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What We Don't See

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Sixty-eight years after the inaugural issue of *The New England Journal of Medicine and Surgery*, Sir William Osler introduced the term "pediatrics."[1] Although "diseases peculiar to children" had figured in Benjamin Rush's lectures at the University of Pennsylvania since 1789, most physicians in the early 19th century did not recognize children as a distinct population with particular medical needs. Indeed, in most medical journals of this period, the words "infant," "child," and "children" figured only in case reports of obstetrical complications or in accounts of epidemic-related mortality. Osler's use of the term "pediatrics" not only differentiated physicians "specially connected with pediatrics" from other physicians[1] but also drew attention to the creation of a "special" discipline. After Osler's introduction of the term, articles entitled "Progress in Pediatrics" began to appear sporadically in the *Journal* from 1904 forward, and the specialty of pediatrics was accorded its own section in the *Journal* in 1954.

However, charting the influence of the *Journal* on two centuries of pediatric medicine is perhaps more thoughtfully addressed by means of a computational algorithm[2] to search the *Journal*'s archives for Osler's designation — pediatrics — so as to gain insight into the increasing emphasis on childhood health over the past 200 years (Fig. 1). This approach allows us to demarcate four periods, albeit somewhat arbitrarily defined, that reflect the emergence and discoveries of pediatrics in the pages of the *Journal* — the recognition of children as a particular population benefiting from medical practice (1812 through 1880), the introduction of public health programs to reduce childhood mortality (1881 through 1930), the development of vaccines (1931 through 1980), and the global dissemination of pediatric practice (1981 through 2012) (see timeline, available with the full text of this article at NEJM.org). Each of these periods also coincides with particular advances against infectious disease — the single leading cause of childhood death yesterday and today (Fig. 2)[3] — that were heralded in the pages of the *New England Journal of Medicine*: the concept of social intervention, the battle against summer gastroenteritis, the defeat of smallpox, and the drive to reduce childhood mortality from diarrhea and the human immunodeficiency virus (HIV).

A timeline is available at NEJM.org

Seminal articles in the *Journal* have also advanced the fields of pediatric surgery, oncology, neonatology, and a host of other pediatric disciplines over the past two centuries. Transformative approaches to noninfectious causes of childhood death — congenital heart disease and leukemia — appeared first in the *Journal*.[4,5] Landmark articles describing functional asplenia in sickle cell disease,[6] legal redress for the battered child,[7] the genetic foundations of population-based screening for phenylketonuria and cystic fibrosis,[8,9] molecular and therapeutic advances in surfactant deficiency,[10,11] and the relationship between prone sleeping position and the sudden infant death syndrome[12] have blazed the trail of progress in pediatrics.

But the fact remains that infectious diseases were the predominant cause of childhood death at the time of the *Journal*'s inception and remain so, globally, today (Fig. 2).[3] Therefore, this review emphasizes how articles in the *New England Journal of Medicine* have directed and illuminated the course of progress against the infec-

