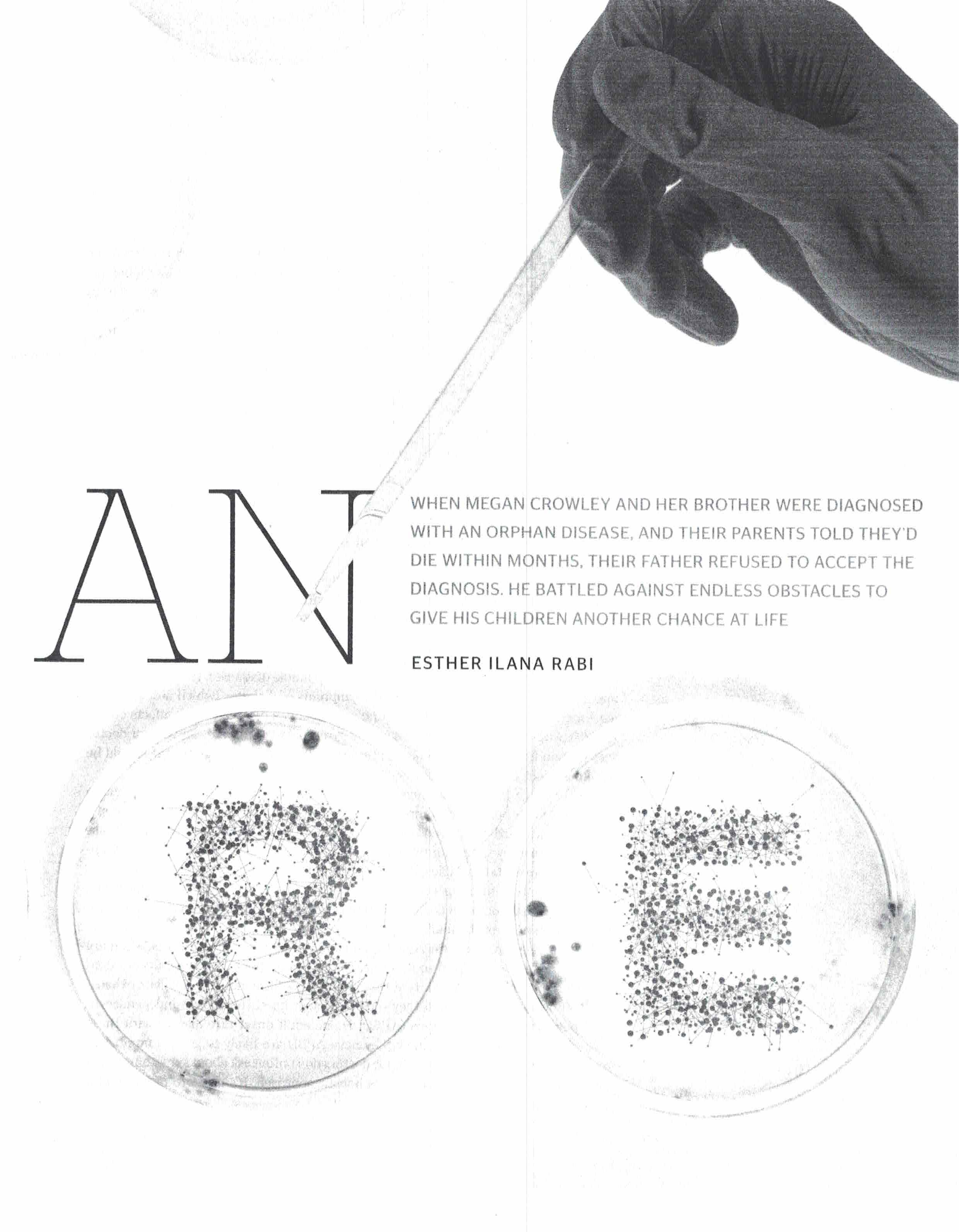
IN SEARCH OF AN ORPH



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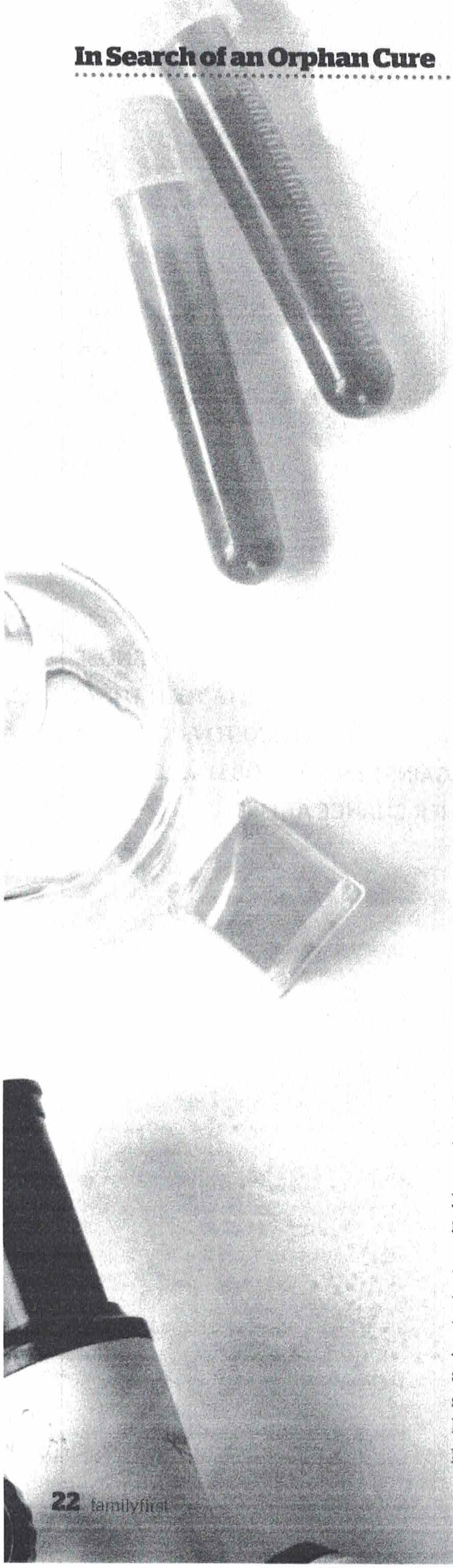
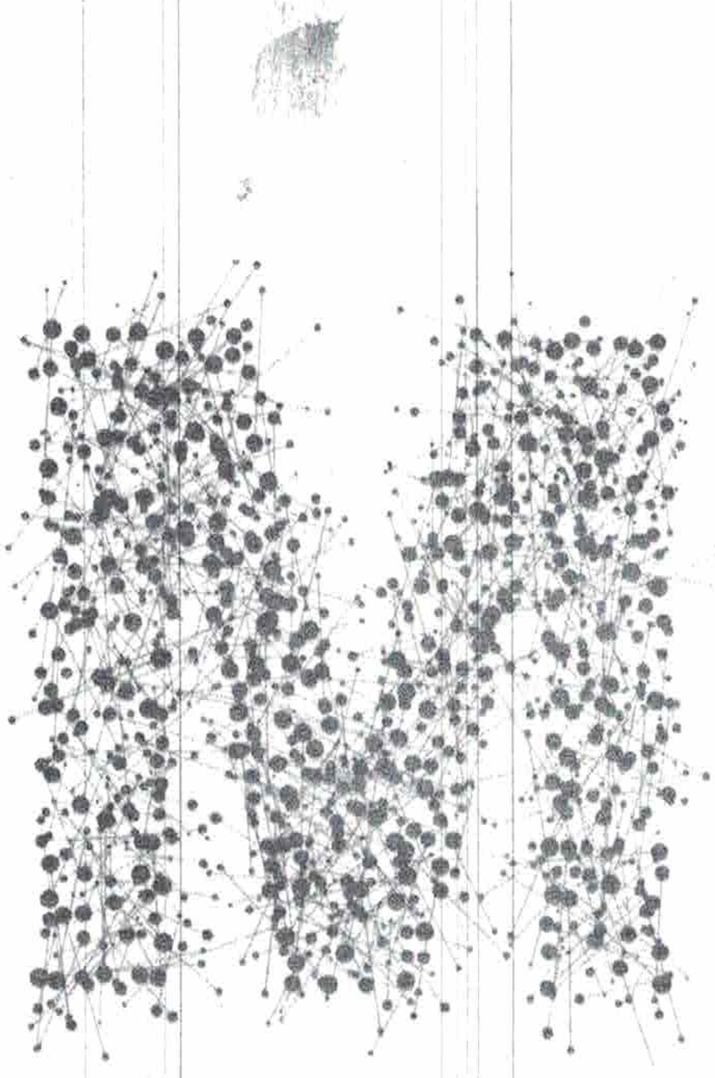
WHEN MEGAN CROWLEY AND HER BROTHER WERE DIAGNOSED WITH AN ORPHAN DISEASE, AND THEIR PARENTS TOLD THEY'D DIE WITHIN MONTHS, THEIR FATHER REFUSED TO ACCEPT THE DIAGNOSIS. HE BATTLED AGAINST ENDLESS OBSTACLES TO GIVE HIS CHILDREN ANOTHER CHANCE AT LIFE

ESTHER ILANA RABI





Megan Crowley seemed healthy when she was born, except for some trouble she had swallowing. But when she was 15 months old and still not pulling herself up to stand, her mother, Aileen, took her to a neurologist. "Your daughter has Pompe disease," the doctor told her. His prognosis was dismal: "There's no cure and no treatment. She only has a few months to live."

