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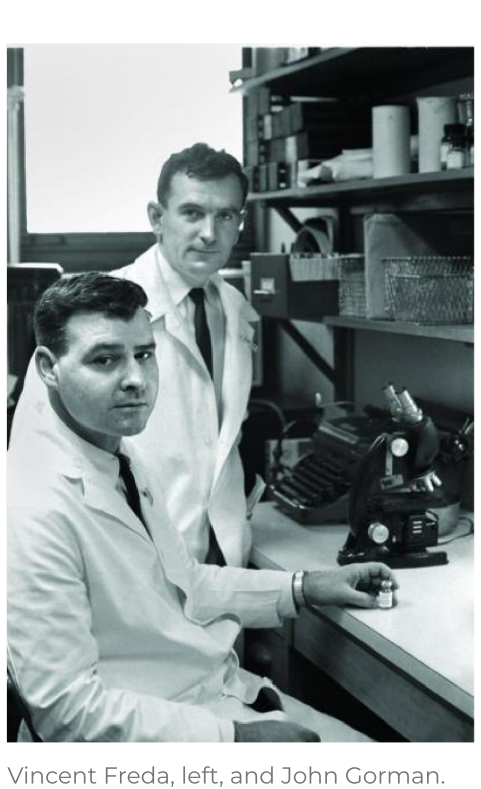
Legacy Unfulfilled

Rh Disease, Mostly Eradicated At Home, Persists Worldwide

By Sharon Tregaskis


Vincent Freda, left, and John Gorman.

Over the past four decades, transfusion medicine specialist Steven Spitalnik, MD, has helped care for hundreds of obstetric patients with Rh incompatibility, an immunological mismatch between maternal and fetal blood types that can lead to blood group sensitization, pregnancy loss, newborn death, or severe disability. Yet at NewYork-Presbyterian/Columbia, where Dr. Spitalnik has been a member of the medical staff since 2003, he sees few cases in which the incompatibility progresses to clinically significant Rh disease.

As in other high-income countries, Rh disease in the United States was largely eliminated before Dr. Spitalnik graduated from college. Credit for the advance owes to groundbreaking work in the 1960s by a Columbia obstetrician, Vincent Freda, MD, and a pathologist, John Gorman, MD, director of the blood bank at NYP/Columbia, working with William Pollack, PhD, chief research scientist at Ortho Pharmaceuticals. Together, they developed Rho-GAM, a plasma derived product that prevents Rh disease. The FDA approved RhoGAM in 1968; its brisk and near-total uptake in the United States has since spared approximately 10,000 babies each year from profound disability and death.

A Global Burden

Today, the Italian pharmaceutical company Kedrion owns rights to RhoGAM, now one of several Rh disease prevention formulations collectively known as "anti-D immunoglobulin." In anticipation of RhoGAM's 50th anniversary in 2018, pharma executives approached Dr. Spitalnik, who was then medical director of the clinical laboratories at Columbia and NYP, to host a celebration. The panel discussion that resulted included Dr. Gorman and experts from across the United States and around the world.

"What I learned, to my dismay and embarrassment," says Dr. Spitalnik, "was that this problem may have been solved in the U.S. and Western Europe, but in many countries there is no access to anti-D. There are economic issues, education issues, and awareness issues among health care providers, government ministers and other policymakers, and patients. It's disappointing that 50 years after this problem was solved in the U.S. there are many places in the world where it's not solved."

At Dr. Spitalnik's request, Kedrion supported Columbia in hosting an international academic conference on Rh disease in late 2018 to address this global health problem. Scholars from Canada, Italy, the Netherlands, Russia, Great Britain, and the United States briefed one another on the global variety of clinical protocols for detecting Rh-incompatible pregnancies and the array of dosing schedules for administering anti-D. "We said we should put together an organization," says Dr. Spitalnik, "and see what we can do to make sure women around the world have access to this life-saving drug."

