

INTRODUCTION

HERE ARE SOME BASIC FACTS: Women live longer than men. Women have stronger immune systems. Women are less likely to suffer from a developmental disability, are more likely to see the world in a wider variety of colors, and overall are better at fighting cancer. Women are simply stronger than men at every stage of life. But why?

I became fixated on this question one summer night as I lay inside an ambulance speeding toward the hospital after a serious car accident. Lying on the stretcher, hooked up to the

monitors, I found myself reflecting on two specific events in my past that had become vivid memories. One occurred when I was a doctor treating premature babies in a neonatal intensive care unit (NICU), and the other was ten years earlier, when I was focused on neurogenetics, working with people in their final years of life. The two events seemed connected in some way, but I couldn't quite put my finger on how.

Then, amid the chaotic activity in the back of that ambulance, the realization hit me. We all have those life events that make us question certain basic assumptions; the two things I thought about that summer night, and the crystallizing moment that followed, all link to the argument I'll be making in this book. And the thesis is this: women are genetically superior to men.

When I started doing research as a neurogeneticist (someone who specializes in the genetic mechanics of neurodegenerative disease), one of the unexpected challenges I experienced was recruiting sufficient numbers of healthy older adults to participate in the studies. Even with the perfect research questions and all the necessary financial support in place to test them, I'd often be stymied and have to delay because I couldn't find healthy older age- and sex-matched volunteers. The recruitment process could take years.

Unless, of course, you've got Sarah on your side. Sarah is in her late eighties and has two titanium hips, but with her walker she's pretty much unstoppable. Her weekly schedule consists of a watercolor course, swimming, and a cardio class, rounded out

with a regular dancing soiree. If that isn't enough, Sarah takes part in almost daily events at different senior centers across the city. She's a member of a volunteer organization that visits hospitalized older adults who may not have any family or friends to spend time with them. She also happens to be my grandmother.

I'm often asked by family members if I'd be willing to speak to Sarah directly about slowing down. Everyone gets worried that she's simply too busy. My response to them is always the same: it's because she's so active and draws so much meaning from her daily activities that she's doing as well as she is. More important, if she stopped being social, I would quickly run out of older adult research volunteers.

My grandmother first started helping me recruit for my studies almost twenty years ago. She wasn't shy about giving advice either. "You'll never get one person wanting to help you with your study with that scary white lab coat and name tag on," she said. "If I were you, I'd try taking it off. And your nurse too—no lab coats. They scare us. It reminds me of my surgeries, and why would I want that? Without it, you can just look like a normal person. After all, you're asking people to give up a piece of themselves, and that's a big deal. You'll see—there are many people who want to help."

So I listened, and I ditched the lab coat. It worked. After I, dressed like a civilian, gave a presentation to prospective volunteers, we had more than the number of research participants we needed. The only problem was that even if everyone

in the room agreed to participate, there would always be a glaring shortage of individuals in one specific demographic group. There just weren't enough men.

Elderly women on average outlive their male contemporaries by at least four to seven years. This longevity discrepancy becomes all the more striking as we start to approach the extreme end of the human life span. Over the age of eighty-five, women can outnumber men two to one. As for centenarians, women's survival advantage is even more exaggerated: out of one hundred centenarians alive today, *eighty* are women and only twenty are men.*



FLASH FORWARD TEN YEARS to an early-autumn evening when the leaves had just started turning color. I was paged by the hospital to the NICU. Rebecca, the nurse on call, met me at the sink and briefed me on two preemies who had been admitted a few days before. Fraternal twins, Jordan and Emily were born at just twenty-five weeks of age—more than three months before their official due date. I put on a clean gown, blue nitrile gloves, and a mask, as the last thing these babies needed was to be exposed to anything I may have inadver-

*We used to think that the mitigating factor explaining the difference in longevity between the sexes was behavioral in nature. More men, for example, have typically perished while serving as soldiers, and while employed in more dangerous occupations. We now know that genetic females' longevity advantage can be attributed to factors that are biological in nature.

tently tracked in from the hospital atrium, where I'd been sitting just a few minutes before my pager went off.

Rebecca had been on staff with the hospital for more than three decades, and despite the long hours and the very difficult work in the NICU, she looked much younger than her sixty-odd years. Rebecca had one of those voices and ways of being that left you feeling reassured, no matter how dire the situation. Most of the staff, including many of the physicians, often deferred to her when thinking about changing a medical care plan for the hospital's smallest patients. The senior nurse in the Level 4 NICU, Rebecca truly was a preemie whisperer. And what she said to me that night would change the course of not only my research but also my life.

