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PART THREE

Treatments

PROLOGUE

Everything That Irritates Us

On August 25, 1996, my dad was cruising down Main Street in our small New Hampshire town in the respectable, boxy four-door sedan that he used to make sales calls during the week. He and his longtime girlfriend, Patricia, were headed out to the beach to enjoy the day surfside. It was 11:20 A.M. and as the sun marched toward its apogee, the temperature slowly rose with it. The car's windows were rolled down, which was typical for my dad. He was an enthusiastic smoker of Marlboro Lights who also eschewed the use of air-conditioning unless it was blisteringly hot. We were New Englanders, after all, and expected to tough out all but the most miserable of weather.

My dad's hand dangled outside his car, a lit cigarette pinched between his fingers, his forearm resting on the warm metal of the car door. The radio was tuned in to an AM station covering the Boston Red Sox. My dad could never get enough baseball. He dialed in to seemingly every game and if one wasn't being played, then he liked to listen to analysis of past matchups and predictions about future ones. As a teenager who was more into reading Dickens and obsessing over Duran Duran, I found his enthusiasm for sports exasperating, especially his addiction to sports radio. As a rule, I would sit in the back seat, trying to concentrate on reading, my eye rolls partially hidden behind a thick paperback book. Sometimes, just to annoy him, I would root for the opposing team until he threatened to pull the car over and let his only child walk home.

But in 1996, I was twenty-four years old. That Sunday in August, I wasn't in the car with my father. I heard about what happened from three sources: the state police, who informed me as next of kin that he was dead; a local funeral director I phoned to see where my father had been taken, who remembered his colleagues discussing the unusual condition of his body; and, twenty-five years later, Patricia, during our first conversation since my father's wake. Yet my dad was such a creature of habit that I have no trouble picturing the events as they likely unfolded. If I close my eyes, I can see him sitting in his car, a Styrofoam cup of hot coffee wedged into the cup holder, his hand loosely resting on top of the wheel.

Growing up, I had a strained relationship with my father. My parents divorced when I was just two months old, and I saw him only a few times throughout my young childhood. The tension that existed between us deepened after my mother's death in a car crash in 1986, when, at fourteen, I moved from my hometown in rural Indiana to live with him and Patricia in suburban New Hampshire. My dad and I were what I euphemistically liked to call "estranged" whenever I tried to explain our familial situation to new acquaintances or friends. I had a father and I loved him; I just never spoke to him.

As my dad drove that day, a solitary bee was on its usual pollen-collecting rounds when its flight trajectory intersected with my father's open car window. The bee became confused and panicked. It stung my dad in the side of his neck, close to his ear. My dad, surprised but still calm, continued to drive.

What happened next was not visible to the naked eye. Events shifted to the microscopic level, inside my father's body. Biology took over.

The bee's stinger introduced its venom—a mixture of water, histamine, pheromones, enzymes, and various amino acids, or proteins—underneath the thin layer of skin into the fatty tissue of my father's neck. Packed tight with blood vessels, the neck is a great circulatory site, so the venom had a unique opportunity to spread rapidly throughout my dad's body. Some of my father's immune cells—his

mast cells and basophils—swiftly detected certain of the venom's components.

White blood cells like mast cells and basophils are produced in our bone marrow and circulate throughout the human body, helping to fight off infection or disease by ingesting foreign or harmful materials like viruses, bacteria, and cancer cells. Mast cells can be found in the connective tissues under our skin, lining our respiratory tract and intestines, and in the tissue around our lymph nodes, nerves, and blood vessels. Basophils are found in our bloodstream. Mast cells and basophils, then, are nearly everywhere inside the human body. Their job, to dramatically simplify it, is both to begin and to amplify the severity of our immune response. Think of them as the conductors of our immune system, modulating its response by releasing various proteins and chemicals.

Bee venom is not a natural substance that the human body responds particularly well to, even under normal circumstances in a nonallergic person. Bee venom is naturally hemorrhagic, meaning that it has the ability to blow apart our blood cells. Even so, bee and wasp venoms are relatively harmless in most humans, apart from causing a painful, localized swelling near the injection sites. Everyone's immune cells react to venom; my father's dramatically overreacted, sending his immune system into the deadly spiral known as anaphylaxis. Anaphylaxis is medically defined by the World Health Organization as "a severe, life-threatening systemic hypersensitivity reaction characterized by being rapid in onset with potentially life-threatening airway, breathing, or circulatory problems." What that means in layman's terms is that my father had an underlying allergy to the bee's venom, a hypersensitivity that he tragically underestimated until it was too late.

Just a few weeks prior, while in the parking lot of Walmart, my father had been stung by another bee. When he returned home, he told Patricia he wasn't feeling well and took some Benadryl—a well-known brand of antihistamine, commonly recommended for coping with milder allergic responses. Soon after, he felt better, but Patricia

nagged him to see a doctor, suspecting he had an allergy to bees. My father, notoriously bad at taking care of his own physical health (he smoked too much, drank too much bourbon, and ate too many servings of prime rib), demurred.

Allergic responses can strengthen over time with repeated exposures. The first time my father was stung, he may not have had more than a small welt at the site of the sting itself. The second or third time, his body's immune cells would have remembered the offending substances and reacted more swiftly and strongly—causing a proportionally larger reaction. My father's body, unbeknownst to him, was already primed to betray him.

The process of anaphylaxis starts as soon as an antigen—a fancy term for any substance, like bee venom, that initiates an immune response—encounters and activates the mast cells and basophils in your body. My dad's mast cells and basophils began the process of anaphylaxis mere seconds after he was stung in his sedan, as soon as they came into direct contact with the venom's proteins and started emitting histamine. Histamine, an organic compound created by the body, is a key part of a normal immune response, released when cells are injured or stressed. It causes blood vessels to dilate and their walls to become more permeable—thereby making it much easier for infection-fighting white blood cells to leak out of blood vessels and move into affected areas. Histamine is also a signal to other nearby cells to release even more histamine. Think of histamine as the body's chemical alarm system; once it goes off, it alerts your entire immune system to go into action. How does this alarm system feel within your body? Histamine acts on receptors on your organs, causing inflammation, flushing, itching, hives, and swelling.

