"*The Beautiful Cure* sets the stage for a coming revolution in immunology, with fascinating stories of how researchers solved puzzles they didn't know existed."
NEW SCIENTIST

THE BEAUTIFUL CURE

The Revolution in Immunology and What It Means for Your Health

DANIEL M. DAVIS

The Beautiful Cure

THE REVOLUTION IN IMMUNOLOGY AND WHAT IT MEANS FOR YOUR HEALTH

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THE UNIVERSITY OF CHICAGO PRESS

The University of Chicago Press, Chicago 60637

Published 2018
Printed in the United States of America
27 26 25 24 23 22 21 20 19 18 1 2 3 4 5

ISBN-13: 978-0-226-37100-9 (cloth)
ISBN-13: 978-0-226-37114-6 (e-book)
DOI: https://doi.org/10.7208/chicago/9780226371146.001.0001

First published by Bodley Head, an imprint of Vintage. Vintage is part of the Penguin Random House group of companies.

LIBRARY OF CONGRESS CATALOGING-IN-PUBLICATION DATA

Names: Davis, Daniel M. (Daniel Michael), 1970– author.
Title: The beautiful cure : the revolution in immunology and what it means for your health / Daniel M. Davis.
Description: Chicago : The University of Chicago Press, 2018. | Includes bibliographical references and index.
Identifiers: LCCN 2018010429 | ISBN 9780226371009 (cloth : alk. paper) | ISBN 9780226371146 (e-book)
Subjects: LCSH: Immunology. | Immunity. | Immunotherapy.
Classification: LCC QR181 .D29 2018 | DDC 616.07/9—dc23
LC record available at https://lccn.loc.gov/2018010429

♾ This paper meets the requirements of ANSI/NISO Z39.48-1992 (Permanence of Paper).

Contents

There are mysteries which men can only guess at, which age by age they may solve only in part. Believe me, we are now on the verge of one.

Bram Stoker, *Dracula* (1897)

A note to professional scientists

Immunology is an extraordinarily rich subject and I can only apologise to any scientist whose contributions I have not included or have mentioned all too briefly. As P. G. Wodehouse wrote in *Summer Moonshine* (1937): 'It is one of the inevitable drawbacks to a narrative like this one that the chronicler, in order to follow the fortunes of certain individuals, is compelled to concentrate his attention on them and so to neglect others equally deserving of notice.' Through interviews with the scientists involved and my own reading of the original research I have sought to describe how advancements were made, but any one book can only ever tell part of a story.

Overview

'Look at that flower; look how beautiful it is,' said an artist to his friend. 'Art appreciates and celebrates that beauty, whereas science just takes it all apart. Science makes the flower dull.'

The friend being addressed was Nobel Prize-winning physicist Richard Feynman, and he thought that the artist's view was 'a bit nutty'. Feynman countered that he too could appreciate the flower's beauty, but as a scientist he knew that the inner structure of the flower is wondrous as well – with its cells, its chemical and biological processes, all of its many intricate systems. In addition, Feynman explained, knowing that the flower attracts insects we might deduce that insects find the flower aesthetically pleasing, which in turn raises all sorts of questions about evolution, cognition and light. 'Science,' Feynman said, 'only adds to the excitement and mystery and the awe of a flower. It only adds.'[1]

Feynman related this now-famous exchange in an interview on BBC TV in 1981, when I was aged eleven. I already knew that I wanted to be a scientist, but Feynman, with his strong New York accent and with roses swaying in the window behind him, captured the reason better than I could say myself. Now, leading a team of researchers to study human immune cells in minute detail, I've seen first-hand how science reveals beauty where otherwise it might have remained hidden. The inside of the human body may not have evolved to be aesthetically pleasing like a flower, but splendour ascends from its details.

In all of human biology, the process that's been studied the most, details excavated the deepest, is the body's response to a

cut or an infection. The familiarity of the symptoms – redness, tenderness and inflammation – belies wonders taking place beneath the skin, where swarms of different cells move in to fight off germs, as well as repair the damage and deal with the debris. Far from conscious control, this reflex is essential for our survival.

A simple view of what is happening here is that the body attacks germs which invade the wound because our immune system is programmed to fight whatever is not part of us. But a moment's reflection shows that this cannot be the whole story. Food isn't part of your body and yet your immune system mustn't react to everything you eat. More subtly, your immune system must be able to tell the difference between friendly bacteria that live in your gut, which should be left alone, and dangerous bacteria that might make you sick, which need to be dealt with.