Thankfully, most of us are not aware of the struggles that newborn premature babies must endure just to make it through the day. Tiny and frail, they have to fight to survive, alone in their diminutive translucent homes. Those incubators, crudely conceived artificial wombs, serve as their controlled environments until the babies are old and strong enough to not need them anymore.

A Level 4 NICU usually houses the youngest and sickest of the premature newborns. Many of the incubators used here have an air-filtration system that keeps the risk of infection lower by protecting the babies from the outside world. The incubators also produce the right amount of moisture in the air. When babies are born very early, their skin often hasn't finished forming yet and is unable to provide the proper barrier needed to avoid dehydration.

An immense amount of technology and human capital is invested in the precious few who occupy these Plexiglas enclosures. Nurses, doctors, and family members are caught up together in a constant struggle to help keep the babies alive, to encourage them to grow and thrive.

You never really get used to the sounds of the equipment in the NICU. The fans hum, the monitors buzz, and occasionally an alarm beeps loud enough to disorient even the most hardened of medical staff. It's no wonder research has shown that the light and sound spectacle of modern medicine can have a negative impact on the health of premature babies (it's something doctors are trying to fix these days).

My introduction to the NICU was hard and fast, first as a medical student and then as a physician. My time there oscillated between pure awe and utter terror, and I often experienced both emotions in quick succession—and sometimes simultaneously.

Mostly, though, there is a lot of waiting. With all the medical advancements we've made over the years, it's still time, more than anything, that these young bodies need. The babies are in the ultimate inverse of a race against time—their biology needs as much time as it can get to mature. They end up in the NICU for all sorts of reasons, of course, but in many cases they're there because a premature birth endangers the brain and lungs, which take longer to develop than the other organs do.

Often one of the biggest challenges for the youngest preemies, and one that determines their chances of survival, is the degree to which their lungs have developed. The lungs of

premature babies have to acquire oxygen and release carbon dioxide at a rate that is compatible with life long before they are meant to. We're still not sure why some babies are born prematurely, but thankfully, over time, we've developed improved interventions to increase their odds of survival.

Regulating body temperature, as well as keeping in check the trillions of microbes always on the lookout for an easy target, can prove to be too much work for some preemies. It's a miracle that these babies, separated from the protective envelopment of the womb long before they're ready to face external challenges, can survive months before their due dates. But survive they do. All sorts of things can ultimately contribute to the death or life of a premature baby—from gestational age at birth to unanticipated bumps along the road. And surprisingly, one of the most important indicators of potential success in dealing with the rough-and-tumble adversities of life comes down to one simple thing, as I was just about to discover.

After I examined Jordan and Emily, Rebecca led me down a long hallway and into a quiet room where I could spend some time with their parents. Hospitals often lack the physical space for concerned family to congregate comfortably. We were lucky to have a room for talks like this.

I sat down with Sandra and Thomas to discuss our care plan for their twins, but before too long they were telling me about their journey to parenthood. After so many failed attempts, numerous rounds of hormone injections, and even in vitro fertilization, they had all but given up on having children of their own.

And then it finally happened. They were overjoyed at finding themselves pregnant, but tried not to get too excited at first. They knew from personal experience how quickly good news could turn to bad. But as the days and weeks went by, they gradually allowed themselves to believe that this pregnancy might actually lead to happiness. When the sonogram showed that Sandra and Thomas were pregnant with not only one child but two, their dream of having a family at last seemed to be coming true.

And just when they let themselves take a breath, trouble struck again. They went from imagining what it was going to be like to have their quiet Brooklyn apartment filled with the lively sounds of two young children to hoping and praying that their twins would survive.

Rebecca had me paged late one night because she wasn't happy with how Jordan was looking. Her years of experience had taught her this: her instincts were almost always right. Having taken care of the twins since their admission, I found myself looking forward to seeing them—they had been changing so quickly from the first day they were admitted. So this news from Rebecca was upsetting. It was true that after two weeks in the NICU, Emily and Jordan had been thankfully breathing well on their own, but I knew that they weren't out of danger yet.

On my way to Jordan's incubator, I tried not to get tangled in all the wires hooked up to the machines that were helping

this child along. Rebecca, after having gone through the same routine that I did every time I went in, without fail—washing hands, gowning, donning gloves and mask—met me at his bedside. We both knew that things can be precarious for patients this young. Rebecca warned me then that I should prepare for the worst in Jordan’s case. And she was right. Twelve hours later, Jordan passed away.

I ran into Rebecca a few years later, this time in the hospital cafeteria. I had moved to a different institution and had come back to give a lecture. After so many years of devoted service, Rebecca was getting ready for retirement at the end of the month and looking forward to spending more time with her own seven grandchildren and two great-grandchildren. I told her that my experience with her in the NICU that night was still very fresh in my mind.