Unfortunately for my father, everything that happened next would be accelerated simply because he was still sitting upright in his car, his body's position partially obstructing the flow of deoxygenated blood returning back to his heart. The allergic surge of histamine circulating throughout his body caused my dad's veins to dilate too quickly, reducing his blood pressure and the flow of blood to his heart even further, a process that can—and, in my father's case, eventually did—

culminate in cardiac arrest. The excess of histamine additionally shifted fluid from his vascular system—the network of blood vessels throughout his body—into his tissues, causing my father's body, including his neck, to swell. In an effort to help protect the lower airways from inhaled irritants, histamine also thickens mucus, increases mucus production, and causes the smooth muscle tissue around your lungs to tighten. During an anaphylactic event, your airways begin to constrict within minutes. My father, sensing all of this beginning to happen to him, pulled over to the side of the road and asked Patricia to drive.

Panicked and miles away from the nearest hospital, Patricia decided to drive to a local pharmacy for more immediate help. Now in the passenger's seat, my father started to gasp for air, his face changing color.

Minutes later, Patricia pulled the sedan into the tiny lot in front of the small drugstore, threw it into park, and ran for help. The pharmacist on duty that day explained that he couldn't give my father a potentially lifesaving shot of epinephrine, also known as adrenaline, because my father didn't have a current prescription for it. Epinephrine, a natural hormone secreted by the adrenal glands during times of stress, helps to stop the process of anaphylaxis by halting the release of histamine and constricting the blood vessels—thereby aiding blood flow. It also binds to receptors on the smooth muscles of the lungs, helping them to relax and allowing the breath to return to normal. An emergency shot delivers a much greater dose of adrenaline to the body than it can produce on its own in a short amount of time. But instead of administering the drug to my father, the pharmacist called for the paramedics.

When the ambulance finally arrived, emergency medical technicians (EMTs) intubated my father, who could no longer breathe due to the swelling in his neck tissue coupled with the constriction of his lungs. The ambulance did not have any adrenaline on hand, and the pharmacist continued to adamantly, if regretfully, refuse to give the EMTs access to the drug my father now so desperately needed. Despite how cruel his decision may appear to us now, the pharmacist's

hands were legally tied. In the 1990s, pharmacists were not allowed to administer adrenaline, even in the case of an emergency. As precious minutes ticked by, my father's body went into shock, the final stage of what is referred to as an inflammatory cascade.

As my father was being loaded into the back of the ambulance, Patricia, hovering over him, asked him to blink if he could still hear her. He softly closed and opened his eyes. She squeezed his hand, still terrified, yet relieved and hopeful. As she climbed back into my father's sedan to drive herself to the emergency room, she listened to the sound of his ambulance's siren as it faded into the distance.

On the way to the hospital, despite all efforts to save him, my father's heart stopped.

James MacPhail—die-hard Boston sports fan, computer chip salesman, Vietnam veteran, Jackie Gleason look-alike, the life of every party, loving son, stand-up comedy aficionado, musical lover, and my father—was gone.

As I was researching this book, I turned forty-seven, the same age my father was when he died, and I often found myself thinking about his unusual death as I talked to experts across the country about the puzzle of allergies. Deadly anaphylactic reactions to bee stings remain incredibly rare. Each year, around 3 percent of adults will experience a life-threatening reaction to an insect sting (bees, wasps, or hornets), yet most will survive.[1] In the two decades since my father's death, an average of just sixty-two Americans, or 0.00000002 percent of the general population, have died annually from an insect sting.[2] My dad's death was an outlier, an unfortunate accident, and a life-changing event for all of his friends and family.

But the more I learned about allergy, the more I kept wondering, *Why him?* Was it something about his genetic makeup (and thus also part of my own) that primed his immune system to overreact in the first place? Or was it something about his environment growing up in Boston or the way he had lived his life? In theory, my dad could have become more sensitized to bee venom after being repeatedly stung—

either in childhood or during his two tours of duty in Vietnam. Or, he could have just been very, very unlucky to die from his second encounter with venom in just under a month. Yet as I write this—having finished my research and now three years older than him—I know that there is no way to know for certain what caused my father's allergy because allergies themselves are complicated.

From a biological perspective, I can explain exactly what happened during my father's last moments on earth. The underlying biology is, in many ways, the easiest part of the story to understand and to tell: My father's immune system response was too effective for his own good. In Greek, anaphylaxis literally means "backward defense." My dad's immune system—built to protect him—was completely functional but overly sensitive, misrecognizing a naturally occurring, relatively innocuous substance as a direct threat. Once a heightened immune system reaction begins, it can be nearly impossible to stop. For the people who live with a severe allergy, the paradox of having such a strong, active immune system is that, in addition to protecting you from germs and parasites, it can kill you. And that's exactly what happened to my dad.

The thing that I continue to struggle with—that I simply cannot grasp—is what my dad must have been thinking and feeling as he helplessly watched his own body fail him. How frightened he must have been in those first few seconds as he felt his throat begin to swell shut and his lung muscles contract, cutting off his ability to breathe. How terrified he must have been as his heart began to slow inside his rib cage. What is it like to incrementally, and yet swiftly, die as your immune system goes into overdrive? Would he even have understood what was happening to him? At the very end, as his heart stopped, did he have time to think once more of me, or my grandmother, or his girlfriend? Did he know how much we would miss him?

Strange as it may seem, I didn't originally set out to research the topic of allergies because of my father. Over time, I had normalized his death and ruminated on it less and less. For years, the only time I

thought about my dad's final moments was when I was sitting outside at a picnic table or walking through a garden and heard a familiar buzzing sound. The mere sight of a bee could send my heart pounding and freeze me in my tracks. But outside of these random encounters with wasps, hornets, or bees, I didn't think all that much about allergies. Until, that is, I was diagnosed with them myself.