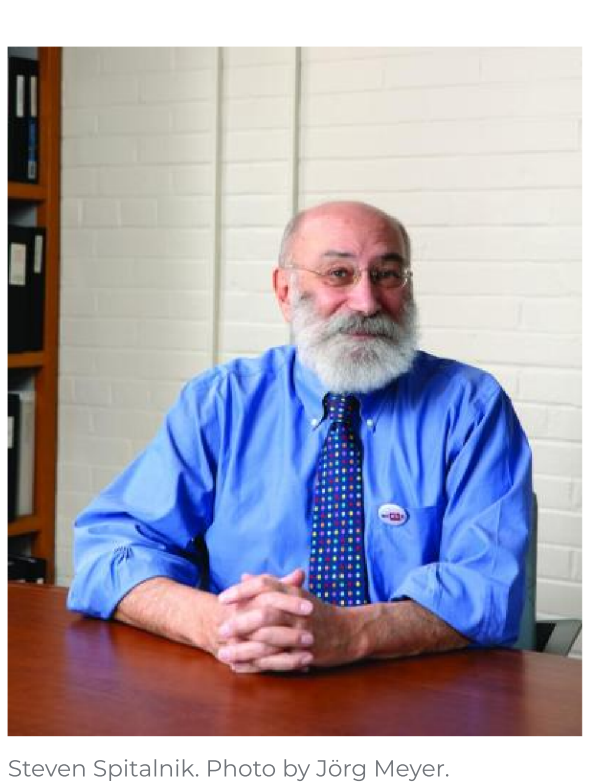
Dr. Spitalnik, professor of pathology & cell biology and former executive vice chair for laboratory medicine for the Department of Pathology & Cell Biology, now serves as founding executive director of the resulting 501c3 nonprofit: WIRhE, the Worldwide Initiative for Rh disease Eradication. "The first thing we did was identify the scope of the problem," says Dr. Spitalnik. In 2020, PLOS ONE published the group's preliminary analysis. The most rigorous public health protocols were effectively eliminating 99% of Rh disease burden in countries like the Netherlands and Denmark, they found. By estimating the annual number of Rh-incompatible pregnancies worldwide and comparing that figure with the total number of doses of anti-D administered annually, the group found a significant opportunity for intervention.

> "We don't need to do the science to show that anti-D immunoglobulin works. We need to figure out how to implement that treatment everywhere."

"Our results suggest that approximately 50% of the women around the world who require this type of immunoprophylaxis do not receive it, presumably due to a lack of awareness, availability, and/or affordability, thereby putting hundreds of thousands of fetuses and neonates at risk for Rh disease each year," the authors wrote. "The global failure to provide this generally acknowledged standard of care to prevent Rh disease, even 50 years after its availability, contributes to an enormous, continuing burden of fetal and neo-natal disease and provides a critically important challenge to the international health care system."

An epidemiological analysis published by the journal Pediatrics in 2013 calculated the annual human costs of preventable Rh disease worldwide at 160,000 fetal and neonatal deaths and 100,000 cases of lifelong disabilities such as cerebral palsy and hearing loss. In many parts of the world, the inability of affected women to carry pregnancies to term carries a deep shame and stigma, compounding the grief of pregnancy loss with divorce and economic disenfranchisement. "Anything that I can do to improve health care for women, particularly pregnant women, is personally important to me," says WIRhE deputy director Brie Stotler, MD, chief of transfusion medicine and cellular therapy in the Department of Pathology & Cell Biology and associate professor of pathology & cell biology. "The world has never realized or has forgotten how vulnerable people are when they're pregnant."

The Rh Factor


Steven Spitalnik. Photo by Jörg Meyer.

Contemporary transfusion medicine recognizes over 300 antigens whose mismatch has the potential to trigger a hemolytic transfusion reaction, in which a recipient's immune system destroys donated blood products. In the early days of transfusion medicine, however, clinicians focused primarily on blood group chemistry—the ABO prefix of modern blood typing introduced in 1900.

Scientists discovered the Rh factor in 1940 in the aftermath of an obstetric blood transfusion gone wrong. The woman's case revealed that a novel antigen on the surface of the red blood cells donated by her husband, who was ABO-compatible, was implicated in her hemolytic transfusion reaction. The same factor, dubbed Rh antigen D, was implicated in the death of her stillborn infant.

The burgeoning fields of transfusion medicine and blood banking promptly implemented strict blood typing and matching standards to segregate Rh positive and Rh-negative blood, the plus and minus suffix now commonly associated with each blood type. Yet Rh-incompatible pregnancies remained at risk.

Approximately 15% of the population in the United States, Canada, and western Europe are Rh-negative. If these women become pregnant with an RhD positive fetus, they can be exposed to small amounts of the RhD protein when fetal blood crosses the placenta during pregnancy and at delivery.

On first exposure to RhD-positive blood—whether through ectopic pregnancy, miscarriage, abortion, delivery, prenatal testing, antenatal fetal-maternal hemorrhage, trauma, or contaminated needles—an adult's immune system can muster a form of anti-RhD antibodies known as immunoglobulin M (IgM). Although these IgM antibodies can obliterate, for example, the fetal red blood cells circulating in the adult's bloodstream, they can't cross the placenta. Thus, whether the mother becomes immunized during or after her first Rh-incompatible pregnancy, her first-born Rh-incompatible infant is typically spared the symptoms of Rh disease.