“Yes, they never leave you,” she said. “I still remember every one of their faces.” She reached for her coffee to take a sip.

“There’s something I’ve been meaning to ask you,” I said to her. “That night in the NICU—how did you know about Jordan? What was it that made you think he wasn’t likely to make it?”

“I’m not sure . . . but once you do this job for so long, you develop a feel for things. And so much of what we do is a judgment call. Sometimes it’s even something that the lab results or testing don’t always show you initially. Maybe it’s just intuition. One thing’s for sure, though: in the NICU, it’s almost always so much harder for boys than for girls. And I guess it’s not just in the NICU . . . I lost my husband twelve years ago now, and most of my girlfriends are widows too.”

I was quiet while I reflected on what Rebecca had just shared with me. I couldn't help thinking about my grandmother and the dearth of men at the far end of the human aging trajectory. It was as if everything I had ever researched and experienced clinically was coming together at that moment, forming a crisp question out of the fog of years of study.

"Males, I was always taught, are the stronger sex. Yet that's the opposite of what I've seen so far, both clinically and in my genetics research. So why do males seem like the weaker sex in fact?" I asked.

"Maybe you're just not asking the right question," she said thoughtfully, stirring the remaining coffee in her cup. "Instead of thinking about male weakness, maybe the question you want to ask is, What makes females stronger?"



THE ANSWER TO REBECCA'S QUESTION came to me six years later: It was a beautiful summer's day—perfect for a drive down to the beach. The sun was finally out after a very long winter and a very wet spring. I promised my wife, Emma, some quiet time for just the two of us, and as I wasn't on call that day, I even turned off my phone. The last thing I remember was reaching over and holding her hand as we were driving westbound on a mostly empty street, singing along with the song that we heard the first time we ever danced together, Leonard Cohen's "Dance Me to the End of Love."

Witnesses later told us that we were hit dead-on broadside

by someone who ran a red light and barreled toward us at more than forty-five miles per hour. Our car rolled twice. The impact was severe, the roof of our car caved in, and none of the airbags deployed. Because of the extent of damage to our car, the first responders were preparing themselves for horrific traumatic injuries. We were lucky to be alive.

We both had some bruising and bleeding from the tempered glass that shattered and rained down on us when the car flipped. Given what we had just experienced, our injuries turned out to be pretty minor and pretty similar—but Emma’s injuries were a bit more serious. So, you know what I was thinking while strapped to a spine board in the back of an ambulance hurtling toward the hospital? I was thinking about how grateful I was that Emma was a genetic female with two X chromosomes.

I thought back to when Rebecca had suggested that I ask myself why women are stronger at both the beginning and the end of life. I knew from my clinical work and research that even if my wife’s injuries were the same as mine, given the odds, she was likely to make a better and faster recovery than I was. Her wounds would heal faster, and she would have less of a chance of subsequent infections because of her superior immune system. All in all, her prognosis was almost assured to be better than mine.

This was because her body had the use of two X chromosomes, while mine had the use of only one. To review the basic chromosomal differences between the sexes, the cells of all genetic females have two X chromosomes, while those

of genetic males have one X chromosome and one Y chromosome.* When it comes to dealing with the trauma of life, genetic females have options. And genetic males don't.

Our two sex chromosomes are given to us by our biological parents before we are born. My wife's genetic superiority began long before we ever met. When she was only twenty weeks old within her mother's womb, she already had a survival advantage over me—one that will continue at every data point throughout our life cycles. That's even if we adjust for other lifestyle and behavioral risk factors such as occupational hazards and suicide. From the beginning, she is likely to live longer than me no matter what life throws our way.

And my wife doesn't win only when it comes to overall longevity. Her risk for developing cancers in organs we both have, for example, is lower than mine. And if she does develop cancer, she has better odds of surviving, as research shows that women respond better than men to treatments. More women of course do develop breast cancer, but overall men still die of cancer in higher numbers per year than women.

The cost women seem to pay for having a more aggressive immune system, one that's better at battling both invading microbes and malignant cells, is being self-critical—immunologically speaking. The immune systems of genetic females are much more likely to attack themselves, which is what occurs in diseases like lupus and multiple sclerosis. So the only thing that I

*Most humans inherit two sex chromosomes, written formally as 46,XX and 46,XY. It's possible to inherit many other variations of the sex chromosomes, including 45,XO, 47,XXX, 47,XXY, and 47,XYY.

have going for me is a lower chance of developing an autoimmune condition.