In 2015, I was a busy new assistant professor teaching a full course load and trying to write a book about influenza. Ironically, I kept getting sick. Very sick. After being diagnosed with my fourth respiratory infection in less than a year, my doctor shipped me off to see an otolaryngologist—an ear, nose, and throat specialist—proclaiming that something must be wrong with my nasal "plumbing." The otolaryngologist listened to my complaints, examined my doctor's notes, and then looked inside my nasal cavities and down my throat with a scope.

"You've got some serious irritation," he said, still peering into the deep recesses of my nose. "Much more than would occur with just an infection. I'd say that you have allergies. That's your real problem."

This was complete news to me. I had never suffered from undue sneezing or sniffling; I had no red or puffy eyes, no itching or redness or tingling of my skin, no upset stomachs. As far as I knew, I was allergy-free. Except that here was a specialist, someone with years of clinical experience, telling me that, actually, I was one of the millions of allergy sufferers living in the United States. And those allergies were making it more difficult for my overwhelmed immune system to combat the seasonal viruses and bacteria—the *real* microscopic enemies—that I was encountering in my day-to-day life. My immune system was reacting to the wrong triggers, mistaking harmless substances for harmful ones, functioning so diligently that it was making me sick in the process.

It turns out that I am my father's daughter after all—we share a similar hypersensitive immune system—though I still don't know if I'm allergic to bees (but more on that a bit later). Over the ensuing months, as I slowly came to terms with the continuing mysteries and frustrations of my allergies and started to think of myself as an allergy

patient, I took some cold comfort in the fact that at least I was not alone. Far from it. Once I revealed my own surprise diagnosis, people began talking to me about their own food, skin, or respiratory allergies. It suddenly seemed to me as if *everyone* I knew had some type of allergic condition; they just hadn't been openly discussing them. And that's when I realized that allergy was a much larger problem than I had ever imagined.

Nut allergies. Hay fever. Asthma. Eczema. Either you have a frustrating allergy or allergy-related condition, or you know someone who does. The latest statistics on allergies are sobering. Over the last decade, the number of adults and children diagnosed with mild, moderate, or severe allergies has been steadily increasing with each passing year. Billions of people worldwide, an estimated 30–40 percent of the general global population, currently have some form of allergic disease, and millions have one severe enough to actively endanger their health. But allergies don't have to be deadly to impact your whole life. People with mild, moderate, and severe—but not deadly—allergic immune responses spend an inordinate amount of time, money, and focus on their conditions. Allergies can be a burden, even when they aren't life-threatening. But because allergies don't normally kill people, as a society we have a tendency not to take them very seriously. We joke about someone's gluten intolerance or hay fever without thinking twice about how a person with those conditions might actually feel. The quality of life of someone with an active allergy is typically lower than someone without one. Their anxiety and stress levels are higher. They feel fatigued more often. Their ability to concentrate and their energy levels go down.

Maybe you already know what having an allergy is like because you have one. There's also a good chance that you've downplayed your own allergy because you've gotten used to the feeling of it. In other words, you've stopped expecting to feel "great" and have settled for feeling "okay" on most days of your life. But even then, even when an allergy sufferer has found ways to cope with their condition, there are times when it is harder to ignore. A bad pollen day. A new patch of red, itchy skin. A potluck dinner party. Allergy sufferers know what

often remains hidden to the allergy-free—that our bodies are constantly bumping up against the billions of invisible particles, microbes, chemicals, and proteins that constitute the space and objects around us. Our immune cells make snap decisions, either to accept or to reject the things we encounter, countless times each day for our entire lives. Our immune systems decide, in essence, what can become a part of us (food), what can coexist with us (some bacteria, viruses, and parasites), what we can tolerate or ignore and what we cannot.

It's clear that our human immune system is becoming ever more sensitive to the panoply of natural and man-made allergens that we come into contact with on a daily basis. The problem is that immunologists working to understand the biological processes involved in allergic reactions aren't entirely sure why. Worsening food, skin, insect, drug, and respiratory allergies remain some of the most pressing medical mysteries of the twenty-first century. Why are we all so irritated?

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After my own diagnosis, I went in search of more information on allergy. I wanted answers to a series of escalating questions that began with the very personal and cascaded into a set of larger historical, economic, social, political, and philosophical questions.

- How long have allergies been around? Are they an ancient problem or relatively new?
- Are allergies getting worse? If so, what might be causing it?
- Are allergies genetic, environmental, or man-made?
- What can we do about them? Can we "fix" our allergies?

After a few weeks of researching, I couldn't find any satisfactory and easily accessible answers. These questions turned into a personal and scientific journey to diagnose the problem of allergy in the twenty-first century. This book is a record of that journey, a holistic examination of the phenomenon of allergies from their first modern medical description in 1819 to the recent development of biologics for their treatment and immunotherapies for their prevention.

What you are about to read is an attempt to tell the whole story of allergies in the twenty-first century: what they are, why we have them, why they've been getting steadily worse globally, and what that might mean about the fate of humanity in a rapidly changing world. It interweaves the latest scientific research, the history of allergies, and the personal narratives of patients and doctors coping with allergies to explore our complicated connections to our environments.

First, we'll tackle the shifting definition of what an allergy is—and isn't. As our scientific knowledge related to immunology—the study of immune system function in all species—has deepened and progressed, so, too, has our understanding of what falls under the category of "allergy" or allergic-type immune responses. As we'll discover, allergies are not so easy to categorize, diagnose, and count. The best statistics we have are estimates based on insurance claims, surveys, and hospital admissions. But any way we do the math, the sheer number of allergic individuals is growing with each passing year—and with no end in sight.