This crucial realisation, that an immune response can't be triggered by just anything alien to the human body, came only as recently as 1989, and it would take many more years before a deeper understanding emerged. In the meantime, a painstaking, game-changing scientific adventure unfolded in which the world of immunity has opened up to reveal what it really is: not a simple circuit involving a few types of immune cells but a multilayered, dynamic lattice of interlocking subsystems, one of the most complex and important frontiers of scientific enquiry we know of. As this book will show, the many discoveries that have resulted from this adventure amount to a scientific revolution in our understanding of the human body and are set to spark a revolution for medicine in the twenty-first century.

For a start, we have come to realise that our body's ability to fight disease is continuously changing. The power of our immune system waxes and wanes, affected by stress, old age, the time of day and our state of mind. Our immune system is in constant flux; our health balanced on a tightrope. For example, the number of immune cells in our blood tends to peak in the evening and is at its lowest in the morning. There are many changes that happen to our immune system during the night,

as our body enters a different state of activity and energy use, and in turn our immune system seems to be affected by how well we sleep. Reduced sleep – less than five hours per night – correlates with an increased risk of the common cold and pneumonia.[2] Among other things, this book will explore the effects of night-shift work on our immune system and whether or not practices that could reduce stress, such as t'ai chi or mindfulness, are able to help us fight infections.

Mysteries remain but already these discoveries challenge the simple view we once held about how our bodies fight disease – and what it takes to be healthy. Even though it's correct – very roughly – that the immune system targets what's not part of you, it has become apparent that layer upon layer of biological checks and balances, run by countless cells and molecules, regulate the process. Resolving the mysteries and the complexities allows us to approach questions of major importance to our health and well-being: why do some people get cancer and can our immune system fight it? How do vaccines work and can we make them better? What exactly is an autoimmune disease and what can we do about it? The vast majority of ailments that afflict us are cured by our bodies' natural defences. Understanding and harnessing this power might turn out to be the one of the most important gifts that science gives for the health of humankind.

While some drugs, such as penicillin, kill germs directly, many human maladies, from cancer to diabetes, may be fought best with new kinds of medicine that enhance (or in some cases suppress) the activity of our immune system. Unlike penicillin, and medicines like it that are made naturally – by a fungus in the case of penicillin – and merely *isolated* by scientists, these new medicines that work with our immune system are *designed* by scientists. Scientists studying the immune system can have ideas which become therapies and multibillion-dollar drugs. But these medicines must be tuned to work with utmost precision. If we over-activate the immune system, healthy cells and tissues will be destroyed, and if we switch it off entirely we will become susceptible to all kinds

of germs that are normally easily dealt with. The potential benefits are transformative but the consequences when things go wrong can be terrible.

The vast endeavour to understand immunity has also thrown up new insights into many other areas of human biology too, such as the ageing process. 80–90% of people who die because of the flu virus are over sixty-five.[3] Why is it that as we age, our defence against infections grow weaker? Why do we heal less easily and are more likely to succumb to autoimmune diseases? We have learnt that part of the problem is that the elderly have fewer of some types of immune cells circulating in their blood. Another is that immune cells in the elderly are worse at detecting disease. Compounding the challenges of ageing itself is the fact that the elderly often struggle with sleep-deprivation and stress, which also affect our immune system. Working out how much each of these various factors affects our health can be extremely difficult because it is almost impossible to isolate any one of them. While stress affects our immune system, it also correlates with sleep loss, making it hard to know the effect of either on its own.

In fact, pretty much everything in the body is connected with everything else – even more so than you might imagine. It has recently emerged that the immune system is intimately connected with a huge range of diseases that appear to be unrelated to its role in fighting germs: heart problems, neurological disorders, even obesity. My first book, *The Compatibility Gene*, discussed one element of the immune system, a handful of genes that influence our individual responses to infections. *The Beautiful Cure* is about the bigger picture: how and why the activity of our immune system varies, how it is regulated and directed, all of its component parts – the whole shebang.

This is also a book about how scientific ideas develop. The quest to understand immunity is one of humankind's greatest scientific adventures, and the impersonal knowledge we have now has been won through a saga of personal hardships, triumphs and sacrifices. Many men and women have devoted their careers, and much of their lives, to understanding a mere

fragment of the whole. This quest has created many deep friendships; passion for science can be a powerful bond. On the other hand, there are a few scientists involved who now can't stand to be in same room together. Countless researchers have contributed, each making wondrous discoveries about particular cells or molecules in our immune system, but in the end, any one person's contribution is small – even the geniuses' – and the sacrifices some scientists have made might seem out of all proportion, beyond what most people would be willing to accept.

