled.

The Gundrums, devout Catholics, would not terminate the pregnancy. Instead, they searched for someone who could give their unborn son his best chance at life. An online video of an encephalocele repair led them to Meara. He reviewed Dominic’s ultrasound. Then he called. “I’ve seen this,” he told the couple. “It’s going to be okay.”

Two Stages of Joy

Plastic surgeon John Mulliken describes his relationship to cleft lip and palate as love-hate. “I love to take care of the kids,” he said, “but I hate that a child is born with a malformed face and lip.”

Mulliken transformed treatment of bilateral cleft lips and palate, the most complex type, by demonstrating that repairing the mouth and nose together produced better results than the traditional staged approach. With chief of dentistry emeritus Stephen Shusterman, he pioneered a two-part repair process that starts with a custom-made appliance that brings together the two parts of the cleft in the gums, followed by simultaneous closure of the lip, nose and gums. He’s given thousands of children reason to smile.
Founding Fathers
Joseph Murray (above right) is renowned for performing the first successful kidney transplant, an accomplishment that won him a Nobel Prize. He later became chief of plastic surgery at Boston Children’s and established the field of craniofacial surgery in the United States. Murray began operating on Boston Children’s patients with facial deformities in the 1950s, at the invitation of Chief of Dentistry Paul Losch. Over the following decades, he built what is today the world’s foremost craniofacial anomalies program. Murray trained with the French surgeon who founded the field, Paul Tessier (below right, with Murray at left). They often operated side-by-side, at Boston Children’s and in France. The split in Dominic’s face is called a Tessier facial cleft.

DOMINIC’S NEW FACE
Their intense planning saved hours in the OR. The team scrubbed in at 8:30 a.m. on December 4, 2012. Seven hours later, Dominic had a new face.

Meara keeps the checklist from that day close at hand not for sentimental reasons but because he has needed it frequently since. Calls from families like the Gundrums come in weekly. While Dominic remains one in 50 million, the team has restored the faces of many other children born with an encephalocele or severe facial cleft.

A HOLOGRAM FOR THE SURGEON
The 3D-printed models that shaved hours from Dominic’s operation are today just one part of a sophisticated surgical planning approach pioneered by SIMPeds, the Boston Children’s Simulator Program. Radiologist Sanjay Prabhu and the SIMPeds team fuse MRI and CT scans of a patient’s anomaly to generate a physical model. Surgeons make their initial cuts on the 3D-printed model, which is then scanned and converted into a virtual version, providing a computer template that can be rotated, measured, cut and recut as often as necessary to perfect the procedure.

Tomorrow’s technology will go even further. A hologram projected onto the child during surgery will mark the exact place and angle for every incision, layer by layer, through skin, muscle, bone or brain. Prabhu and team have begun work on a prototype.

The Gundrums traveled from Wisconsin to Boston Children’s to give Dominic his best chance at a normal life.

The Gundrums traveled from Wisconsin to Boston Children’s to give Dominic his best chance at a normal life.
Martha Murray was a graduate student headed for a career in engineering when she ran into a friend hobbling around the Stanford University campus on crutches. He’d torn the anterior cruciate ligament (ACL) in his knee and was nervously awaiting surgery. As he explained that surgeons would remove his ACL and replace it with a tendon graft, Murray became puzzled. “Why can’t they just sew it back together?” she wondered. That chance meeting set Murray on a new life course. She left graduate school, enrolled in medical school and became an orthopedic surgeon devoted to finding a better way to repair ACLs. She is well on her way to success.

SIDELINED

A torn ACL is one of the most common sports injuries. Each year some 400,000 patients in the United States undergo the graft procedure Murray’s friend dreaded. This standard-of-care operation restores knee stability but is highly invasive and may lead to osteoarthritis, a high risk for those who tear an ACL as children or young adults. Most develop arthritis in their knee within 10 to 15 years after reconstructive surgery.

Far too many ACL patients coming to Boston Children’s Hospital will suffer from arthritic knee pain in their 30s. At an age when they should easily kneel to scoop up a toddler or sprint to make a killer tennis shot, even walking can hobble them. There are no good solutions. Thirty-year-olds are too young for a total knee replacement, and an effective method to reduce the pain has yet to be found.

RESEARCH BEARS RESULTS

Murray began her quest for a knee-saving remedy by figuring out why ACLs don’t self-repair. She made a fundamental discovery: when other ligaments suffer injury, a blood clot forms that stimulates the torn tissue ends to heal. In the ACL, a clot never forms. Fluid bathes the ACL and protects the knee during daily use, but this lubricant also washes out the blood clot that tries to form when the ACL tears. There is no “bridge” to rejoin the two ends.