Pompe (pronounced **pom**-pay) disease is an extremely rare genetic disorder that weakens the muscles, enlarges the heart, and causes difficulties in breathing. The Crowleys hadn't yet digested the news when tests came back showing that their son Patrick, a year younger than Megan, also had Pompe.

Despite the grim prognosis, the fact that the doctor even knew about Pompe and correctly diagnosed both Megan and Patrick with this "orphan" disease — a name for a disease that's found in fewer than one in 1,500 people — was nothing short of a miracle.

First-year medical students have a mantra: When you hear hoofbeats, think horses, not zebras. In other words, when there are two possible diagnoses, the more common one is usually correct. For example, the symptoms of diabetes (which afflicts one in *ten* Americans) are similar to the symptoms of Fabry's disease (which affects one in *117,000* people), although the cause of the symptoms is different. So when a doctor sees protein in the urine, high blood pressure, and frequent urination, she should be thinking about diabetes, not Fabry.

The challenge is that sometimes a patient *does* have a "zebra" disease. Only one in 40,000 babies is born with Pompe. It's so unusual that few doctors have ever seen a case, or even heard of it. Even doctors who are knowledgeable about a rare disease may be hobbled by the small number of cases they can study to learn about symptoms, environmental variables, biomarkers, and patient perspectives.

Because "zebra" diseases are routinely ruled out, patients can sometimes waste years going from doctor to doctor, treating one symptom after another, without ever getting to the root of them all.

This is a bigger problem for adults than children. Diseases that affect children are usually more aggressive, and so it's easier to hone in on the problem; adults are used to having a number of complaints at the same time — for instance, back pain, exhaustion, and bladder issues — and they seek treatment for each problem independently. Adult polyglucosan body disease (APBD) is one adult-onset rare disease with these symptoms. Adults who don't know they have APBD are likely to go to a number of specialists to deal with their symptoms; doctors don't often ask about symptoms unrelated to their specialty, and don't take a holistic approach. It's unheard of for all of a patient's doctors to convene for a consultation.

"It takes seven to eight years for an adult to find the right diagnosis, and all that time, the disease is doing damage that might have been halted, or at least slowed, if we'd known what was wrong"

"The symptoms of my disease are common, even though the disease is not," says Zalman Goldstein, a well-informed APBD patient. "That's why it's easy to misdiagnose. The dragging feet might be caused by ALS. The numbness and fatigue might have been caused by multiple sclerosis. Frequent urination is a common annoyance for men my age.

"Dr. M., a neurologist who is dealing with my disease, has an office on the same floor as the clinic I visited before my diagnosis. His students and colleagues must have seen me hobbling around, but there are hundreds of reasons a person might stumble like me. Even if they'd been walking down the hall discussing APBD with Dr. M. while I passed, they'd have had no reason to think they might be the ones who could help me."