My own research involves using specialist microscopes to watch what happens at the point of contact between immune cells when they interact with one another, and to watch the contacts immune cells make with other cells to decide whether they are healthy or diseased. My discoveries have helped show how immune cells communicate with each other and how they detect signs of disease in other cells, which in turn helps us understand precisely how the immune system is regulated. We each add a little, focusing on one part of the system at a time.

When we divide an integrated system into separate elements in this way, it doesn't make it dull – as Richard Feynman's artist friend thought – but it's not entirely fulfilling either. Things work together and each component only makes sense when it's seen as part of a whole. Textbooks about the immune system tend to discuss the role of each molecule or cell in turn, but that's like explaining a bicycle by describing what a wheel is, and then what a handlebar is, and then what a brake is. None of these single elements are properly understood without the others; their meaning lies in the relationships between them. Just as much as the parts build up a system, the system defines the parts. We marvel at the details but we must also pan out to the big picture, because it's only when we do this that we can begin to exploit our knowledge of immunity for a revolution in health.

We will explore that revolution in the second half of the book. First, *The Beautiful Cure* charts the global scientific adventure that has led to it, revealing a world of unsung heroes and rebels who have discovered how and why the immune system

works the way it does. If solace or joy can ever be gleaned from the beauty of nature, then what they have uncovered – the complexity, delicacy and elegance of our immune system – is as inspirational as any other frontier of science, from the substructure of atoms to the birth of stars.

Part One

The Scientific Revolution in Immunity

1 Dirty Little Secrets

What does it take to do something great? In 2008, an experiment was conducted in which experienced chess players were shown a game that could be won using a well-known sequence of five moves. But there was also a more dramatic, unconventional way to win the same game, in just three moves. When asked for the quickest way to win the game, experts usually pointed out the familiar five-move plan, missing the optimal three. Only the very best chess players – the grandmasters – saw the three-move win; ordinary experts stuck to what they were familiar with.[1]

It's in our nature to try to resolve problems using what has worked before. But knowing what worked before can blind us to the insight required for major leaps forward.[2] Our greatest scientists are those who, despite their expertise, remain free to think differently. By this measure, Charles Janeway, an immunologist working at Yale University, was indeed one of our greatest scientists. He was also said to be 'one of the most exciting, decent, and thoughtful immunologists on the planet'.[3]

Born in Boston in 1943, Janeway studied chemistry and then medicine at Harvard. His path to medicine was influenced by his father, an eminent Harvard paediatrician and a department head at Boston's Children's Hospital,[4] but Janeway felt that 'surgery was going to condemn [him] to a life of routine procedures'[5] and he switched his focus to basic research. He married when young but in 1970, aged twenty-seven, he split up from his wife Sally, when their child was aged one. As a result, he 'felt lonely for many years',[6] but gained time and freedom for

his research. In 1977 he joined the faculty of Yale, where he met his second wife, Kim Bottomly, also a well-known immunologist.

In 1989, Janeway puzzled over what he called the 'dirty little secret' in our understanding of immunity. The problem concerned vaccines and the way in which they were thought to work. The basic principle of vaccination follows the familiar idea that an infection, caused by a virus or bacteria, is dealt with much more efficiently if your immune system has encountered that same virus or bacteria previously. So – the dogma goes – vaccines work by exposing you to a dead or harmless version of a germ. By provoking your immune system to build up defences against it, it prepares you to respond rapidly if you encounter the same germ again. This works because the particular immune cells that are activated by a particular germ multiply and persist in the body for a long time, long after the germ has been eradicated, meaning they are ready for action if they encounter the same germ again. And with this, so it seems, one of humankind's greatest medical triumphs can be explained in just a few lines.

But take one step deeper and it turns out that vaccination has a touch of alchemy about it too. The 'dirty little secret' is that vaccines only work well when so-called 'adjuvants' are added. Adjuvants (from the Latin word *adiuvare* meaning 'to help') are chemicals, such as aluminium hydroxide, which, as discovered by chance, help vaccines be effective. At one level it seems such a small thing – aluminium hydroxide somehow helps vaccines be effective – but to Janeway this small technical tip revealed a crack in our basic understanding, because no one could actually explain *why* adjuvants did this. Understanding vaccination is unquestionably important – nothing apart from providing safe water, not even antibiotics, has ever saved more lives[7] – and Janeway was determined to understand precisely why adjuvant was necessary. In doing so, he uncovered a whole new way of thinking about how the human immune system *really* works.