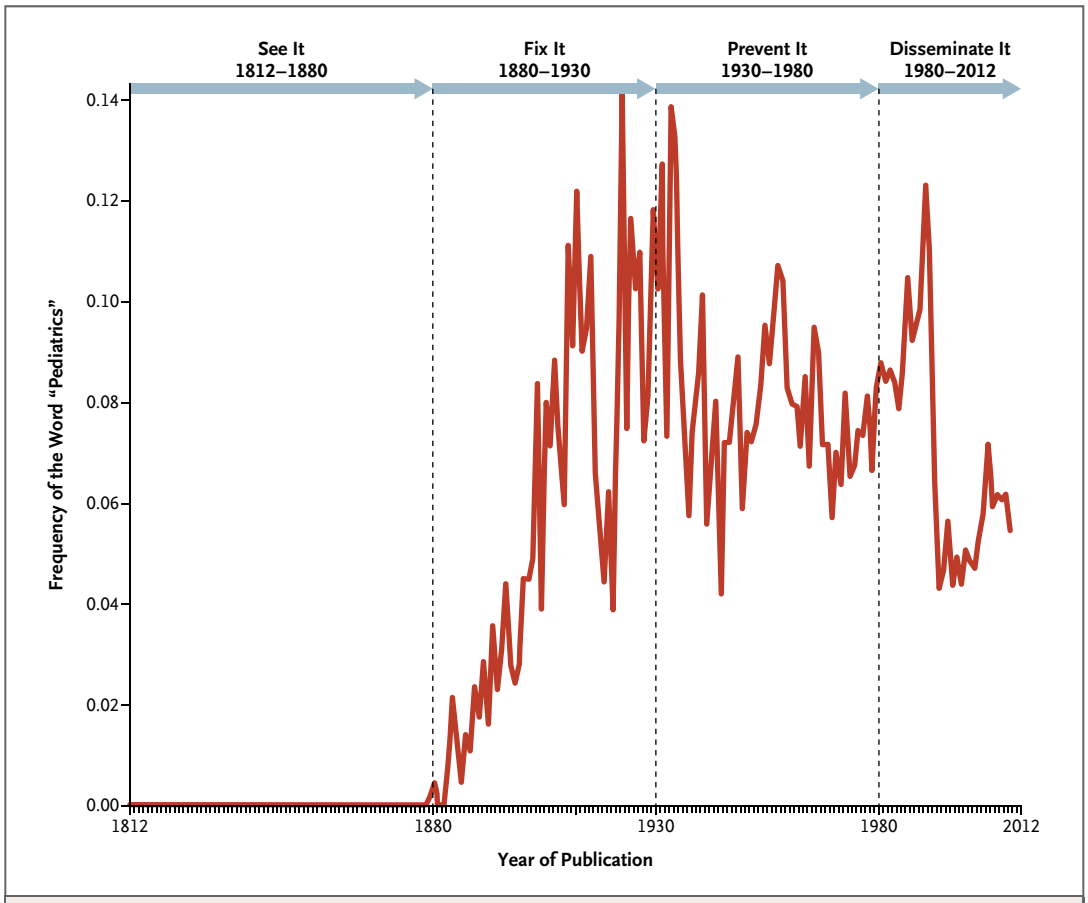

Figure 1. Frequency of the Word "Pediatrics" in the *New England Journal of Medicine*, across the 200 Years of the *Journal*'s History.

In the four periods of pediatrics research reported in the *Journal* from 1812 to 2012, the frequency of the use of the word "pediatrics" grew substantially, starting in the early 20th century.

tious diseases of childhood across these four eras. By reviewing some of the *Journal*'s most celebrated contributions, we can recognize what we don't see today and realize what we must see in the future.

1812 THROUGH 1880 — SEE IT

For centuries, the cumulative weight of experience fostered the conclusion that childhood deaths were inevitable. Many families, even those of plentiful means, lost half or more of their children. Seemingly nothing could be done — medically, politically, or economically — save to let nature take its course. Indeed, the mind of the public had changed little since the 2nd century, when the emperor Marcus Aurelius wrote, "One man prays, 'How I may not lose my little child', but you must pray, 'How I may not be afraid to lose him'" (Meditations 9.40).

One has but to view the tombstones in colonial cemeteries to understand that death in childhood represented a grievous but seemingly inexorable trajectory. The death toll from infection among the very young was often obscured in colonial epidemics, when smallpox, diphtheria, cholera, dysentery, and measles typically killed without respect to age. In November 1713, for example, the wife of the Puritan minister Cotton Mather died in a measles epidemic, along with her newborn twins, a 2-year-old daughter, and a servant. Two sons and four daughters, all older than 7 years of age, survived.[13] Apart from these individual tragedies, however, there was little recognition of the special susceptibility of children, particularly those under 5 years of age, until the diphtheria epidemic