Armed with this knowledge, Murray devised an ingenious solution. She implants a sponge-like scaffold into the knee to bridge the torn ends of the ligament. The sponge is made of collagen, a natural building block of connective tissues, and infused with the patient’s own blood. It allows a blood clot to form, which stimulates ACL regeneration for the first time. She calls the technique Bridge-Enhanced ACL Repair (BEAR®). Patients have already benefited.

ACL tears are among the sports injuries that land more than 775,000 children aged 14 or younger in the ER each year.
ON THE MOVE

Murray launched a pilot study in 2015, based on the strength of results in animals. In large animals, BEAR® repairs had proven as strong as traditional ACL reconstruction, and the animals hadn’t developed arthritis.1 Data from the pilot clinical study are equally promising: patients appear to experience less postoperative pain and show increased knee function and muscle strength when the ACL is regenerated instead of replaced.2

MULTICENTER TRIAL KICKS OFF

In October 2018 the NIH funded a $6 million, five-year, multisite trial of the BEAR® procedure. The trial will enroll 200 individuals between 18 and 40 years of age who have complete ACL tears. It will compare outcomes of the BEAR® procedure and standard reconstruction at six months, one year and two years after surgery. Murray has launched a biotech company, MIACH Orthopaedics, to provide the manufacturing required for such a large trial. Murray’s BEAR® procedure has the potential to be less invasive, less expensive and less time-intensive than traditional ACL surgery. Indeed, the researchers expect to see earlier improvement and fewer side effects in the BEAR® patients. Their goals: return patients to active, healthy lives and change the standard of care for ACL surgery.

Keeping Kids in the Game

Nearly 21.5 million kids aged 6 to 17 participate in organized sports, and the number injured each year exceeds the population of Boston. Some 40,000 a year turn to Boston Children’s Sports Medicine for help. The first-in-the-nation program was founded in 1974 by sports medicine pioneer Lyle Micheli. It has set standards for promoting optimal health and fitness in young athletes of all ages and abilities, from Little Leaguers to Olympians, ever since. With specialty clinics in concussion, spine and sports, dance medicine and more, Boston Children’s Sports Medicine gets kids back in the game and keeps them there.

DOING WHAT NATURE CAN’T

The articular cartilage that lines joints forms only during fetal development; it doesn’t grow back once injured. The result: many a one-time athlete or aging adult with a titanium hip or knee. But in a world first, stem cell biologist April Craft has made articular cartilage from human stem cells.3 It is strong enough to restore knee stability in an animal model. Much work lies ahead, but this research holds hope for reversing currently untreatable tissue damage.
Boston Children’s neuroscientist Beth Stevens was captivated by some peculiar cells in the brain. While the vast majority of brain cells come from the nervous system, a highly unusual group, called microglia, does not. More than just outsiders, microglia hail from the immune system—a part of the body, it was believed, that was excluded from healthy brains. What could these interlopers be up to?

Some early clues emerged from Stevens’ work as a postdoctoral fellow in the Stanford University lab of Ben Barres. There she studied the connections that brain cells forge with one another. Early in life, these connections (called synapses) are plentiful. But as the brain matures, only the best ones are maintained; others are trimmed away like wayward leaves on a vine. “This pruning process gives the brain’s circuitry precision and enables things to wire up just right,” explained Stevens.

Microglia Malfeasance

While scientists are only now beginning to understand the complex lives of microglia, the cells were first identified some 200 years ago. One early observer is said to have believed they resembled aliens from a far-off universe—an astute observation, as it was discovered many decades later that they originate not from within the brain, but from the immune system. Microglia help shape how the brain’s circuits get wired up early in life. They also destroy synapses in a range of neurological disorders, from Alzheimer’s to schizophrenia. Shown here (left to right): an artist’s rendering of a synapse, microglia, Beth Stevens and microglia surrounding Alzheimer’s plaques.

In a set of landmark studies pursued at Stanford and later in her own lab at Boston Children’s, Stevens and her colleagues discovered that a fundamental part of the immune system, called complement, tags synapses for pruning. Further, of all the cells in the brain, only microglia respond to complement’s signals. They are the workhorses that remove young synapses from the developing brain. Microglia thus represent a critical point of intersection between the brain and the immune system, a node that went unrecognized for decades. This finding has not only catalyzed an exciting new field of research but also provided unexpected insights into neurodegenerative diseases and hope for new treatments.