What I knew that night as we rushed to the hospital was that my wife's cells were already starting to divide, undergoing a process of cellular selection to deal with the microbes that likely entered her body on impact. They were already starting to draw on their collective genetic wisdom to undertake repair work on her tissues. And in each area of her body, be it her leukocytes, which are part of her immune system, or the epithelial cells that make up her skin, her cells would be going through an empowered and flexible genetic process of selection. My body, being composed of cells that are genetically identical, didn't have this option.

Although every genetic female has two X chromosomes in each of her cells, every cell has the use of only one. My wife's cells use either the X chromosome she inherited from her father or the one from her mother. My cells don't have that luxury. Every one of my cells has to use the same exact X chromosome, the one I inherited from my mother, while my Y chromosome couldn't do that much after the accident we experienced but sit there watching helplessly.

The ability to use different X chromosomes is one of the main reasons for my wife's genetic superiority. As our room filled with GET WELL SOON balloons, cells in her body were using different Xs and continuing to rapidly divide. What began as a fifty-fifty split between cells that were using the X from her mother and those that were using the X from her father was now rapidly skewing toward using one particular X, whichever one happened to be more effective at doing the job required.

Even before the first emergency responders arrived, more of those white blood cells were dividing, using one X over the other. And to deal with the challenge of healing, the same cellular competition of using only the best X for the job was likely happening everywhere else in her body as well. If you'd looked inside *my* blood expecting to find the same thing, you'd have been disappointed.

Having the use of two X chromosomes makes females more genetically diverse. And the ability to rely on that diverse genetic knowledge is why females always come out on top. Whether it's an infant girl's survival in the NICU, a woman's ability to fight infections, or a genetic female's decreased risk of having an X-linked intellectual disability, it all boils down to the simple fact that females have a degree of genetic flexibility that males lack.

Although we belong to the same species and are more similar than we are different, there's an important reason that females are more genetically endowed. Our very existence has depended on it for millions of years. Being the stronger sex, genetically speaking, is what allowed females to survive long enough to ensure the survival of our offspring—which in turn means the survival of us all.

My original genetics research and clinical discoveries, my life experiences, the groundbreaking work of my colleagues, and the findings of pioneering scientists challenging the doctrines of their time have culminated in this undeniable understanding: women are the stronger sex.

In *The Better Half*, I will explore the key challenges that

occur throughout life and show how genetic females conquer them, leaving males behind when it comes to longevity, resilience, intellect, and stamina. I will tackle how medicine and pretty much everything else have all dismissed this fact.

When I was in medical school, I learned to expect that more of my female patients would report myriad side effects from the medications I would prescribe. I was also taught that the likely reason for this was behavioral—that women were just more vocal about any problems and generally saw their physicians more often than men did.

But if it's just a reporting bias, then why are so many women experiencing serious side effects that require significant medical intervention? A U.S. General Accounting Office review of ten drugs taken off the market revealed that eight of them were withdrawn because they were found to be dangerous to women. In addition, it's women who are more frequently overdosed unintentionally by the doctors aiming to treat them.

Although we've known for years from a medical perspective that women are more sensitive to chemical compounds such as alcohol, we still, for the most part, prescribe drugs to both genetic sexes as if they're exactly the same. This needs to change. Almost twenty years ago the Institute of Medicine of the National Academy of Sciences published a report that claimed the following: "Being male or female is an important fundamental variable that should be considered." So let's consider it.

Outside obstetrics and gynecology, the incredible advances in modern medicine that we're all benefiting from have been almost entirely produced from research that exclusively used

male participants, male research animals, and male tissue and cells. The chasms created by the lack of female research animals and female tissue and cells in preclinical drug trials leave most physicians having to estimate or at worst outright guess what might be the best dose or treatment for their genetic female patients.

When I was designing studies to test the microbe-killing power of an antibiotic I discovered almost twenty years ago, I remember how naive I was regarding the inclusion of women in basic and clinical research. To further test the effects of one of the drugs I discovered, I contacted a company that specialized in running experiments independently, so that I could corroborate or refute my findings. While designing the studies for the company to perform on my behalf, I assumed that it would be using an equal number of male and female mice.

I was wrong. It used only male mice. As I came to learn, that company wasn't alone in this. Everyone else was doing exactly the same thing. When I inquired as to why, I was told at the time that it was easier (and cheaper) to use males. Interestingly, as I was to discover, female mice can have much stronger immune systems, which could complicate the results of an experiment that's trying to cure infections equally in both sexes.

Indeed, we've misunderstood the physical abilities of women and discounted their genetic strength for far too long. In *The Better Half*, I will outline how our perceptions, health care, and research culture need to change. The future of medicine and our survival as a species depend on it.