Once primed by that initial exposure, however, the adult's immune system makes immunoglobulin G (IgG). This immune response lasts virtually forever, remaining on high alert for RhD, ready to muster these IgG antibodies to attack the proteins; these adults are now fully "sensitized" to RhD.

The viability of future pregnancies hangs in the balance. Thus, when a sensitized woman becomes pregnant with another Rh-positive fetus, the IgG antibodies can cross the placenta to attack the fetus's red blood cells inside the womb. Depending on the timing and intensity of the parent's immune reaction, outcomes can range from a temporary case of jaundice in the newborn to fetal complications so severe that the pregnancy ends within the first few months.

An Ounce of Prevention

In a series of experiments published from 1964 to 1967 by Science, JAMA, and the New England Journal of Medicine, Drs. Freda, Gorman, and Pollack showed that they could prevent Rh disease by interrupting the process of immune sensitization. Dr. Gorman has credited a textbook he encountered in 1959, as a resident in clinical pathology at Columbia, with sparking the team's approach. "The presence of circulating antibody, whether produced actively or received passively, depresses and may completely inhibit the immune response to the relevant antigen," he read in Lord Howard Florey's "General Pathology."

Dr. Gorman had seen the devastation and death caused by Rh disease while working in pediatrics at a hospital in the South Bronx before starting a pathology residency at Columbia. "Well, I knew in five minutes after I read that, that this would stop the Rh antibody," Dr. Gorman told a news outlet in his native Australia in 2022. "If we gave the mothers Rh antibody, they would not make any themselves."

Yet Rh antibody was precisely what was killing fetuses and newborns with Rh disease. "There was immediate pushback and skepticism from pretty much the entire blood banking community at the time," Dr. Gorman recalled in 2018 during the RhoGAM celebration at Columbia. Yet Dr. Freda had the full backing of Columbia's obstetrics department, Dr. Pollack found significant financial support from Ortho, and the team continued its investigation.

The trio of scientists went on to isolate anti-D immunoglobulin from the blood plasma of sensitized donors and showed that it could successfully prevent RhD sensitization—first in Rh-negative male volunteers, then in Rh-negative female volunteers, and finally in Rh-negative women who had just given birth to an Rh-positive baby. In each case, passive immunity induced by the anti-D injection prevented Rh sensitization.

Near-simultaneous publications by teams in England and Canada confirmed the approach. Introduction of this approach into clinical use was brisk in countries where blood banking, prenatal blood typing, and hospital births were most advanced. To address the small number of cases in which sensitization happens before delivery, the U.S. standard of care since the late 1970s has included prenatal anti-D immunoglobulin injections for all Rh-negative obstetric patients, as well as a postnatal injection if cord blood testing indicates that the newborn is, indeed, Rh-positive. In 1980, Dr. Freda, Dr. Gorman, and Dr. Pollack—along with two English investigators—were collectively awarded the Albert Lasker Clinical Medical Research Award for their efforts to illuminate the genetics of the Rh factor and for directing essential research into hemolytic disease of the newborn.

A Wicked Problem

Worldwide access to Rh prophylaxis constitutes what engineers know as a "wicked problem." A term coined in the 1970s, the problem represents the apex of social and technical complexity—solving climate change, for example, or eliminating world hunger. Each stakeholder understands the issue and what might constitute its successful resolution differently. Such problems lack a definitive formulation, occupy an open-ended timeline, and resist simplistic cause-and-effect analyses.


Brie Stotler. Photo by Jörg Meyer.

WIRhE team members, in other words, have their work cut out for them. The good news, says Dr. Spitalnik, is that the groundwork has been laid. "We don't need to do the science to show that anti-D immunoglobulin works," he says. "We need to figure out how to implement that treatment everywhere."

As a frame of reference, consider the overlapping protections against RhD sensitization in the United States, says Dr. Stotler. Here, most people don't know their Rh status, and they don't need to. "Our system is set up on autopilot to prevent Rh disease. If you become pregnant, you have blood work during your first prenatal appointment. Your providers know at six or eight weeks whether you're Rh positive or negative and give you the treatment if you need it. The patient doesn't need to ask for it."