“Pruning synapses is critical for healthy brain development. But it is also possible to have too much of a good thing, particularly in the mature brain. Abnormal synaptic pruning underlies several conditions, including Alzheimer’s disease. In fact, research suggests that destruction of synapses is among the earliest manifestations of Alzheimer’s, occurring years before overt signs, such as memory loss.

In a pioneering study published in 2016, Stevens’ team laid blame on microglia. The scientists showed that by conspiring with complement, microglia destroy synapses in mouse models of Alzheimer’s, and they do so early in the course of the disease. We’re just beginning to dissect the relationship between the brain and the immune system. If we can understand how they talk to each other, it could transform how we treat disease.” — BETH STEVENS

DEVELOPMENT RUN AMOK

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Beth Stevens has been widely recognized for her transformative research. In 2015 she was honored with a prestigious “genius” grant from the MacArthur Foundation. In 2018 she was named an investigator of the Howard Hughes Medical Institute, a highly sought-after appointment for researchers whose work shows the greatest promise to solve the biggest challenges in biology and medicine.
MICROGLIA TO THE RESCUE

Microglia cells patrol the central nervous system, acting as a first line of defense. Because these cells can be functionally replaced through blood stem cell transplantation, they hold promise as vehicles for delivering gene therapy.

Alessandra Biffi, director of the hospital’s Gene Therapy Program, is exploiting this opportunity to treat a handful of devastating childhood illnesses that affect the brain. In her pioneering work, Biffi genetically corrects the patient’s own blood stem cells and returns them to the body via a cell transplant. The stem cells then do what they always do: differentiate into blood and immune cells, including microglia-like elements within the central nervous system. Once inside the brain, these cells can halt the progression of incurable neurodegenerative diseases.

Biffi is working to improve this approach so that genetically modified cells can be introduced directly into the brain. This direct route should provide faster results than the traditional transplant method. She is also teaming up with other scientists to explore how they might harness these extraordinary capabilities for Alzheimer’s disease and other neurodegenerative conditions. Novel therapies that target microglia could revolutionize treatment, making it possible to grow older without the fear and devastation that come with progressive memory loss.

Of Mice and Men

The brain is the most complex organ in the body—and also the most challenging to study in the lab. But a new approach to creating mouse models allows scientists to replicate human brain disorders as never before. A Boston Children’s team led by Frederick Alt combined stem cell and gene editing technologies to introduce specific gene mutations into cells within a discrete region of the fetal mouse brain. Scientists can explore the effects of the mutation as the mouse grows, sparking deep insights into how genes conspire to make our own brains vulnerable to devastating diseases such as Alzheimer’s, schizophrenia, autism and others.

These findings hold enormous promise for treatment: therapies that block excessive pruning might be able to preserve synapses and, with them, memory. Some biotech companies have already sprung up to harness these results—for example, by engineering therapies aimed at disrupting the conspiracy between complement and microglia.

Stevens and her colleagues continue to unravel the complex biology of microglia. New evidence, especially from studies of human genetics, further implicates microglia dysfunction as a primary driver of Alzheimer’s disease. However, exactly what goes wrong to trigger that dysfunction remains unclear and a topic of active research by Stevens and her team.

Gene-edited stem cells (bottom) used to build a better mouse brain for research give rise to a genetically distinct forebrain (green, top).

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Autism affects a significant swath of the world’s children. In the United States, roughly 1 percent are diagnosed with the disorder. While earlier diagnosis, behavioral therapies and medications to control anxiety and sensory overload enable many of these children to thrive, others remain profoundly limited. Their disease blunts communication. It reduces play to repetition. It saps relationships of the full, rich span of human emotion.

As clinicians and scientists worldwide seek to unearth the root causes of autism and develop treatments, they have been mining the genes passed from parents to child for clues. But a team of researchers led by Boston Children’s Chief of Genetics Christopher A. Walsh has discovered that these inherited mutations are not the only genetic culprits in autism.

MOSAIC BRAIN
This revelation stems from a 2015 study in which Walsh’s team scrutinized the DNA of neurons within healthy human brains. They uncovered a surprising amount of genetic diversity: individual neurons differed from their neighbors at as many as 1,000 points within the genome. These single-letter changes are not inherited but arise after conception, from the earliest stages of embryonic development onward, even stretching into adulthood.