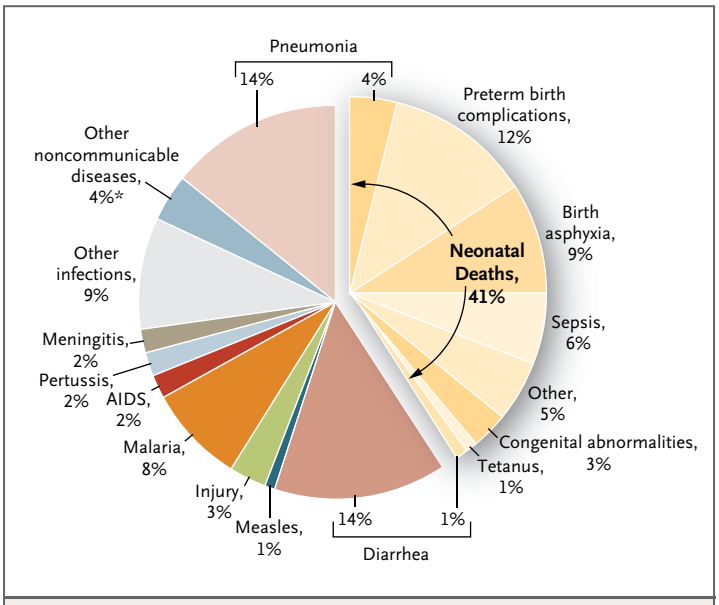

Figure 2. Causes of Childhood Deaths Worldwide in 2008.
The causes of death during the first 27 days of life are shown in yellow shades. The remainder of the graph shows the causes of death in children 1 to 59 months of age. The asterisk denotes that the data include deaths from congenital anomalies, accidents, and injuries.

in New England (1735 through 1740), in which 80% of its 5000 victims — almost 2.5% of the population — were children.[13]

By the middle of the 19th century, a child's death, far from intolerable, was frequently viewed as blessed, a release from the torment of hectic infection or the lingering complications of diseases such as rheumatic fever. A contemporary physician's description of death from croup reflects this view:

> his inarticulate appeals and beseeching looks for relief . . . constitute one of the most touching scenes which we are called upon to witness in the practice of medicine. Happily the extreme suffering usually, though not always, subsides towards the close of life, and death takes place at last with comparative ease[14]

and prefigures, in its resignation, the death of the fictional character Beth in Louisa May Alcott's novel *Little Women*:

> As Beth had hoped, the 'tide went out easily', and in the dark hour before dawn, on the bosom where she had drawn her first breath, she quietly drew her last, with no farewell but one loving look and a little sigh. . . .When morning came . . . the spring sunshine streamed in like a benediction. . . .

But gradually, the attitude of helplessness changed, first to inquiry and then to responsibility. The recognition that social, as well as divine, intervention could influence the life and death of children took hold. Notably, the *Journal*'s annual summaries of childhood deaths in Massachusetts not only tallied the deaths but also began to include prescriptions for change. Reporting on infant mortality in the *Journal* in 1873, J.O. Webster concluded with the "point[s] that strike us most forcibly . . . that sanitary reform, as a means of reducing our infant, as well as general mortality, demands our earnest attention."[15]

1881 THROUGH 1930 — FIX IT

Reforms surged. Photographs such as those by Jacob Riis in *How the Other Half Lives*[16] (Fig. 3) pricked the societal conscience to see children as a group to be protected. The visible symbol of this new recognition was the children's hospital, opening first in Philadelphia (1855) and then in Boston (1869) and Cincinnati (1887). Many of these institutions arose from the efforts of ladies' auxiliaries, which typically provided food, clothing, nursing, and free care for all patients in the early days of each hospital.[17] The Harriet Lane Home, a much larger institution, was endowed in Baltimore in 1903 with a $400,000 gift from its benefactress, and the end of the 19th century marked the establishment of more than two dozen children's hospitals.

An editorial in the *Journal* drew on the charter statement for Children's Hospital Boston to emphasize not only the charitable nature of these enterprises but also their importance for scientific progress and national stature:

> We believe that, apart from the actual medical treatment of sick and injured children, there is a want in our community which has long been felt in our medical schools, though provided for in foreign cities; namely, an opportunity to study infantile disease. . . . For people forget that on the health of the growing up generation hangs that of generations more.[18]

Attendant protections extended to the prohibition of child labor and the guarantee of education. The *Journal* reported on French legislation prohibiting boys less than 13 years of age and girls less than 14 years of age from working more than 6 hours per day[19] and published lectures addressing the necessity and content of compulsory education for girls as well as boys.[20] Child labor laws, first enacted in New England in 1832, gained momentum throughout this era, as did standards of compulsory childhood education that were patterned on those introduced in the Massachusetts Bay Colony in 1647. The *Journal* did not hesitate to give voice to these political initiatives, and their coverage in a leading medical journal underscored their profound medical implications.