Once we've learned the basics about allergies, we'll explore the various theories about their causation. Depending on how you define allergic immune responses, they are either very old—the ancient Egyptian king Menes is believed to have died from a bee or wasp sting—or very new. The first clinical description of an allergic response, an analysis of a case of hay fever, was penned just over two hundred years ago, and evidence suggests that respiratory allergies were not widespread until at least the beginning of the Industrial Revolution. Ideas about why rates of allergies have been steadily rising ever since are complex and heavily debated. If you want easy answers, you will not find them here. But you will learn what the likeliest combination of culprits are.

And, finally, we'll take a look at what treatments we have for allergy and what the future of allergy medicine is likely to be. Not much about allergy treatment has changed in the last two centuries, but a new class of biological drugs on the horizon might provide a glimmer of hope for better, and more consistent, relief of our worst symptoms. At the same time, new scientific understandings of our allergic im-

mune responses might lead to better regulations and social policies. In the end, understanding what is irritating us and why, then and now, might help us to cooperate in order to craft better environments in the future—ones in which we can all breathe easier.

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My father on duty in Vietnam. [AUTHOR'S PHOTO]

This book is dedicated to my father. My dad was an avid reader and a lifelong learner. Although he never finished his first year of college, he was a natural autodidact and enjoyed discovering new facts about the world until the day he died. In that way, too, I am firmly his daughter. I inherited not only his allergic tendencies but his curiosity and his constant quest for the truth—no matter how complicated and opaque that truth turned out to be. I think he would be entertained, enlightened, and fascinated by the story of allergy told within these pages. And whether or not you, my dear reader, have an allergy yourself or you love someone who does, I hope that by this book's end you not only have a better understanding of allergies but also have developed a few new questions about our incredible immune system and its complex relationship to our shared environments. Thank you for going on this journey with me. Let's get started.

PART ONE

Diagnosis

The first step in our quest to better understand allergy in the twenty-first century is to survey all our current symptoms. In the next three chapters, we'll take a closer look at the problem of allergy today by analyzing the latest statistics and hearing from individual allergy sufferers about what it's like to have hay fever, allergic asthma, allergic dermatitis or eczema, food allergy, drug allergy, or insect allergy. To complicate things, it's not always easy to diagnose an allergy or to officially differentiate it from an intolerance or a sensitivity. Our immune system function is complex, and allergy is on a spectrum of possible immune responses ranging from full-blown allergic response to mild or moderate irritation to complete tolerance. To better understand what an allergy is and what it isn't, we'll explore the history of the immune system and how allergy fits into it.

CHAPTER 1

What Allergy Is (and Isn't)

Before I began researching this book, I had no idea just how massive the problem of allergy truly is. Approximately 40 percent of the entire human population already has some form of allergic condition.[1] And by 2030, experts estimate that statistic will increase to 50 percent. But before we can dive more deeply into what these numbers might mean, and why allergies are projected to rise over the next few decades, we need to answer a more basic and fundamental question: *What exactly is an allergy?*

When I first started talking with scientists and allergists, I assumed I knew what an allergy was. If someone had quizzed me, I would have said, confidently, that an allergy was a negative bodily response to something a person had eaten, touched, or inhaled. If pressed for more details, I probably would have trotted out what I had learned long ago from an introductory biology course—that the human immune system is similar to a defense system. It reacts to foreign substances, such as viruses, bacteria, and parasites, and helps to protect us against infection. But in people with allergies, that same immune system is triggered by something in the environment—like pollen or milk or nickel in metal jewelry—that is harmless to nonallergic people. I would have listed sneezing, runny or stuffy nose, coughing, rashes, redness, hives, swelling, and difficulty breathing as possible symptoms.

Whenever I ask normal people (i.e., not scientists or biomedical

experts) to explain what an allergy is, I usually hear something similar to my own initial definition. People of all ages and backgrounds tend to think of allergy and allergens as, as one young nonallergic man described them to me: "Some sort of imbalance with whatever is entering your system. It just doesn't mesh well with whatever is in your body and it causes your body to try to get rid of it." Another man described allergy as the body being "self-destructive" when it doesn't know how to handle something like pollen or a particular food. In one memorable interview, a man with several allergies who had grown up in Chihuahua, Mexico, near the Texas border, suggested that his body is in a constant defense mode—but sees this as primarily positive. He thinks of himself as well defended and described his body as more "careful" and alert than the bodies of nonallergic people. These are all more or less accurate depictions of allergic-type immune responses and they work well enough . . . until they don't.

Even people who have allergies don't always understand what, in exact terms, they are or how to distinguish them from nonallergic conditions with similar symptoms.

Take "Chrissie,"[2] for example, one of the first allergy patients interviewed for this book. By the time we spoke, Chrissie had been coping with respiratory allergy symptoms, hives, sporadic swelling of her eyes, and frequent stomach issues for years. She had been diagnosed with hay fever, or seasonal allergic rhinoconjunctivitis, and occasionally visited an ear, nose, and throat specialist (ENT) for treatment when her symptoms changed or worsened. She also experienced gastrointestinal symptoms and skin rashes if she accidentally consumed milk or gluten. Years ago, Chrissie went to see an allergist and was tested for reactions to the most common allergens. Her skin was completely nonreactive to all food allergens, and the allergist told her that it was extremely unlikely that the symptoms she experienced were due to a food allergy. Chrissie's ENT has repeatedly encouraged her to get retested, but she hasn't; instead, she goes online to research her symptoms and crowdsource possible remedies.

When asked to define what an allergy is, Chrissie said that it is what happens when the body can't handle something, especially if the

body has come into contact with something too often or in too great a quantity. Over time and with repeated exposure, she explained, the body ceases to be able to process those things, giving rise to symptoms like her own. She doesn't believe the results of her skin tests for food allergens and insists that she has a food allergy; since wheat and milk are ingredients in most foods, she posits that her body has learned to reject them over decades of consuming them.