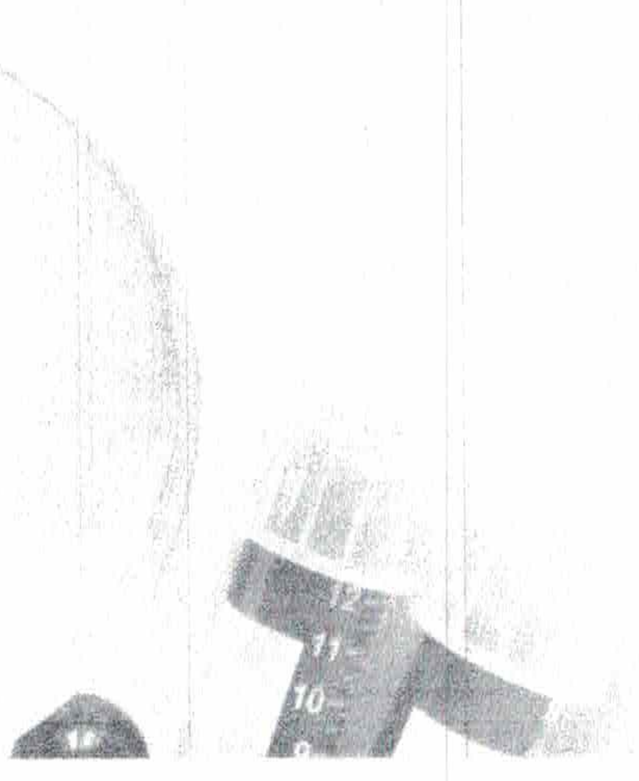
When Zalman joined an APBD support group, he discovered he wasn't the only one who'd spent years searching for a correct diagnosis. "Almost everyone in my support group wasted years on worthless evaluations and useless, misguided treatments because we were misdiagnosed. We're talking major interventions, like prostate removal, and back surgeries that left people worse off than they'd been. On average, it takes seven to eight years for an adult to find the right diagnosis, and all that time, the disease is doing damage that might have been halted, or at least slowed, if we'd known what was wrong."

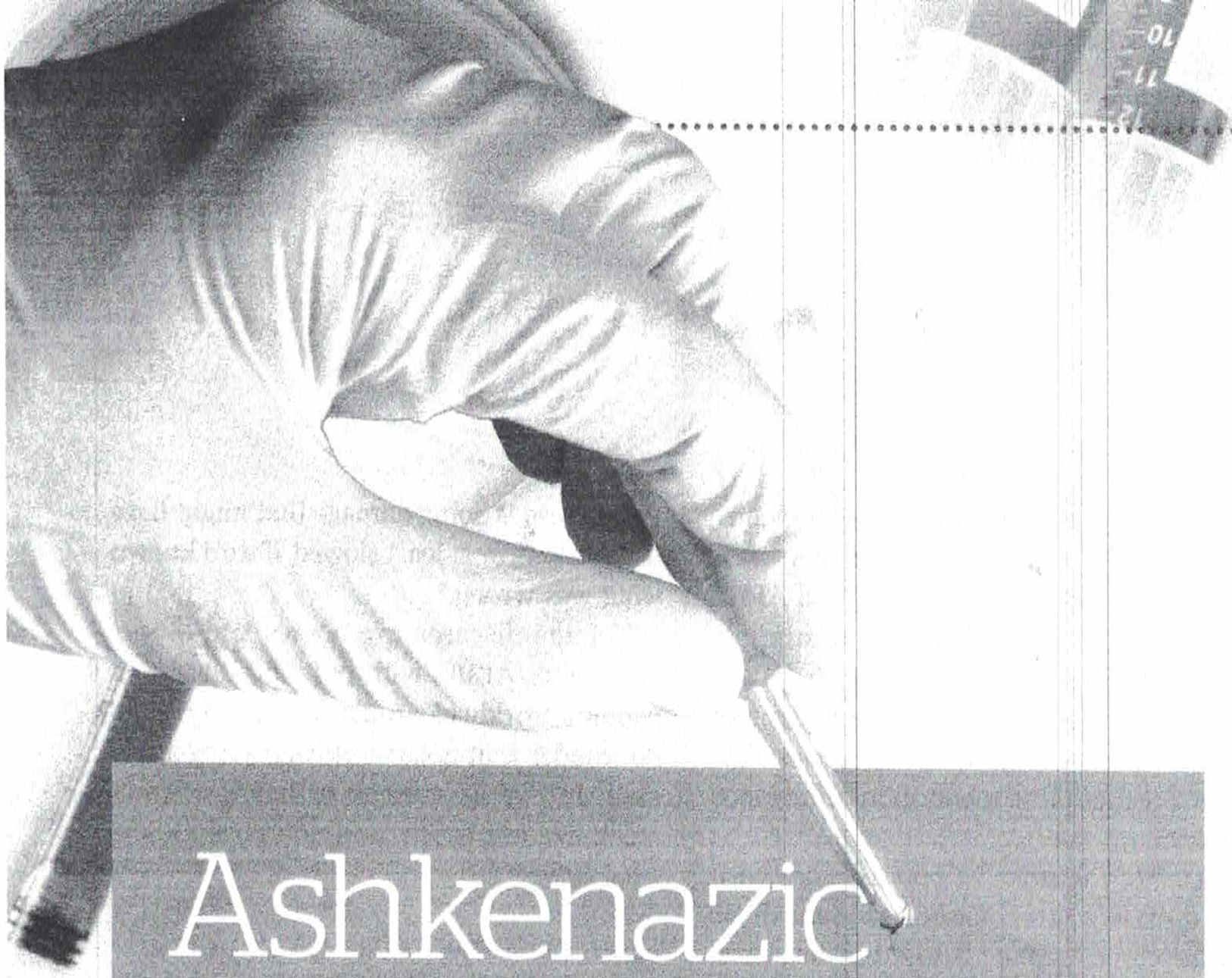
If some diseases are horses and others are zebras, APBD, with only 160 diagnosed patients worldwide, must be a unicorn. It's no wonder that doctors encountering a disease they've never seen or heard of can't recognize a unicorn, and don't even know what to test for.