★

The use of vaccination as a medical procedure long pre-dates any scientific knowledge of how the process works. The first descriptions of this vital life-saver can be found in folklore.[8] Deliberate infections to provide protection – inoculations – were practised in China, India and some African countries, long before any formal medical procedure was established.[9] The scientific story begins, however, in 1721, when an epidemic of smallpox made the British royal family anxious, especially for the safety of their children. The royals had heard of rural traditions and stories from other countries about how to inoculate against the disease, but details varied as to how, exactly, the procedure should be performed. Was an application of blister fluid best? Or were hand-squeezed smallpox scabs preferable? It was widely known that people only ever got smallpox once, and so the real issue was whether or not a small dose of smallpox could be given to someone without it killing them. A test was needed to determine the safety and efficacy of inoculation before it was used on the royal family – and prisoners seemed appropriate for the honour.

The first recorded 'clinical trial' in the history of immunity[10] was performed on 'volunteers' who had been recruited on the basis that they could either participate in the potentially deadly trial or face the certain death of judicial execution. On 9 August 1721, incisions were made on the arms and legs of six convicts. Skin and pus from a smallpox patient was rubbed in. Another prisoner was given a sample of skin and pus up her nose – needless to say, to her great discomfort. Twenty-five members of the scientific elite witnessed the event, including fellows of the Royal Society (which had been granted its Royal Charter in 1662 but still only had vague criteria for membership).[11] In accordance with folk wisdom, each prisoner became ill with symptoms of smallpox for a day or two, and then recovered. The woman inoculated nasally became especially ill, but recovered nonetheless.[12] On 6 September 1721, King George I pardoned the convicted volunteers and they were released. Their immune systems had saved them from two death sentences: the gallows and the pox.

A few months later on 17 April 1722, the Prince and Princess of Wales – who in five years would become King George II and Queen Caroline – had two of their own daughters inoculated.[13] The event was covered by all the newspapers and led to considerable interest in inoculation (a reminder that high-profile leaders or celebrities have enormous influence on public attitudes to new scientific ideas).[14] Even so, the procedure remained controversial, in part because, some claimed, the intervention went against Nature or God – a London preacher spoke in 1722 on 'the dangerous and sinful practice of inoculation' for example – but also because around 2% of people died after being deliberately inoculated with smallpox.[15]

Forty-eight years later, a twenty-one-year-old man named Edward Jenner began three years' training at St George's Hospital, London, under John Hunter, one of the most prominent surgeons and anatomists in England. Hunter helped sharpen Jenner's critical faculties and cultivated his passion for experimentation, but he never got to see how his protégé blossomed. Hunter died in 1793, three years before Jenner discovered a way to circumvent the acute danger of inoculation while achieving the same effect.

As a country physician who spent most of his life in his small hometown of Berkeley, Gloucestershire, Jenner was familiar with the fact that milkmaids never get smallpox. His revelatory idea was that perhaps their exposure to cowpox – a mild viral infection that humans could catch from cows – provided protection against smallpox, and that pus from non-fatal cowpox blisters might therefore be used for inoculation instead of pus from smallpox victims, which was far more dangerous. His now-legendary experiment was performed on 14 May 1796. Jenner took pus from dairymaid Sarah Nelmes, who had been infected with cow pox from one of her cows, Blossom, and inoculated his gardener's eight-year-old son, James Phipps. James was then given pus from a smallpox patient and he didn't get ill.

This experiment is often said to mark the birth of immunology but at the time, Jenner had trouble just publishing his findings. The Royal Society said the observation was merely

anecdotal – which it was – and suggested that Jenner should first test many more children before making such bold claims. Jenner did repeat the test on others, including his own eleven-month-old son, but even so, he didn't try to publish with the Royal Society again. Instead, Jenner self-published his work in a large-print seventy-five-page book. Initially available in just two London shops, the book was released on 17 September 1798 and became a huge success.[16] The term 'vaccine' was coined a few years later by a friend of Jenner to describe the process he had discovered, from the Latin word for cow, *vacca*.[17] Smallpox became the first disease fought on a global scale and was officially eradicated in 1980.[18]

Jenner always believed that his work could lead to a global annihilation of smallpox, but he never had a deep understanding of how vaccination worked.[19] By the time of Janeway's epiphany in 1989, the consensus view was that the presence of a germ in the body triggers an immune reaction because the body is primed to detect molecules that it has not encountered before; in other words, that the immune system works by reacting against molecules that are *non-self* – not from the body.[20] After exposure to molecules alien to the body, the immune system is poised to react rapidly if the same non-self molecules are encountered again. But an experiment performed by two different scientists working independently in the early 1920s (it's unclear precisely when),[21] didn't fit this simple view of vaccination, and this puzzled Janeway deeply.