I am beginning this chapter with Chrissie's story—her misconception of what an allergy is and isn't, and her palpable confusion and frustration—to illustrate what we typically get right about allergy as well as what we typically get wrong. When it comes to her respiratory allergies, Chrissie is correct in thinking that her body is responding to something that it has had repeated exposure to, but she is wrong about her body being unable to process pollen. (As we'll soon see, it's more that her body isn't able to tolerate it or ignore it.) Chrissie likely doesn't have a true food allergy, despite having very real symptoms, because she doesn't show any sensitization to milk or gluten (as evidenced by the results of her skin-prick test). In other words, her immune system is likely *not* reacting to the foods she's ingesting. Her immune system *is* reacting to pollen, however, which causes her hay fever. What Chrissie is really confused about, then, is the difference between an intolerance (in this case, to certain foods, possibly caused by another condition like irritable bowel syndrome or a lack of the enzyme lactase that aids in breaking down the lactose in milk products) and an allergic response (to airborne allergens). And who could blame her? Even as a medical anthropologist with a decent understanding of immunology, I had to discover some of these distinctions the hard way.

The deeper I waded into the scientific literature on allergy and the more conversations I had with allergists and immunologists, the murkier the definitional waters got. To my initial surprise and frustration, the more I learned about how the intricacies of our immune system function, the harder, and not easier, it was to understand allergy. It turns out that what we commonly refer to as "allergy" is actually a grab bag of various conditions. The one thing they all have

in common is this: They all involve a hypersensitive immune system reaction to an otherwise innocuous substance—an allergen—that doesn't typically produce any immune response in nonallergic people. The symptoms of an allergy vary depending on how the allergen enters the body (via the skin, airway, or intestinal tract), the individual genetics of the person, and the many different "allergic pathways" the allergen can trigger.

So, then, what is an allergy? It's a harmful immune-mediated hypersensitivity reaction to a harmless antigen, which is defined as any toxin or foreign substance that activates an immune response. That's the technical scientific definition, but it likely doesn't mean much to you—yet. To fully comprehend what an allergy is, we have to understand how the definition of the term itself shifted and changed over the past century. The concept of allergy is just over a century old, born out of early studies of the function of the mammalian immune system.

In the end, and as you'll soon see, I learned that an allergy is perhaps best defined by what biological processes it sets in motion.

THE EVOLUTION OF A HERETICAL IDEA: A SHORT HISTORY OF ALLERGY

Before we dive into the complicated, intertwined history of allergy and our understanding of the immune system, it's important here at the outset to underline that an allergy really isn't a "thing" at all, at least not in the ways we're used to thinking about other concrete things that exist in the world—like tables or viruses or cats. Instead, it's better to think of an allergy as a complex biological process involving many different, intersecting components of our immune system. Allergy is more about the actions our immune cells decide to take than it is about the symptoms we might experience because of those actions. The story of how our knowledge of immunity evolved and made the discovery of allergic reactions possible begins in earnest at the turn of the last century.

Our ideas about the immune system, both past and present, owe a lot to our earliest understanding of microbes. By the late 1800s, famous scientists like Louis Pasteur, Joseph Lister, and Robert Koch were busy conducting experiments to definitively prove that living organisms we cannot see—such as anthrax, tuberculosis, and cholera bacteria—can make us sick, infect wounds, and rot food. This new understanding of contagion and the workings of microorganisms—typically referred to as the "germ theory" of disease—gave birth to the modern medical concept of immunity, or an organism's ability to stave off illness.

To be immune is to be protected from or defended against infection from any particular external organism. The biological mechanisms behind immunity became the focal point of scientific research in germ theory throughout the late nineteenth and early twentieth centuries. By the 1900s, scientists were focused on understanding the basic biological mechanisms that produced either immunity or disease in an individual animal after it was exposed to a disease-causing organism like the anthrax bacillus. The ultimate goal of these early immunologists was to learn how to induce immunity. At the time, vaccines and serums containing small amounts of altered microbes and disease-fighting antibodies were already being used in medical clinics and hospitals, either to prevent or to treat commonplace maladies, such as smallpox, diphtheria, or tetanus, but the process by which they worked remained almost completely shrouded in mystery.

Spurred on by the success of these early vaccines and serums, scientists and doctors firmly believed that it might be possible to produce immunity to *all* infectious human diseases and toxins. All that was needed, they thought, was a better working understanding of how animals developed immunity in the first place. Global efforts to produce immunity and treat a variety of diseases provided the backdrop for the accidental discovery of allergy.

The term "allergy"—meaning "different activity" from its combined Greek roots *allos* and *ergon*—was first coined by Clemens von Pirquet, a doctor working in a pediatric clinic in Vienna, Austria, at the turn of the last century. Pirquet and his colleague Béla Schick no-

ticed that some children given smallpox vaccines made of horse serum (a common medical practice at the time) would react poorly to a second dose, developing a rash at the injection site, itching or inflamed skin, and a fever. Surmising that something in the serum itself was causing these negative biological reactions, the duo started to methodically observe their patients after repeated injections of smallpox vaccine.

Initially, Pirquet used "allergy" to indicate *any* altered biological state, good or bad, that had been triggered by an exposure to a foreign substance—in this case, the serum.[3] For Pirquet, a negative altered state or reaction might refer to the rash or fever produced by injections of a vaccine; a positive altered state or reaction might refer instead to the development of immunity produced by the same injections. Allergy, in its original framing, included *both* immunity and hypersensitivity. It was a neutral term meant only to indicate that something had induced a change in a patient's biological state of being.

In 1906, when Pirquet invented the term "allergy," immunity itself was still a fairly new and extremely limited concept, used only to refer to the body's natural defenses against disease.[4] As an idea, immunity had its beginnings in the realm of politics, not medicine, and was originally used to refer to an exemption from legal punishment or obligation.[5] Early scientists borrowed the term "immunity" and altered its meaning—but only slightly. In the realm of medicine, immunity referred to a natural exemption from infectious disease and indicated the status of being wholly protected against the "punishment" of illness, and perhaps death. The "immune system" itself was named for this version of immunity and, at that point, was essentially a working theory, meant to allude to any biological processes going on inside the body that were responsible for conferring it. At that point, the immune system's sole function was thought to be defense—*and only defense*. Early clinicians like Pirquet and Schick, who observed their patients reacting negatively to the same substances that should have produced immunity, thought that what they were witnessing had to be a phase in the systematic development of defense

against that substance. They saw rashes, fevers, and itching at injection sites as evidence that the vaccines or serums were working; they were causing their patients' defense mechanisms to kick in.