Most of these “somatic mutations” are harmless, but some disrupt important developmental genes in the brain, including those that contribute to autism. In a landmark 2017 study, Walsh and his team analyzed the genomes of 5,800 families—autism patients, their parents and, in some cases, their unaffected siblings. The pattern that emerged provides intriguing hints that somatic mutations may play an important role in the disease. Mutations unique to the patients were more likely to occur in genes that are active in the fetal brain and in a part of the brain, the amygdala, already implicated in autism spectrum disorder. Some were in genes known to contribute to the disease.

Although more research is needed to dissect the roles of these somatic mutations and their contributions to autism risk, the findings help illuminate the neural underpinning of the disease. “Somatic mosaicism is helping lead us to a deeper understanding of the biology of autism,” said Walsh.

THE EARLIER THE BETTER
When it comes to diagnosing autism, the earlier the better: interventions aimed at slowing or halting the condition’s course are most effective at an early age. But if a child is very young, especially under two years old, the earliest signs of autism can be misinterpreted or even missed altogether.

Neuroscientist Charles Nelson and bioinformatician William Bosl are developing a new tool that promises to move diagnosis into infancy. In preliminary studies it reliably distinguished infants who are at highest risk for autism, including those as young as three months. The test, which uses measurements of the brain’s electrical activity, is painless and inexpensive and could be incorporated into routine pediatrician visits.

Seeking to Simplify
Tuberous sclerosis complex (TSC) is a rare neurological disorder that causes autism spectrum disorder. Yet, unlike many forms of autism, its genetic roots are simple: just two genes are involved. Boston Children’s neurologist Mustafa Sahin was among the first in the world to demonstrate that brain circuit development is disrupted in TSC and that these abnormalities can be reversed in animal models. Propelled by these and other studies, Sahin is now leveraging the enhanced knowledge of TSC to discover novel ways to treat autism. At right: Sahin helps a patient understand his disease.
Had they been born 500 years ago, Leonard Zon and George Q. Daley might have taken to the high seas in search of new continents. They are driven by a passion for discovery. So it’s no surprise that, as hematologists confronting the ravages of blood cancers and genetic blood disorders, they set their sights on a scientific frontier as yet unconquered: a safe, rejection-proof and limitless source of blood stem cells.

Blood stem cells give rise to oxygen-rich red cells, disease-fighting white cells, platelets to stop bleeding—every bit of our blood. A limitless supply would transform the blood donation system, ending shortages and fear of tainted transfusions. A rejection-proof supply could provide a whole new way to treat leukemia, anemias and genetic blood disorders.

THE JOURNEY BEGINS

Zon and Daley launched the Boston Children’s Stem Cell Program to deliver on this promise. It was 2004, a time of as much controversy as excitement for stem cell research. The field’s great potential lay in creating cells a patient’s body won’t reject, but embryos were the only source for the cells. Then Daley’s team accomplished the seemingly impossible. It was one of three worldwide to turn skin cells back into stem cells. These induced pluripotent stem cells (iPSCs) were an immediate boon for research. They moved a patient’s disease into a dish for study and drug discovery. But more, they meant patients could one day be the source of their own cures. iPSCs would be made from a patient, genetically corrected if necessary, and then matured into the right cells and returned to the patient. They would correct disease with no risk of rejection.

ROUGH SEAS

Progress came swiftly. Zon discovered a drug that improves blood stem cell transplant, and Daley created the first repository of disease-specific iPSCs, an accomplishment Science named breakthrough of the year for 2008. A final challenge remained: to mature iPSCs into blood stem cells and create them in quantity. Daley would mature the cells while Zon used a unique zebrafish drug screening platform to find chemicals to expand their numbers.

They expected smooth sailing. But transforming iPSCs into blood stem cells turned out to be one of the toughest challenges in stem cell research. The team could make blood stem cell progenitors. They could make red cells and white cells. But they could not make blood stem cells. No one could.

Universal Donor Cells

Stem Cell Program researchers can now produce functional red blood cells, platelets, and T and B cells as well as blood stem cells. This opens the extraordinary possibility of generating off-the-shelf blood products—transfusion products to replace donated blood and plasma, for example, or T cells for cancer immunotherapy.