But perhaps the most important movement during this period was the emphasis on public health, as exemplified by the fight against cholera infantum, or summer gastroenteritis, the cause of 15 to 22% of childhood deaths across New England and New York.[15] By the middle of the 19th century, breast-feeding rates had declined considerably, especially among the urban working poor, who were forced to avail themselves of unstandardized cow's milk powders that necessitated mixing with milk or water, which frequently came from contaminated sources. Abraham Jacobi, a New York pediatrician, advocated the universal pasteurization of milk, and New York merchant Nathan Straus implemented this principle in his free "milk stations," the first opening in 1893.[13] Providing guidance, the *Journal* promoted scholarly analyses of the ideal composition of milk-based products for infant nutrition, which definitively stated which additives were needed for milk from a Jersey cow (5% fat) as compared with the milk from a Holstein (3% fat).[21]

Nevertheless, as the 20th century dawned, infant deaths due to summer gastroenteritis failed to decline, despite mandatory pasteurization and the best efforts of the milk stations. It remained for S. Josephine Baker, a physician and the first director of the New York City Bureau of Child Hygiene, to demonstrate the profound effect of maternal education on breast-feeding, home hygiene, and infant care. Over a period of just 10 years, between 1907 and 1917, the infant mortality rate in New York decreased from 144.4 to 88.8 deaths per 1000,[22,23] and the continued implementation of practical principles of household hygiene and child protection — what pediatricians today call "anticipatory guidance" — led to a dramatic fall in childhood deaths from diphtheria 10 years before the vaccine was in widespread use (Fig. 4).[24]

Figure 3. Boys Sleeping on Mulberry Street, New York City, 1890.
From *How the Other Half Lives,* by J.A. Riis.[16]

1931 THROUGH 1980 — PREVENT IT

Progress in public health fixed many problems that had been present for decades. Moving to the next stage required a paradigm shift: the belief that some problems could actually be stopped before they occurred. The concept of immunity and the development of vaccine technology expanded dramatically the list of diseases we don't see. Beginning with von Behring's diphtheria vaccine in 1913,[25] the *Journal* reported on trials of vaccines that became the conquerors of common childhood diseases — the field trial of pertussis vaccine in Michigan by Drs. Pearl Kendrick and Grace Eldering from 1934 through 1937,[26] the diphtheria–pertussis–tetanus vaccine trials in the 1940s,[27] and the intramuscular and oral poliomyelitis vaccine trials in the 1950s and 1960s.[28-31]

In the mid-1950s, twice as many children died from measles as from poliomyelitis,[13] and the immunologic principles and clinical efficacy of the attenuated measles virus vaccine in a variety of childhood populations were thoroughly detailed in a series of eight landmark articles, all published in the July 28, 1960, issue of the *Journal*.[32-39] The combined measles, mumps, and rubella vaccine, developed by Maurice Hilleman in 1971, was a boon for pediatrics and obstetrics alike.[40] The principles underlying the development of successful protein-based vaccines, in turn, opened the door to large-scale trials of polysaccharide and conjugate vaccines for *Haemophilus influen-*

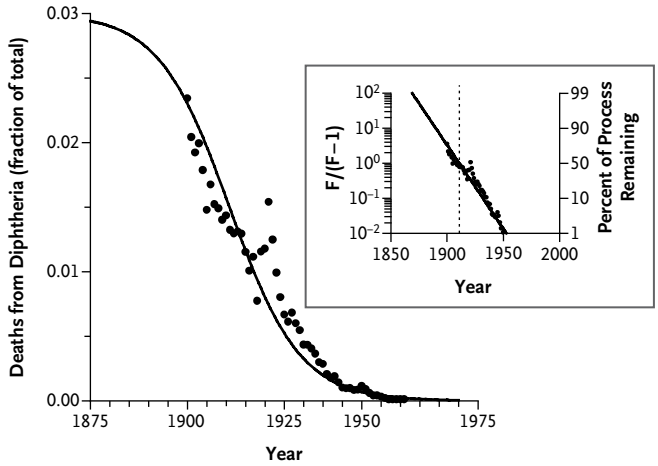

Figure 4. Diphtheria as a Fraction of All Deaths in the United States, 1900–1956.

Diphtheria declined as a cause of death in the United States over the period from 1900 through 1956. The large panel shows the raw data and a logistic curve fitted to the data. The inset shows the same data and a Fisher–Pry transform that renders the S-shaped curve linear and normalizes the process to 1. F denotes the fraction of the process completed. The time it took for the reduction of diphtheria to go from 10% to 90% is 40 years, and 1911 is the midpoint. Data from the U.S. Bureau of the Census.[23] Adapted from Ausubel et al.[24]

zae type b[41,42] and subsequently for *Streptococcus pneumoniae*.