But what if, as Pirquet and Schick began to realize, the immune system could make a mistake? What if our immune systems could make us sick as well as protect us? What if it wasn't just bacteria or toxins that could cause illness, but the so-called immune system itself?

This idea was revolutionary, heretical, and—at least initially—reviled and rejected. It was inconceivable for early scientists working in the field of immunology to accept that a person's immune system could play a role in causing them harm. The human body's production of antibodies[6]—the immune system's ability to create specialized cells that work to counteract harmful invading organisms—was thought to be purely beneficial. The realization that the same immune system responsible for fighting off bacteria might be the root cause of hypersensitive reactions to things like horse serum and pollen flew in the face of decades of work. Pirquet's theory of allergy directly challenged a fundamental tenet of the new field of immunology and, as a result, was largely dismissed. It would take more than a decade for scientists to realize not only that it was basically correct, but that it could be medically useful.

As more and more clinical and laboratory evidence piled up, scientists slowly began to realize that Pirquet's description of allergic reactions was far more prevalent than they had anticipated. At the same time, physicians started to recognize that so-called allergic reactions could also more easily explain many of the chronic illnesses—periodic asthma, seasonal hay fever, recurring hives—they were used to seeing in their clinics. As the years rolled by, the concept was more widely adopted as doctors working to treat otherwise perplexing maladies began to see "allergy" as a way of giving these patients a diagnosis that could at least partially explain what they were experiencing. Over time, the definition of "allergy" shifted to refer almost exclusively to these more troublesome and harmful immune system responses, so-called *overreactions* to otherwise harmless agents.[7]

By the mid- to late 1920s, the nascent field of allergy was just be-

ginning to professionalize as a subfield of immunology.[8] As a term, it was regularly being used interchangeably with words like "sensitivity," "hypersensitivity," and "hyper-irritability" to indicate any overreactive immune response to an otherwise "harmless" substance. One of the leading allergists of the period, Warren T. Vaughan, defined allergy as a "hyper-irritability or instability of a portion of the nervous system."[9] As both a physician and an avid scientific researcher, Vaughan was puzzled by the idiosyncrasy of his individual patients' reactions to allergens. There was no pattern that made sense to him and no explanation for why, when controlling for all other variables, two people might react so differently to the exact same exposure to an allergen. Even more confusing, *the same patient* might respond differently to *the same stimulus* on different occasions or at different times of the same day. It was as if allergic reactions followed no biological rules whatsoever—at least none that Vaughan could easily discern.

By 1930, Vaughan had surmised that the overall purpose of the mammalian immune system was to maintain some kind of "equilibrium" or balance between the organism and its environment. An allergic person's symptoms, then, were simply signs of a temporary or chronic imbalance between that person and the rest of the biological world. Vaughan thought—correctly, as it would turn out—that an allergic reaction began on the cellular level rather than on the humoral, or whole body, level. When an allergic person's cells encountered a foreign substance or experienced an exogenous, or outside, shock, they overreacted, throwing their own biological systems off balance, either temporarily or chronically. The goal of the allergist was to help bring their patient back into a "balanced allergic state"—and then keep them there. The delicate equilibrium between "normal" and "allergic" states of being, at least according to Vaughan, could be upset by any stressor in the patient's life—a bad respiratory infection, a sudden change in temperature, a shift in hormones, or a generalized increase in the patient's level of anxiety.

Other early allergists defined the affliction in a similar way and posited many of the same causes for its onset in their patients. In the United Kingdom, Dr. George W. Bray defined allergy as "a state of

exaggerated susceptibility to various foreign substances or physical agents"[10] that are otherwise harmless. For Bray, both anaphylaxis and allergy were best viewed as "accidents in the course of defense." Dr. William S. Thomas defined allergy as an "altered reaction"[11] and questioned the relationship of allergy to the development of immunity after repeated bacterial or viral infections (itself a faint echo of Pirquet's original thesis that immunity and hypersensitivity were related).[12] By the time of Thomas's writing in the 1930s, allergy researchers had already noted that asthma was often precipitated by a bacterial infection of the lungs and had started to surmise that there was a connection between a patient's prior respiratory illnesses and the development of an allergy. In a publication meant for medical practitioners, Dr. G. H. Oriel argued that there were only three possible states of immune system function: normal (neither allergic nor immune—neutral), sensitization (allergy), and immunity.[13] By the end of the 1930s, the term "allergy" had firmly gone from being a more neutral connotation of *any* biological change induced by an outside stimulus to a wholly *negative* description of a much more limited set of physical reactions to the introduction of any outside substance into the body. As a medical term, "allergy" had definitively shifted "to represent the dark side of immunity" by the 1940s.[14]

This reputation of allergy as "the dark side of immunity" was bolstered in the late 1950s when the famed immunologist Frank Macfarlane Burnet discovered that certain diseases such as lupus and rheumatoid arthritis were ultimately the result of the human immune system's inability to tell "good" cells from "bad" cells, or "self" from "nonself." Autoimmunity—when the body attacks itself—took center stage in immunological research after Burnet realized that the immune system's main function was *not* defending the body from infectious invaders but recognizing the body's own cells from everything else. After coming into contact with something from its immediate environment, the immune system could either choose to tolerate the foreign or "nonself" substance (as it does with most proteins ingested as food) or to attack it (as it does with many viruses and bacteria). In someone with an autoimmune disorder, the immune system

makes a fundamental error, confusing the body's own cells for foreign cells, and becomes hypersensitive—or overreacts—to them. In essence, the immune system triggers a response to the body's own tissues.