The experiment was performed by French biologist Gaston Ramon and London physician Alexander Glenny. They each discovered that a protein molecule made by the bacteria which cause diphtheria – diphtheria toxin – could be inactivated by heat and a small amount of the chemical formalin. Potentially this meant it might be used as a safe vaccine against the disease. To their surprise, however, when the inactivated protein molecule was injected into animals, the immunity it produced was only short-lived. The observation was seen as mildly curious at the time, and largely forgotten, but decades later Janeway reasoned that protein from the bacteria was non-self – not part

of the human body – and so, according to the consensus view of the 1980s, there was no explanation for why it would not work well as a vaccine. How come the pus from cowpox blisters worked well as a vaccine, Janeway wondered, whereas protein molecules such as diphtheria toxin, which had been isolated from germs, did not?

Glenny was a workaholic, and though extremely shy and not easy to get on with, he was skilled in organising his research, streamlining procedures so that he and his co-workers could perform huge numbers of experiments with great efficiency.[22] He had no time for proper statistical analysis; results were either 'obvious and useful, or doubtful and valueless'.[23] This attitude – go-getting, fast-moving – was an important factor in his lab's ability to screen an enormous number of experimental conditions, seeking a way to make diphtheria toxin work as a vaccine.[24] Eventually, in 1926, Glenny's team found that when diphtheria protein was purified by a chemical process that involved combining it with aluminium salts, it became an effective vaccine. Glenny's explanation was that the aluminium salts helped the diphtheria toxin stay in the body long enough for an immune reaction to develop, but no one knew of any process which could explain how or why this might be.[25] After Glenny, other substances such as paraffin oil were discovered to help vaccines work in the same way that aluminium salts did, and collectively they became known as adjuvants. But still, there was no obvious common feature that explained *why* they worked.

In January 1989, Janeway and his wife, fellow immunologist Kim Bottomly, were discussing what happens in the body when you get a cut or an infection. They realised that they could not easily explain how an immune response starts: what exactly was the trigger? As Bottomly recalled, they often argued about scientific matters in their car and later simply forgot what had been said, but this time they were attending a conference in Steamboat Springs, Colorado, so they had their notebooks with them.[26] The debate stuck with Janeway. For the next few months, he mulled over the problem – how does an immune reaction

start? – as well as the question of how adjuvants work, and it was by thinking about the two problems together that he had a revelatory idea.

An important clue was that a chemical normally found in the outer coating of bacteria (a large molecule with the cumbersome name of lipopolysaccharide, or LPS) had been shown to be an especially effective adjuvant. What if, Janeway reasoned, the presence of something that has never been in your body before was not the *sole* indication that an immune reaction should occur? What if there has to be something else – *a second signal* – that's needed to kick off an immune reaction, a second signal that can be provided by an adjuvant, which might in turn replicate the presence of actual germs? This might explain why protein molecules separated from their originating germ were ineffective as vaccines, but a molecule such as LPS, from the outer coating of bacteria, worked well as an adjuvant.

With great gusto, Janeway first presented his idea in a now-famous paper entitled 'Approaching the asymptote? Evolution and revolution in immunology', published in the proceedings of a prestigious meeting at Cold Spring Harbor, New York, held in June 1989.[27] In it he suggested that everyone seemed to be studying the immune system as if the knowledge was approaching 'some sort of asymptote, where future experiments are obvious, technically difficult to perform, and aim to achieve ever higher degrees of precision rather than revolutionary changes in our understanding'.[28] As a result, they had all missed something big: the 'tremendous gap' in our understanding of how immune reactions start.[29] He suggested that distinguishing between self and non-self was not enough: the immune system has to be able to tell when something is likely to be a threat to the body before an immune reaction takes place, and that therefore the immune system must, he reasoned, be able to detect telltale signs of actual germs or infected cells. He predicted that there had to be a whole part of our immune system, yet to be identified, with this very purpose, and he even predicted a way it could work.