EXTRAORDINARY MEASURES

Countless doctors' visits and medical interventions leave most "zebra" and "unicorn" patients and their families too overwhelmed to do anything but cope with day-to-day problems. But some heroic families do what they can to help the researchers. They register patients, encourage scientists to take an interest, and raise funds for research, sometimes raising more money than the National Institutes of Health gives for a year.

John Francis Crowley must be the poster-boy of involved parents. When his children, Megan and Patrick, were diagnosed with Pompe in 1998, he quit his job as a financial consultant and teamed up with a scientist to find a cure for his children – both of whom had defied expectations and were still alive, though very weak. Borrowing $100,000 against his house and his 401(k),





Ashkenazic Genetic Pitfalls

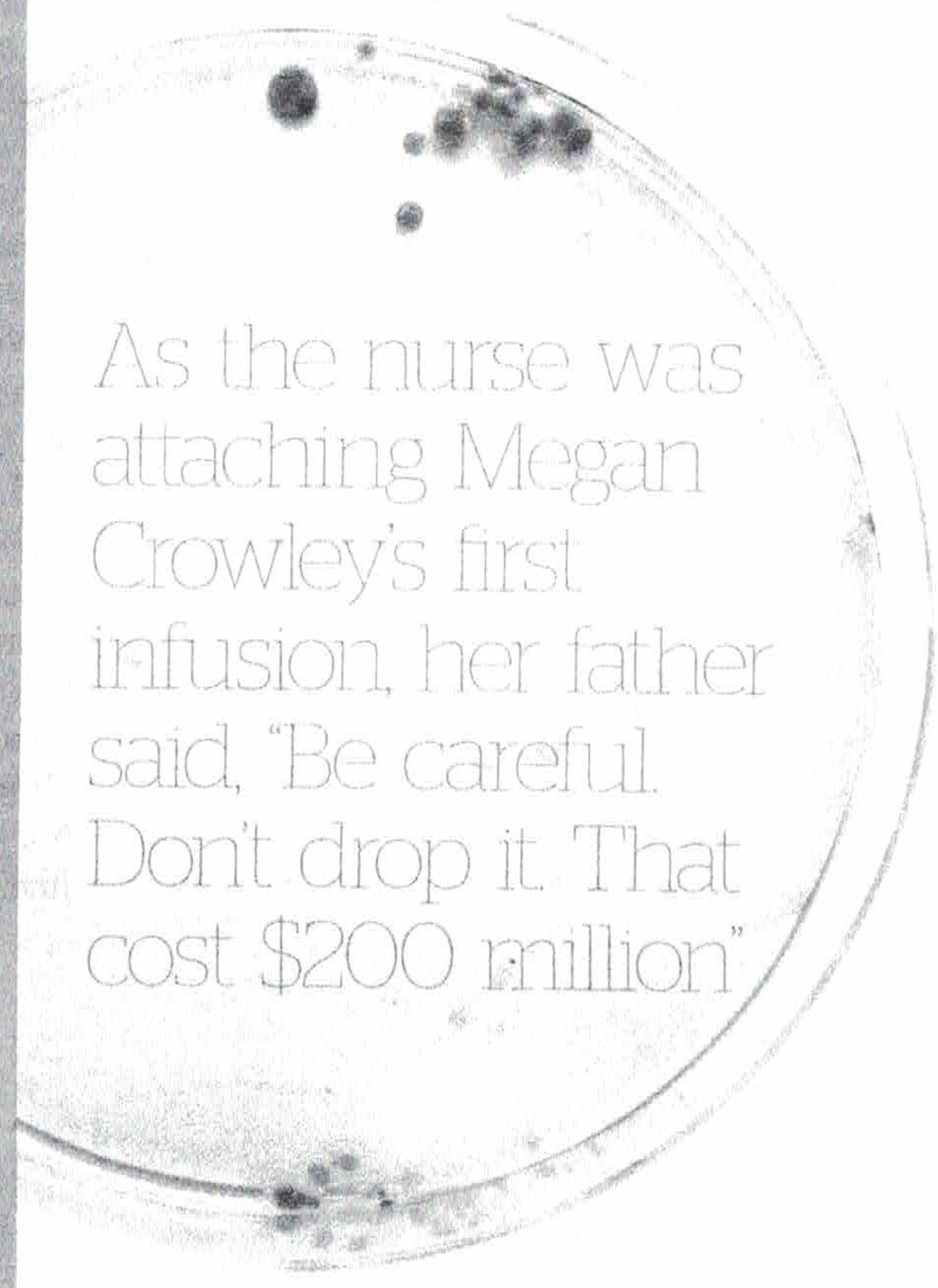
When Rashi lived, there were fewer than 25,000 Jews in Europe, a relatively small gene pool that was kept small by frequent pogroms. As their numbers grew, genetic faults spread among their children, but stayed within the tight-knit community, whose children would only marry other Ashkenazim. The rate of non-Jewish blood, free of the genetic faults that slipped into the Ashkenazic gene pool, was about 0.5 percent per generation for a thousand years. The blocks of genes that identify someone as an Ashkenazic Jew are as distinctive as a signature.