Burnet's insights about autoimmunity would provide the groundwork for further scientific research on immune function for much of the twentieth century, as the field of immunology became more and more focused on understanding the development of immune tolerance rather than defense. Today, allergy and autoimmunity are largely seen as variations on the same theme rather than as entirely different problems. Both highlight how the biological mechanisms behind our immunity to disease and our tolerance of natural and man-made substances can go awry. In the twenty-first century, Pirquet's original suggestion that our immune systems could just as easily harm us as protect us is no longer a heresy but rather a commonplace understanding of our overall immune function—and dysfunction.

More recent work in immunology has shifted once again, this time away from Burnet's self/nonself paradigm toward a model that reflects our current understanding of how our own cells interact with the trillions of nonhuman cells, particles, and chemicals in our intestinal tracts, in our nasal cavities, and on our skin. How do our bodies decide what things to tolerate and what things to fight? In other words, our immune cells need to determine when our bodies are in harm's way from something in our environments and when they aren't. How they do this, however, remains a mystery. Dr. Pamela Guerrerio, one of the top food allergy researchers and clinicians working at the National Institutes of Health (NIH), explained that "we still don't understand the mechanisms behind immune tolerance, to be honest, or why we tolerate some things, but not others." Dr. Avery August, an immunologist at Cornell University, told me that debate still rages over what the ultimate function of our immune cells might be. While it is clear that they provide protection against infection, August prefers to think of immune cells as the "curators" of our body, constantly sensing everything we encounter and making millions of microdecisions about which things should become part of the

human body or coexist with us and which things should not. The only thing we seem to know for certain about our immune system is that, as it becomes more irritated in the twenty-first century, it is less and less able to tolerate even some of the stuff that is "good" for us in our environment.

HOW ALLERGY IS DEFINED TODAY

As we've seen, defining exactly what an allergy is has been a problem since its inception. In 1931, the renowned allergist Dr. Arthur Coca argued that using "allergy" as a medical term wasn't particularly useful because clinicians and other nonspecialists tended to use it to mean anything.[15] It had become a "grab bag" diagnosis, used to assuage patients when all other diagnoses and treatments had failed.

Allergists and scientists I talk to often echo Coca's lament: They tell me that one of the toughest and most consistent problems they face is the general misconception about what an allergy really is. In conversations with me they repeatedly argued that the public often uses the term indiscriminately to describe almost any uncomfortable set of symptoms they might experience. If people have frequent indigestion or experience pain after a meal, they may attribute it to an allergic reaction to something they've eaten—like dairy—even though they never visit an allergist to confirm or disprove their suspicions.

Over the past one hundred years, allergy has become a popular and widely used medical concept, but one that isn't always applied appropriately or effectively. Allergists and immunologists want everyone to understand that an allergy is not the same as a sensitivity, an intolerance, or an autoimmune disorder. The main difference lies in the biological processes or immune mechanisms that are activated.

A Quick Primer on Our Immune Systems

The first thing you should know about the human immune system is that it is actually made up of two different systems that work in con-

cert. The innate immune system, fully functional from birth, is a brute-force, first line of defense against foreign invaders like pathogens. Because it reacts in the same way no matter what foreign object it encounters, it is sometimes referred to as the "nonspecific" system. Your skin and mucous membranes—or the outside and inside linings of your body—are part of the innate immune system. If something gets past these barriers, then the innate immune system can activate inflammation to ward off microscopic invaders. Mast cells and basophils (which we've already seen at work during anaphylaxis) are involved in this process. Special scavenger immune cells called phagocytes can engulf or "swallow" bacteria, killing them, and natural killer cells can use toxins to destroy any cells that have already been infected by a virus. These different components of the innate immune system are often enough to ward off infection.

The adaptive immune system kicks in if the innate immune system hasn't been able to deal with the threat. In this book, we're going to pay the most attention to the adaptive immune system because it's behind our hypersensitivity reactions (which include autoimmunity and allergy). As a second line of defense, the adaptive immune system is a "specific" system because it is capable of remembering the specific things it encounters and, upon a subsequent exposure, reacts accordingly. T lymphocytes, a type of white blood cell produced in our bone marrow, have detection features on their surface that attach to foreign invaders like germ cells in our bodies. After coming into contact with a specific foreign invader, some of these T cells can become "memory" T cells. The next time they encounter a similar organism, they can activate the adaptive immune system much more quickly. B lymphocytes, another type of white blood cell produced in our bone marrow, are activated by T cells. B cells can quickly produce large amounts of antibodies and release them into the bloodstream to help fight off foreign cells. Antibodies are Y-shaped proteins that circulate throughout your blood and whose main function is to neutralize foreign substances like viruses and bacteria. Antibodies attach themselves to foreign microorganisms thereby preventing them from being able to attach to or penetrate our own cell walls. At the same time, antibodies

can attach themselves to other immune cells and activate them, aiding in and promoting an overall immune system response. Antibodies are specific to the type of B cell that is producing them and the type of T cell that triggered the process, so they are "ready-made" to defend against a specific type of foreign material that has entered the body—one that the body has "remembered" from a prior encounter.

Our bodies produce five different types of antibodies: IgM, IgD, IgG, IgA, and IgE. We'll meet both IgG and IgE again, but it's IgE that will be the main focus for much of this book. While not all Type I hypersensitivities—also known as allergic immune responses—are mediated by IgE, most allergic responses typically involve the activation of IgE. In contrast, Type II and Type III hypersensitivity immune responses, which include immune conditions like Graves' disease and autoimmune disorders like lupus and rheumatoid arthritis, are mediated by IgG antibodies. For better or for worse, an IgE antibody response has become the main indicator of an allergic-type immune response and is synonymous with allergy. A genetic predisposition to IgE sensitization to allergens in the environment is called atopy. So (and this will be important later), atopy is different from allergy because *while you can have an allergy without an IgE response, you cannot have an atopic reaction without IgE.*

This connection between IgE and atopy was an important discovery that led to major innovations in research on allergic responses and their treatment. However, it also causes confusion when it comes to parsing the differences between allergy, atopy, and things like intolerances or sensitivities (as we'll see in chapter 2 on diagnosis). Because of IgE's central importance as a marker of allergic response, I want to pause here and take a quick detour to explore the discovery of the antibody itself.