As we have seen and as Janeway pointed out, nobody at this time paid much attention to how an immune reaction started,

and most (if not all) researchers focused on understanding another aspect of immunity, related to inoculation and vaccination: namely, how the immune system is able to respond to germs faster and more efficiently a second time around. It was known that at the heart of this process are two types of white blood cells called T cells and B cells. These white blood cells have an especially important receptor molecule at their surface, not so imaginatively called the T cell receptor and the B cell receptor. These receptors come from the class of biological molecules known as proteins, which are long strings of atoms that fold up into elaborate shapes well adapted for a specific task in the body. In general, proteins bind or join with other molecules, including other proteins, to complete their tasks, and the precise shape of a protein dictates which types of other molecules it is able to connect with, in the same way that two jigsaw pieces interlock by having complementary shapes. The receptor on each individual T cell or B cell has a slightly different shape, allowing it to interlock with a different foreign molecule. It reaches out from the immune cell's surface into its surroundings, and if it connects with something that hasn't been in your body before, it 'switches on' the immune cell, which then kills the germ or infected cell directly, or summons other immune cells to help. Crucially, the activated immune cell also multiplies, populating your body with more cells that have the same usefully shaped receptor. Some of these cells stay in the body for a long time, which is what gives the immune system a *memory* for germs that have been encountered before – which is, of course, at the heart of how vaccination works.

Importantly, receptors on T cells and B cells are not made to bind germs per se; these receptors have randomly shaped ends, which allow them to lock onto all kinds of molecules. The way in which the body ensures they only latch onto germs is one of the greatest wonders of the immune system, and works as follows. Each T cell and B cell acquires its receptor while developing in bone marrow. A shuffling of genes as the cell develops gives each cell a uniquely shaped receptor. But before entering the bloodstream, each individual T cell and B cell is tested in case its receptor

is able to bind to healthy cells. If it is, then that particular T cell or B cell is killed off, because it would be dangerous to have such an immune cell in the body. In this way, only T cells and B cells that won't attack healthy cells are allowed to defend the body, and by the same logic, if a receptor on a T cell or B cell does bind to something, that something must be a molecule that hasn't been in your body before. In formal language, this is how the immune system is able to distinguish *self*, the components of your body, from *non-self*, anything that's not part of you.

What Janeway predicted was that this is not the whole story. Specifically, he predicted that there must be receptors (which he called *pattern-recognition receptors*) that are not randomly generated and then selected, but rather have fixed shapes that interlock specifically with germs or infected cells (or rather with *molecular patterns* that are found only on germs or infected cells).[30] Because this appeared a much simpler way for immune cells to detect germs compared with the elaborate process of making immune cells with randomly shaped receptors and then killing off those which might react against healthy cells, Janeway suggested that receptors with fixed shapes probably evolved first to defend against disease, and only later, when life on earth became more complex, did a more elaborate immune system develop, which then included T cells and B cells.

The simpler system of fixed pattern-recognition receptors that Janeway predicted forms part of the system often called *innate* immunity, by contrast with the aspect of our immune defence that accounts for its memory of past infections, which is called *adaptive* immunity. The term 'innate immunity' was already used before Janeway – to describe early-acting defence mechanisms provided by skin, mucus and the immediate actions of immune cells that move into a cut or wound – but the subject was given only a few pages in textbooks, including the bestselling one written by Janeway himself.[31] What made Janeway's ideas revolutionary was that he essentially changed the immune system's mission statement. Before Janeway, the *raison d'être* of the immune system was to react against things that have never been in your body before. But Janeway said that the immune

system must respond to things that haven't been in your body before – *and are from germs*.

In hindsight, it's blatantly necessary that the immune system has to do more than merely react to things that have never been in your body before. Things such as food, harmless gut bacteria or dust from the air – all not part of the human body – pose no danger and should not trigger an immune reaction. But as George Bernard Shaw put it in 1930: 'science can never solve one problem without raising ten more problems'.[32] Leaving aside the biggest problem Janeway's ideas faced, which was a lack of experimental evidence to support them, there was a theoretical problem too: germs increase in number rapidly. Just how fast germs multiply is mind-boggling. One virus-infected human cell can produce a hundred new virus particles. This means that just three copies of a virus going through four rounds of replication – taking a few days or so – leads to 300 billion new virus particles.[33] It's not just viruses that behave like this; bacteria divide every twenty minutes in optimal conditions, which means one bacterium can produce 5 billion trillion (5×10^{21}) bacteria in a single day – something like the number of stars in the universe.[34] In practice, germs can't multiply to such an extent within the human body because this level of growth requires an unlimited amount of resources, but even so, germs reach enormous numbers fast; far quicker than our measly average of about two offspring per couple's lifetime.[35] This leads to a crucial problem with Janeway's idea: each time a germ reproduces, it acquires random changes in its genes – mutations – and through these changes it seems likely if not inevitable that some will lose the molecular signature detected by the immune system. In other words, in the whole population of viruses or bacteria, some of them will by chance – because there are so many – have acquired a genetic change which alters the part of the germ which the pattern-recognition receptor was designed to lock onto. Microbes lacking the 'molecular pattern' would escape detection by the immune system and multiply readily.