For the majority of Ashkenazim who dodge the genetic-faults bullet, this has advantages. The average Ashkenazic Jewish IQ is between 107 and 117, while the world average is 100. The book *Abraham's Children: Race, Identity and the DNA of the Chosen People* suggests that "single variations of the neurological diseases that typify Ashkenazim may juice the brain, while two may cause crippling health problems."

Or is the assumption that Ashkenazic Jews are more prone to genetic disorders inaccurate? Dr. Daphna Birenbaum-Carmeli at the University of Haifa is convinced that Jews are over-represented in genetic literature. She claims that Ashkenazim have been studied more than other populations because:

- Many geneticists are Ashkenazic.
- Ashkenazim are ideal research candidates because of their tendency to marry each other, and yet there are a lot of them (an estimated 11 million), unlike other ethnic groups that mostly marry within the group, like Icelanders (an estimated 300,000) and Amish (an estimated 250,000).
- Jews tend to live near good medical centers.
- Almost all Orthodox undergo Dor Yesharim testing, the results of which are shared, anonymously, with researchers.

The number of those afflicted with Ashkenazic diseases is set to fall, as Ashkenazic-Sephardic marriages become more common, and more non-Jewish blood is brought into "the tribe" by *geirim* and *baalei teshuvah* who have a non-Jewish father.



As the nurse was attaching Megan Crowley's first infusion, her father said, "Be careful. Don't drop it. That cost $200 million"

Crowley and his partner eventually started a biotech company.

In less than a year, they were so close to their goal that Genzyme Corporation bought them out for $135 million. The buyout was a lifesaver, because they needed the backing of a big firm to get through the labyrinth of the Food and Drug Administration's clinical trials regime.

Crowley became Genzyme's senior vice president in charge of Pompe research, but that didn't mean his own kids received the first treatments. The first obstacle was the amount of medicine needed to start treatment. Genzyme hadn't produced much of it yet; it had to be grown in live cells from the ovaries of Chinese hamsters. They'd invested tens of millions to build bioreactors that could make it in large doses, but they wouldn't be functional for at least another year. So they started the first trials on infants, who need smaller doses. Megan and Patrick, then five and four, would need more medicine than Genzyme could manufacture. "That was heartrending," Crowley remembers.

Another reason his kids couldn't be treated was government interference; all drug trials must be approved by the FDA. When the disease shows up in newborns, the approval process is streamlined, because they have only eight months to live before the build-up of glycogen weakens their muscles so much that their hearts and respiratory systems fail. Megan and Patrick had the late-onset form of the disease, which has a better prognosis, although their muscles were becoming weaker all the time.

Crowley considered snatching some vials of medicine from the storeroom. "I thought about it all the time," he says, "but it has to be given intravenously twice a week. The kids' veins were so fragile, they'd need surgery to implant a port, which would mean hospitalization, and hospitals can't administer experimental drugs without government approval."

He arranged treatment for a child in Spain, where regulations are laxer, in the hopes that success there would speed approval in the US. He remembers thinking, "With two phone calls, I saved a kid in Madrid who I've never met, but I can't save my own kids." He wanted to take Megan and Patrick to Europe for treatment, but the disease had eaten away at their muscles while the drug was being developed. Patrick had lost so much strength that he could no longer hold his head up. They were both too weak to travel.