The researchers are now devising ways to create cells that are immune-invisible and could be used by anyone, anywhere. Their first product, platelets, is in development with collaborators in Japan and slated to enter clinical trials in 2019 or 2020. The ornament-like globes above are platelets forming in the lab.
LAND HO!
Ten years of further research finally brought them to promising shores. Daley’s lab has now generated blood stem cells that give rise to all blood cell types, the closest anyone has come to a transplantable cell. Even the T cells function, a world first. 4, 5 Plus, Zon found a chemical that boosts blood stem cell formation to levels appropriate for transplantation.6

These long-sought achievements open wide new opportunities to study blood disorders and find drugs to halt disease. But more, they put the Stem Cell Program on track for the first clinical trial of a stem-cell-derived blood product (platelets) and bring the field closer than ever to custom cures for blood disorders.

Drug Discovery
Leonard Zon brought two drugs to clinical trial in record time—within three years of initial discovery. This remarkable accomplishment is thanks to a fast, efficient drug discovery system he developed. Zon uses cells from zebrafish embryos to quickly find chemicals that push stem cell differentiation in the desired direction. He then tests promising chemicals in human iPSCs. A biotech company, Fate Therapeutics, formed around his first drug, which promises to improve bone marrow transplantation. The second drug targets cancer stem cells in melanoma.

Long clinical experience shows that transplanted blood stem cells can take up residence in the bone marrow and produce billions of functioning blood cells. Lab-grown, custom cells would make this option available to any patient who needs it and end the anxious wait for a matched donor who may never be found. Shown here: conceptual image of blood stem cells in a needle.

Break Through: Stem Cells
2007 One of the first three labs to reprogram skin into stem cells
2010 Drug to improve bone marrow transplant enters clinical trials
2017 iPSCs turned into blood-forming cells
2018 Functioning T cells generated from iPSCs

50,000 patients worldwide now get bone marrow transplants each year. Tens of thousands more could benefit.
SCAFFOLDS OF SILK
Growing new cells is essential to repairing injured or malformed organs, but the cells need a foundation on which to grow. This is especially true for hollow structures like the bladder. Providing that support system has been a major challenge, one that scientists Joshua Mauney and Carlos Estrada are solving. Remarkably, Mauney, Estrada and their colleagues have discovered that silk-derived scaffolds, devoid of any cells, can support tissue regeneration in animals with bladder defects.10 Their findings could open a new path to bladder augmentation surgery—a very complicated procedure—and lead to new approaches to repairing other hollow organs, too, such as the esophagus and trachea.

SPINAL CORD, HEAL THYSELF
Perhaps the greatest aspiration of stem cell technology is to regrow damaged or missing body parts, including the severed nerves in patients with spinal cord injuries. If these nerves, also known as neurons, could be regenerated, a new world of therapeutic options would open. Neuroscientist Zhigang He has been working toward this goal. His team used a three-drug cocktail to reawaken neural stem cells, which in turn stimulated nerve regrowth and improved motor function in mice with injured spinal cords. The cocktail improved mobility in a mouse model of stroke, too.9 This discovery offers a paradigm for future efforts aimed at stimulating neuronal regeneration in humans. Above: Axons regenerate across the site of injury in a mouse’s spinal cord.

MATTERS OF THE HEART
Boston Children’s pediatric cardiologist William Pu, together with collaborators at the Wyss Institute for Biologically Inspired Engineering, created a tiny device—known as a heart-on-a-chip—that harnesses patient-derived cells to recreate a rare genetic disorder in the laboratory.7 The condition, Barth syndrome, causes severe heart failure and often requires a transplant. With the heart-on-a-chip, Pu and his colleagues discovered a potential treatment for Barth syndrome. Now, the researchers are leveraging stem cells to model the heart and its chambers in three dimensions, constructing miniature ventricles (above) whose pressure, volume and contractions can be measured just as they are in patients. This revolutionary approach could spark new treatments for a range of congenital heart diseases.

THE SKY’S THE LIMIT
Blood stem cells to treat diseases such as anemias, immune deficiencies and leukemia have been the Stem Cell Program’s prime target because they offer a fast-track to the clinic: the method for delivering the cells, bone marrow transplantation, is well established. But stem cell therapies could improve treatment for almost any disorder in which an organ is damaged or defective. They promise better medicine at lower cost as one-time cures replace a lifetime of treatment for chronic diseases.

More than 40 Boston Children’s labs, within and beyond the Stem Cell Program, pursue stem cell research. Here are three to watch.

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AUTHOR’S ACKNOWLEDGMENTS

Robert Gross, the great Boston Children’s heart surgeon, kept a journal listing the operations he performed. It’s organized by condition and notes each patient’s name, age and date of surgery. Some listings also have a brief comment. Under “coarctation of the aorta,” you’ll find the following for patient 340: “graft, multiple aneurysms.”