Janeway realised this and so he predicted that 'the pattern recognised should be the product of a complex and critical

[process] in the microorganism'.[36] In other words, the telltale structure of a germ would have to be something so critical to its lifecycle that it would be exceptionally difficult, if not impossible, for the germ to alter it. Janeway had evidence that germs do have features such as these, which are both intrinsic to their survival and also vulnerable to attack, because a feature such as this is what allows penicillin to work. Every time one bacterium divides, it needs to build a cell wall to envelop its two daughter cells. Importantly, the process is so complex that bacteria can't easily change it. Penicillin works by interfering with the last stage of the process. As a result, there isn't any simple genetic mutation that would allow bacteria to escape penicillin's effects. True, bacteria *can* become resistant to the antibiotic by making their cell walls with a very different process, but it's not easy, which is why penicillin remains effective against a huge number of microbes: it locks onto bacterial protein molecules involved in an essential and complicated process.

One scientist recalls that when Janeway presented his paper the audience was 'intrigued but not convinced'. Another recalls that the 'community was not ready for Charlie's thinking'.[37] Standing before many of the world's greatest immunologists, Janeway had the confidence to claim that everyone had missed a hugely important part of how the immune system works, even though, as he put it himself, 'experimental verification … is not available'.[38] Quite simply, at the time, nobody could say if Janeway's ideas were revolutionary or fanciful bunkum.

Janeway's paper was all but forgotten; hardly referred to in another scientific paper for the next seven years.[39] But it touched one person – 4,500 miles away – who would, against the odds, bring Janeway's ideas out of obscurity. In autumn 1992, a student at Moscow University, Ruslan Medzhitov, read Janeway's paper and it changed his life.

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Born in Tashkent, Uzbekistan, Medzhitov was working for his PhD in Moscow, studying how molecules have evolved to stick

to each other, when he read Janeway's paper. The Soviet Union was breaking up and scientific research in the country was in trouble; Medzhitov remembers it as 'a time of huge chaos, with no funds available'.[40] As a result, he could not gain practical experience of working in a lab and had to spend his time thinking and reading, with easy access only to old textbooks that he found quite confusing.[41] Students weren't actually allowed in the library that held a copy of Janeway's paper, but Medzhitov charmed his way in. Browsing the shelves, he stumbled upon Janeway's paper and was immediately gripped by its logic. 'It was one of those moments when a light bulb goes on … it felt visceral … it seemed to explain everything,' Medzhitov recalls.[42] He spent half his monthly stipend on photocopying the paper.[43]

Excited to discuss its ideas further, Medzhitov started sending emails to Janeway. To do so, he was given permission to use the department's email account which had a limit of 300 words per day on account of the costs. Medzhitov recalls how he had to save his message for Janeway onto a floppy disk, which he then gave to the person in charge of the one computer in Moscow University that was connected to the Internet. Any reply that came back would also be copied onto a floppy disk and returned to him that way.[44]

Janeway was proud of his ideas about innate immunity and felt dismayed that they were largely ignored by the immunology establishment, so he was thrilled to receive emails from a student in Moscow wanting to discuss things further. Eventually, Medzhitov asked if he could work in Janeway's lab at Yale. Janeway bounced the idea off his wife but she was sceptical. Medzhitov, meanwhile, won a research fellowship to work for three months at the University of California, San Diego. He borrowed the cost of the flight from a cousin and began working there in 1993, writing software that could scan and organise genetic code – a new area of research at the time. Crucially, he gave a seminar on his work, in broken English, attended by then president of the American Society of Immunology, Richard Dutton.

Dutton was impressed. Medzhitov told him that his fellowship was ending soon and that he was in correspondence with

Janeway by email and he would love to work there. So Dutton left a message on Janeway's answering machine to tell him he thought Medzhitov was a good scientist. And the next morning Medzhitov had an email from Janeway offering him a job.[45]

On 2 January 1994, Medzhitov finally met Janeway face to face. Both were big-picture thinkers, passionate about ideas, and a lifelong partnership and friendship began. The duo's immediate mission was to find out if human immune cells really did have 'pattern-recognition receptors' able to detect telltale signs of germs. One example was all they needed but the problem was formidable, and it didn't help that Medzhitov had so little practical experience. As Roald Dahl wrote in his final children's book, it always pays to 'watch with glittering eyes the whole world around you because the greatest secrets are always hidden in the most unlikely places'.[46] And so it was for Medzhitov, whose eventual success had its roots in an unlikely source: insects.