"It was a constant struggle to keep the children alive," their mother, Aileen Crowley remembers. "Nurses and therapists were coming and going all day, every day." Both children were put on respirators and feeding tubes.

"I felt like a huge snowball was rolling down the hill and I wanted to get in front of it and stop it," Crowley says. His solution? Design a trial to solve the mystery of why different patients responded differently to the disease. The ideal test patients for this trial would be Megan and Patrick. They were siblings, with identical genetic mutations, but Patrick was much more severely affected.

It didn't pan out, though. "Even though the FDA was comfortable with Megan and Patrick being part of the trial," says Crowley, "the hospital's internal review board rejected them. They claimed it was a conflict of interest for me to be an executive of the company and have my children treated."

So Crowley resigned from Genzyme. Two weeks later, the Crowley children were ready for their first infusion, and they've been receiving them twice weekly since then. "The treatment has stabilized them," Crowley reported then, "and they're able to go to school, although it takes two hours to get them ready for the four hours they can spend there."

While the Crowley kids are still dependent on ventilators, feeding tubes, and wheelchairs, the infusions have improved their breathing, helped them regain some mobility, and increased their life expectancy.

THE PRICE OF A CURE

Recent breakthroughs in gene sequencing are spearheading major advances in the treatments of rare orphan diseases. But they're expensive. As the nurse was attaching Megan Crowley's first infusion, her father said, "Be careful. Don't drop it. That cost $200 million." There's no limit to what a sick person, or her parents, would pay for health.

This is good news for Jews. Nineteen rare diseases are common in Ashkenazim — one in four Ashkenazim is a carrier of at least one of them — and five rare diseases are associated with Sephardim.

Why are insurance companies (and all of us who underwrite them by paying for

Test My Saliva, Please

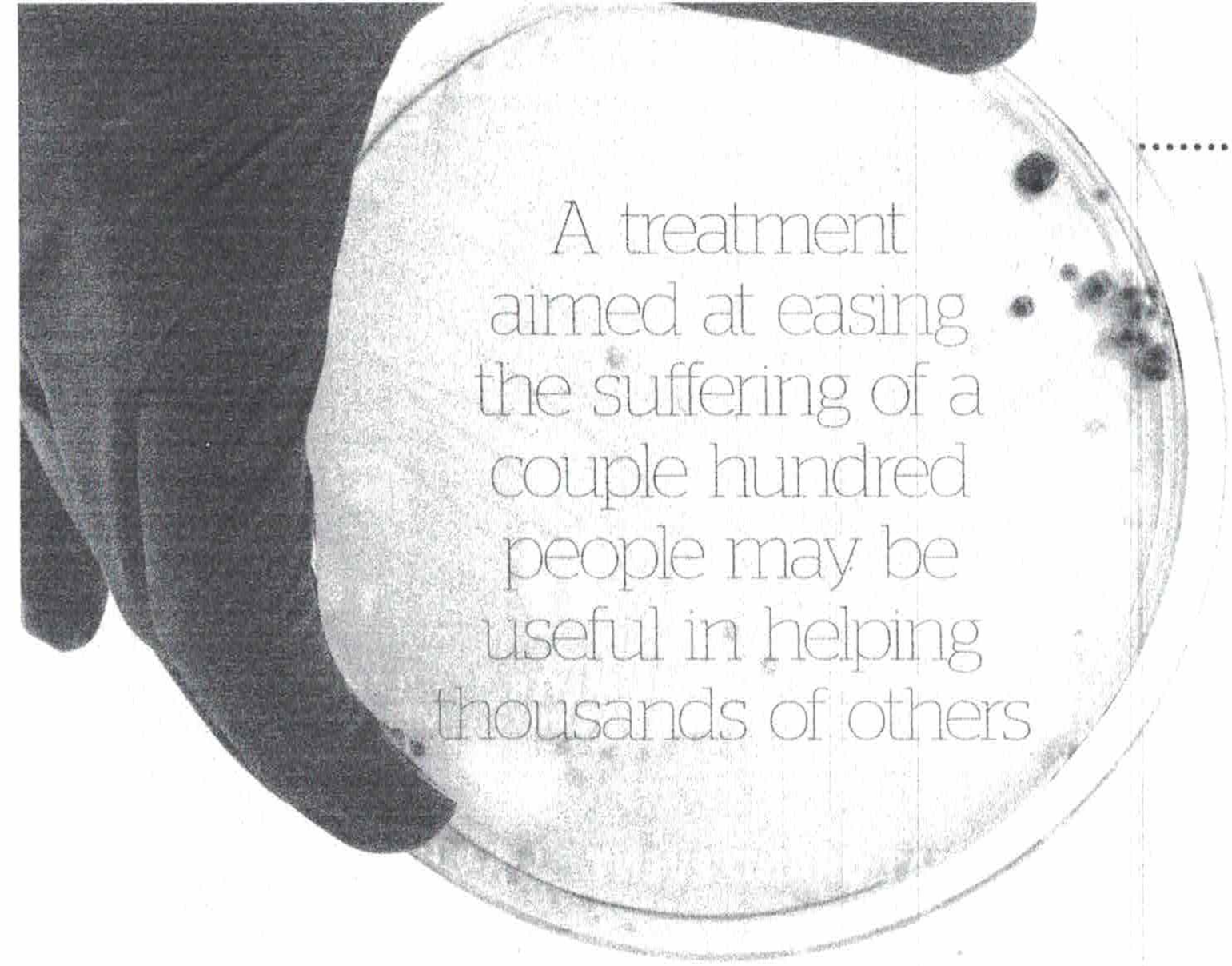
The research foundation for adult polyglucosan body disease (APBD) — a disease caused by the cells' inability to get rid of toxins, which causes progressive weakening of the muscles — is eager for people who might be suffering from APBD to step forward and be tested.