But the incontrovertible capstone of this era was the worldwide eradication of smallpox by means of vaccination campaigns, trumpeted in the *Journal* in 1980.[43] The subject of 13,968 articles in the *Journal* since 1812, the perils of smallpox and the benefits of vaccination had long been recognized. An article from 1814 states, "In the report of the National Vaccine Establishment of Great-Britain, it appears that the prejudices against vaccination have greatly declined, and that in the city of London three-fourths of the children born are submitted to that salutary operation."[44]

Mandatory vaccination, however, incited fervid public debate in both the United Kingdom and the United States, until the publication of Charles Dickens's *Bleak House.* That novel seared into the public consciousness the meaning of the death of a child — the orphaned street sweeper Jo, whose illness, unnamed but readily recognizable as smallpox, arose from the miasma of impoverished London and enveloped both the middle-class heroine and her aristocratic mother:

> Dead! Dead, your Majesty. Dead, my lords and gentlemen. Dead, Right Reverends and Wrong Reverends of every order. Dead, men and women, born with Heavenly compassion in your hearts. And dying thus around us every day.

"And dying thus around us every day." Even the House of Lords listened. Within the year, the British Parliament mandated that every child born in England and Wales after August 1, 1853, be vaccinated for smallpox within 3 months after birth.[45] It took 50 years for the United States to follow suit.

In 1967, when the World Health Organization (WHO) established its smallpox eradication unit, 131,000 cases were reported worldwide, but 10 million to 15 million cases were believed to have occurred, with a 15 to 20% fatality rate.[43] Three years later, correspondence in the *Journal* from leaders of the WHO initiative addressed the requisites for progress, and subsequent improvements in surveillance, communication, and coordination led to the elimination of the disease in 1980 — the first (and only) infectious disease to have been eradicated from the face of the earth. It is not overly optimistic to hope that polio and malaria will vie for second.[46]

1981 THROUGH 2012 — DISSEMINATE IT

As these practices transformed childhood life expectancy throughout industrialized nations, the ease of intercontinental travel and the rise of global economies brought the conditions of developing countries into sharp focus. Thirteen years after the first report of HIV infection, in 1981, Pediatric AIDS Clinical Trials Group Protocol 076 established that the use of zidovudine ante partum and intrapartum in the mother and post partum in the newborn child reduced the mother-to-child transmission of HIV by 67.5%.[47] The ability to prevent vertical transmission of HIV infection spurred the widespread adoption of state legislation requiring the testing of pregnant women, their infants, or both,[48] and the numbers of new cases of vertically transmitted HIV have plummeted in virtually all U.S. cities. In adapting these approaches for global use, highly effective regimens of single-dose antiretroviral agents were eventually developed to meet the needs of economically disadvantaged countries.

Despite commendable progress in controlling mother-to-child transmission of HIV, the leading causes of death in children under 5 years of age worldwide are not HIV infections but pneumonia and diarrheal diseases, each of which killed more than 1 million children in 2008 (Fig. 2).[3] Ironically, the 15% global fatality rate from diarrhea today differs not one whit from its toll in Massachusetts in 1873.[15] The *New England Journal of Medicine* has championed the dissemination of vaccines from industrialized countries by publishing critical analyses of their efficacy in resource-poor countries.[49] Concerted efforts from public and private partnerships may soon ensure that the major killers of children — pneumonia and diarrhea — will enter the archives of diseases we don't see.

As we celebrate the impact of the *Journal* during the past 200 years, we must applaud its expanding influence on the practice of pediatrics — from the children of Massachusetts to those of the United States, and now to the children of the world. As each era of progress amply demonstrates, the best place to begin a healthy life is at the beginning. In the coming century, by publishing premier research on such topics as fetal programming and the fetal–maternal interface or the genetics and treatment of birth defects and chronic illnesses, the *Journal* must continue to heighten the visibility of children to physicians and philanthropists, statesmen and statisticians, educators and economists. As we look back, the diseases we don't see represent a triumph; as we look ahead, what we don't see will require the *Journal* to light the way.

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Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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