Like us, insects are also under threat from germs, such as bacteria and fungi, and yet, as scientist Pierre Joly noted in the mid-1960s, insects never seem to suffer from an opportunistic infection. Working in Strasbourg, Joly observed this to be the case even when he transplanted organs from one to another and surmised that insects must have some kind of especially potent immune defence. Joly was joined in his lab by a twenty-three-year-old PhD student named Jules Hoffmann, keen to study insects because his father was an entomologist. Hoffmann set out to understand the insect immunity that Joly had observed and began working with grasshoppers.

When Joly retired in 1978, Hoffmann, then aged thirty-six, became the head of the lab. Over time, Hoffmann shifted the team's focus away from grasshoppers and onto a small fly, drosophila, which feeds and breeds on fruit. Fruit flies were initially used for research in the early 1900s because they're easy to keep, with a simple diet of food scraps, and have a short, two-week lifecycle. Subsequently they have played an enormous role in biomedical research and are at the heart of no fewer than six

Nobel Prize-winning discoveries.[47] But for Hoffmann, another practical reason for switching to fruit flies was that half of his team had become allergic to grasshoppers. Hoffmann's wife Danièle, who had also been his PhD student, was affected especially severely.[48]

Hoffmann's team injected bacteria into the fruit fly and then periodically tested the fly's blood for its ability to kill other bacteria. Once the fly's blood had gained antibacterial properties, Hoffmann knew an immune response had been switched on. His team then set about answering two crucial questions. What kinds of molecules had endowed the fly's blood with an ability to kill germs? And second, which genes controlled the fly's immune response? The first question turned out to be quite easy to answer. Specific kinds of molecules (short pieces of protein, known as peptides) had been identified in silk moths as being antibacterial, and Hoffmann's team found similar molecules in their flies, with different ones being able to kill different kinds of germs.[49] From 100,000 flies, for example, Hoffmann's team isolated the peptide which flies use to kill fungi (nowadays it could be done using about twenty flies).[50]

To answer the second question – which genes are important for a fly's immune response – it turned out that Hoffmann's choice of the fruit fly as the subject of his enquiries was crucial because the insect's genetic make-up was being investigated in other labs for all kinds of other reasons. This separate work gave Hoffmann's team vital clues. One clue was that an insect gene named toll – from the German word *toll*, meaning 'great' – which was important in the development of the fruit fly embryo turned out to be similar to a human gene (called the IL-1 receptor) already known to play a role in immunity. Also, certain genes present in both flies and humans (known as NF-kappa-B transcription factors) had recently been discovered to be important for human immune responses.[51] Spurred on by these recent discoveries, Hoffmann's team set about testing if flies with specific genes inactivated had any difficulty in dealing with infections.[52] Crucial experiments were performed by Bruno Lemaitre, who had joined Hoffmann's team in November 1992.

Over a series of experiments spanning 1993–5, he discovered that flies were dependent on the toll gene to be able to clear fungal infection.[53] This was a spectacular discovery – firmly establishing that genes involved in the embryonic development of the fly were also part of its immune system – and was immediately recognised as such.[54] In September 1996, the front cover of one of the world's most prestigious science journals, *Cell*, showed a striking photo of a fly with an inactive toll gene, covered in a fuzzy-looking fungus.

In June 1992, before this discovery had been made, Hoffmann had travelled to Yale to meet Janeway because, Hoffmann recalls, he 'didn't want to live all his life in an insect ghetto'.[55] These discussions had led to a joint research programme to compare immunity in insects, mice and humans, and, in 1993, Hoffmann organised what was probably the world's first meeting devoted to innate immunity, which was held in Versailles.[56] In spring 1996, at a follow-up meeting in Gloucester, Massachusetts, Hoffmann first told Janeway and Medzhitov about his team's discovery: that the toll gene was important in the insect's defence against a fungus. Janeway and Medzhitov were thrilled.

The precise sequence of subsequent events varies according to who's telling the story. Medzhitov says that he had already been working on a human gene similar to toll for some time, while others suggest that the discoveries in insects *led* him and Janeway to then search for something similar in humans.[57] Either way, Medzhitov, working in Janeway's lab, ramped up work on the human equivalent of the insect toll gene and the important thing is that he discovered that it could switch on the activity of other genes (specifically NF-kappa-B transcription factors) known to be involved in immune responses.[58] Put together, the implication of these discoveries was profound: they showed that life forms as different as insects and humans share a genetic heritage for fighting disease.

Other research teams then uncovered many more genes, in mice as well as humans, like the insect toll.[59] Collectively, they are called toll-like receptor (TLR) genes – named for being a set of genes where each encodes for a receptor protein