One in 68 Ashkenazim is an APBD carrier, yet there are only a couple hundred people with a confirmed diagnosis. That means that there are thousands of people who have APBD and don't know it. They may have been told that they have MS, Lou Gehrig's, prostate disease, Hereditary Spastic Paraparesis or some form of nerve damage, and are suffering through years of tests and treatments that won't help.

Do you know an Ashkenazi who is experiencing the following symptoms?

- numbness of fingers and feet, with numbness moving up the arms and legs
- difficulties with balance; dragging feet
- a frequent need for bathroom breaks; poor bladder control
- fatigue

If so, encourage them to be tested. The APBD Research Foundation needs 200 patients with a confirmed diagnosis to be considered for a free drug initiative. New York's Mount Sinai Hospital has recently added APBD to the list of Jewish diseases they'll test for with a saliva sample. This can be done by mail and is free (info@apbdrf.org).



insurance) willing to pay for a drug that targets a rare disease?

Since so few people need these expensive treatments, they don't make much difference to insurance companies' profits. And insurance companies are anxious to avoid the terrible name they'd get by denying treatment to sick children; most of the 5,000 known orphan diseases kill victims in childhood.

Also, it's a case of spending to save. Without treatment, sufferers face repeated expensive hospital stays and end up dependent on caretakers for the rest of their lives, which can cost insurers and governments more than $1 million over a lifetime.

More importantly, the medical community sees orphan drugs as a worthwhile investment. Many genetic diseases stem from similar malfunctions. Tay-Sachs, Fabry, Gaucher, Pompe, and almost 50 other diseases stem from a cell's inability to digest. Research done on Pompe may be useful for related cell-digestion diseases, including APBD, which together affect one in every 5,000 live births. So a treatment aimed at easing the suffering of a couple hundred people may be useful in helping thousands of others.

And orphan disease studies have a ripple effect on the general population as well. Rare diseases are usually caused by the malfunction of a single gene, which needs to be understood before researchers can tackle more common, complex problems. The genetic malfunction that causes Gaucher's also plays a part in Parkinson's, and if a treatment is found for Gaucher's, it will probably help patients with Parkinson's. What researchers learn about unicorns and zebras can help horses, too.

Before turning 16, Megan Crowley reminded her parents that they might never have the chance to pay for her wedding, and convinced them that they might as well spend liberally on a gala birthday party instead. Pretty in a bright pink-sequined gown, Megan used her moment in the spotlight to address her father's colleagues: "Thank you for all that you have done for so many and for the work you continue to do to make a better medicine for me and Patrick." Patrick just managed to choke out, "I love you, Megan."

Now 20, Megan is a straight-A student at Notre Dame. On February 28, Rare Disease Day, Megan was a special guest at President Trump's first address to a joint session of Congress, and received two standing ovations.

Megan's muscles have become too weak to support her spine, so she "puddles" into her hot-pink electric wheelchair. She can move her arms enough to type on her iPhone and operate her wheelchair but she's going to lose more strength. Still, her father says, "she thinks there's more therapies coming for her down the road, so there's hope." ◌