Patient 340 was my father. Thirty-three when Robert Gross saved his life, he lived into his 90s. I, my son and granddaughters, my brother, niece and nephews, owe Boston Children’s Hospital our gratitude. And so my acknowledgments start with Dr. Gross. Without his competent hands I would have had a very different life, one unlikely to have included the honor of writing this book.

Break Through is in your hands thanks to:

● The patients and families featured on its pages. For many, retelling their stories meant reliving the most harrowing time of their lives. They are courageous and inspiring and have my deepest admiration and thanks.

● More than a hundred astonishingly generous leaders, faculty and staff of Boston Children’s Hospital. They shared their knowledge of the hospital’s past, their vision for its future and the stories that shake dust off old facts. They are far too numerous to name, although you have read about many of them here. Special mention is due department chiefs, emeritus and current, and my fellow Boston Children’s history devotees: Harry Kozakewich, Fred Lovejoy, Sam Lux, Claire McCarthy and Mark Rockoff.

● Our archivists and librarians. They put Sherlock Holmes to shame. There was no fact too arcane, no photo too obscure for them to track down. Special thanks to hospital archivist Alina Morris, her assistant, Katie Loughrey, and librarians Chloe Rotman and Anna Dorste at Boston Children’s and Jessica Murphy at the Countway Library of Medicine at Harvard Medical School.

● A team of exceptionally talented bookwomen. Mary Ann Guillette is a book design wonder. Her rare combination of visual clarity, playfulness and sophistication brings every page of Break Through to life. Thanks, too, to science writer Nicole Davis, whose prose makes the complexities of neuroscience and immunology seem simple; eagle-eyed copyeditor Kellie M. Hultgren; production assistant Prairie Clayton; and my Boston Children’s colleague Maggie Kolb, for assistance with patient consents and photos.

Break Through literally would not have come to pass without Pediatrician in Chief Gary Fleisher, who, when asked what should be done to commemorate the hospital’s 150th anniversary, said, “We should write a book.” Gary’s idea became reality thanks to Carola Cadley, the doyenne of all things 150th, who championed the
project, and CEO Sandra Fenwick, who enthusiastically embraced it. They were joined by Surgeon in Chief James Kasser and Chief Scientific Officer David Williams in guiding Break Through from its inception through the difficult task of deciding what to include through multiple reviews as the book took form. Their love of the children, admiration for their colleagues and devotion to the hospital shone through in every decision. I am so grateful not only for their guidance but also for the privilege of working with them.

Finally, my husband, Lloyd Prentice, read every word and improved many. For subheads and so much more, there are not enough thanks.

— Laurie Beckelman March 22, 2019

ENDNOTES

1891: The Purest Milk
1 Rotch, TM. (1893). The value of milk laboratories for hospitals. In Medical and Surgical Report of the Children’s Hospital, 1869–1894. Boston Children’s Hospital Archives, Boston, MA.

1900: X Rays
1 Sosman, MC. (1951). Medicine as science: Roentgenology. Medical and Surgical Journal of Medicine, Boston, MA.
4 Ibid, 70.
5 Thirty-Fifth Annual Report of The Children’s Hospital Annual Reports. Boston Children’s Hospital Archives, Boston, MA.

1923: Dehydration
1 Gamble, JL. (Undated manuscript). Our internal environment. Papers of James Lawder Gamble, 1915–1957 (inclusive). Box 2: Countway Medicine Rare Books, Countway Library of Medicine, Boston, MA.

1927: Pediatric Surgery
1 Koop, CE. (2002). Interview by J. Heskel, the Winthrop Group. Oral history. Boston Children’s Hospital Archives, Boston, MA.
2 Ibid.

1932: Rh Disease

1938: Polio

1932: HB Disease
1935: Anesthesia
Boston Children's Hospital Archives, Boston, MA.

1939: Esophageal Atresia


5  Uncredited. (1967). Winning the war against viruses. Oral history. Boston Children's Hospital Archives, Boston, MA.


1944: Epilepsy


1953: Immunodeficiency

1955: Cystic Fibrosis

1971: Cancer


5  Uncredited. (1967). Winning the war against viruses. Oral history. Boston Children's Hospital Archives, Boston, MA.


1976: Airway Disorders


1976: Drug Delivery


1984: Sickle Cell Disease


2. Ibid.


1984: Gene Therapy


1986: Duchenne Muscular Dystrophy


3. Ibid.


1997: Palliative Care


2000: SIDS


2006: Digital Health


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