The Discovery of IgE

As early as 1906, when he coined the term "allergy," Clemens von Pirquet posited (correctly, as it turns out) that allergens were activating an antibody response in his patients. In 1919, Dr. Maximilian

Ramirez reported that one of his patients had developed an allergy to horse dander after receiving a blood transfusion from an allergic donor.[16] This was proof of Pirquet's guess that something in the blood could transfer an allergic sensitivity, possibly a new type of antibody itself. Then, in the 1920s, Dr. Carl Prausnitz, a doctor working in Germany who was allergic to rye grass, attempted to transfer his own natural allergic sensitivities to pollen to his assistant Heinz Küstner, who was allergic to cooked fish, and vice versa.

By this time, it was clear that skin-prick tests worked to elucidate sensitivities to different allergens (more on this in chapter 2), but the biological mechanism behind those reactions remained a puzzle. After transferring Küstner's blood serum into his own arm, Prausnitz developed a wheal response to fish allergen during a subsequent skin-prick test. Despite several attempts using different blood serums derived from patients with more severe allergic reactions to rye pollen, Küstner never developed a positive skin reaction to pollen himself. Yet Prausnitz's own positive skin reaction to fish proteins had proven that allergic sensitivity could be transferred via blood serum infusions. The pair's research led to the development of the Prausnitz–Küstner reaction, or the P-K test for allergic sensitization, and was widely used by allergy researchers for decades. But even though the P-K test was useful for immunological research on hypersensitivity, the biological mechanisms behind it were clouded. After decades of scientific investigation, immunologists thought it was likely that *some* type of antibody was responsible for inducing sensitivity during the P-K test, yet most of the known antibodies had been ruled out as the culprit.

The stage is now set for the discovery of IgE.

In the late 1960s, two Japanese researchers decided to study P-K activity in the serum of patients allergic to pollen. At the time, immunologists were suspicious that the reactivity of the skin during P-K tests might be related to the action of the antibody IgA. But after several experiments, Drs. Kimishige and Teruko Ishizaka determined that the biological activity they were witnessing could not be caused by any of the known antibodies—IgM, IgA, IgG, or IgD. The Ishizakas' work revealed that a new antibody, which they named IgE, was

binding to mast cells and basophils, helping to drive the allergic response. The Ishizakas' subsequent careful scientific research on IgE function definitively proved it was the antibody involved in most sensitivities or immune overreactions to otherwise harmless antigens or allergens.

An antigen is any substance that initiates an immune system response; an allergen is a type of antigen that triggers an IgE antibody immune system response. In this sort of response, your body's immune cells trigger what's called the Type I allergic "pathway" (which is why researchers refer to allergy as a Type I immune response). Some of your immune cells—a subset of the white bloods cells known as $CD4^+$ T cells known as T helper type 2 (Th2)—signal B cells, another type of white blood cells, to produce IgE antibodies. Of the five types of antibodies found in mammals, IgE is the only one known to regularly bind to allergens to begin an immune response. And unlike the other antibodies, which are found in the blood, lymph, salivary, and nasal fluids, IgE antibodies are localized in our tissues, where they are tightly bound to the surface of our mast cells (some of your immune system's first responders). IgE antibodies are primarily responsible for binding to parasites like intestinal worms, but in an allergic reaction, they trigger your mast cells and basophils (the other first responders) to release histamine and other compounds that then cause inflammation and all of the symptoms you typically associate with your allergy. Atopic, or allergy-prone, people tend to have not only higher levels of IgE but also more receptors for IgE on their mast cells, which is likely part of the reason they are more sensitive to things in their environments in the first place and tend to develop allergic responses to multiple allergens. However, someone who is non-atopic—that is, a person who doesn't have a biological tendency toward sensitivity (we'll look at the difference much more closely in chapter 4)—can still develop an allergic response to bee venom or penicillin, for example, if repeatedly exposed.

The discovery of IgE's role in allergy paved the way for more scientific research on the specific mechanisms or "immune pathways" that a person's body might take to spiral into a hyperactive immune re-

sponse. Scientists and clinicians today distinguish between IgE-mediated allergies (e.g., allergic rhinitis, food allergy, atopic eczema) and non-IgE-mediated allergies (e.g., drug allergy, serum sickness). But in essence, and for all practical purposes, the term "allergy" in the twenty-first century has come to mean *any negative immune reaction driven by IgE antibodies*. The presence of IgE in response to an exposure to an antigen has become the standard of measurement and confirmation for what is known as a Type I hypersensitivity or "allergy."

The Problem with Relying Solely on IgE to Define Type I Hypersensitivity

Using the presence or absence of IgE antibodies alone to categorize an allergy quickly becomes problematic if a patient has low levels of the antibody to begin with. It might also exclude other allergic conditions like eosinophilic esophagitis (EoE) and nonallergic eczema because they are thought to be non-IgE mediated. In fact, serum sickness, or the reaction that Clemens von Pirquet observed in his Kinderklinik and used to coin the term "allergy," falls into the category of non-IgE-mediated allergic disease. People who have asthma or atopic dermatitis and who do not make IgE in response to exposure to an allergen can be classified as having a "Type I allergic disease" because the same core physiological responses are involved, but not an "allergy" in the strictest definition of the term if we use IgE as the litmus test.

It is important to note that some of the experts I interviewed for this book were very comfortable with calling eczema or asthma an allergy; others were adamantly opposed to it. Some felt that the trigger of an asthma attack or an eczema outbreak mattered more than the response. For example, if someone has an asthma attack during strenuous exercise, it would not be accurate to lump that person in with people whose attacks are triggered by *allergens* like the level of grass pollen in the air. Those who argue that the underlying biological mechanisms that drive the response in each case are the same—and