Transfusion medicine worldwide is relatively streamlined due to centralized requirements for manufacturing, testing, storing, and distributing blood products. In contrast, pregnancy and childbirth vary wildly. Ideally, an RhD-negative person carrying an RhD-positive fetus would receive both antenatal and postnatal anti-D. "That requires a person going to medical care when they're pregnant," says Dr. Stotler. "In some places, women are not even going to a hospital to deliver. They might not have access to a hospital. To give this drug two to three times, you have to have the infrastructure for the pregnant woman to present for that care."

Worldwide, additional barriers exist, depending on the state of local health care access, practice, documentation, and reimbursement. In some low-income countries, for example, blood typing and detailed medical records are fairly uncommon. Awareness among patients of their need for anti-D injections is low and they may pay as much as two months' wages to private pharmacies for a single dose. Furthermore, the incidence of Rh-negative status varies widely, so interest among public health advocates and government officials also varies. In Madagascar, just 1% of the population is Rh-negative, while in Ethiopia, the prevalence is 15%. In northern Africa and the Middle East, prevalence ranges from 6% to 13%. In China, while only 0.5% of adults are Rh-negative, disease burden remains high due to the country's huge population and shifting emphasis from a one-child policy to encouragement for larger families. Families there do not have access to anti-D, however, because of import restrictions on blood products and a lack of local production in-country.

A Leveraged Approach

WIRhE is an all-volunteer consortium with a shoestring budget; consortium members pursue external funding for their Rh-related work, whether research or implementation. Dr. Spitalnik and Dr. Stotler each put in a few hours each week. "Mostly," says Dr. Spitalnik, "we support one another with enthusiasm, editing, and reviewing funding proposals for research and implementation projects." Still, WIRhE remains a potent force, in large part due to the global network members are cultivating.

For example, Dr. Spitalnik serves on the African Initiative for Rh Eradication (AFRICARhE), a partnership among hospitals in Ethiopia, Malawi, and Tanzania with scientists in the Netherlands. The team is testing a shelf-stable, point-of-care blood test to assess Rh-negative prevalence. The team also is documenting Rh disease burden, implementing screening and prophylaxis protocols, and planning to evaluate a monoclonal anti-D preparation formulated in India that is not approved in the United States or Europe but is widely used in Africa and India.

In 2023, the journal Transfusion published an abstract describing a public health analysis of the state of care in Mexico by Dr. Spitalnik, Dr. Stotler, and WIRhE collaborators. While the 11-question survey the collaborators sent to every obstetrician in the country revealed significant variations regarding testing for Rh-incompatibility, as well as availability and delivery of anti-D immunoglobulin, the investigators saw cause for hope. "We think Mexico may be a particularly good place where we can make a difference," says Dr. Spitalnik, who is pursuing funding for an implementation study that analyzes patient acceptance and physician practice across regions of Mexico that differ economically, ethnically, and in terms of religiosity. "Every OB in Mexico reports through a series of administrative bodies to a director for the whole country, and he was one of our coauthors on the survey."

> "RhoGAM has turned out to be by far the most cost-effective drug ever produced."

In Pakistan, WIRhE collaborators have multiple efforts underway, including peer-to-peer patient education and outreach, training programs for public health workers and traditional birth attendants, and an implementation study showing the efficacy of the same shelf-stable point-of-care blood test being evaluated in the AFRICARhE study.

And Dr. Gorman is doing his part while in his 90s and living in retirement in California. He prefers to leave history in the rear-view mirror. "I don't want to talk about the '60s. I just want to talk about the future." The future, from his vantage point, is the imperative for WIRhE to raise approximately $250 million annually for testing and for providing anti-D injections to prevent maternal RhD sensitization worldwide.

As the holder of multiple global patents for intellectual property relevant to novel techniques for total lab automation in the fast-growing $230 billion clinical laboratory industry, Dr. Gorman sees promise in a business plan he's developed dubbed "Prometheus" to commercialize his intellectual property and apply the royalties to WIRhE's international work. He believes that these patents can be the nucleus of a unique financial opportunity—that the patents will enable a very select partnership of five Fortune 500 companies, acting in their own commercial interests, to generate future royalties with more than enough present discounted cash flow value to fund WIRhE completely and immediately.

In the meantime, Dr. Gorman has no doubts about the value of anti-D immunoglobulin for global health. "RhoGAM has turned out to be by far the most cost-effective drug ever produced," says Dr. Gorman. "That's because more than 75 quality-adjusted life years are gained for each of the hundreds of thousands of babies that have been saved since 1968. I still marvel at how such a low-tech idea could have such a huge, huge, huge payoff."