VINTAGE

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About the Author

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Also by Daniel M. Davis

The Compatibility Gene
The Beautiful Cure

To Katie

Come with me
On a journey under the skin
We will look together
For the Pan within.

The Waterboys

A Note to Professional Scientists

Human biology is a vast realm of science. None of it – the journey, the knowledge or its implications – is simple. I can only apologise to anyone whose work I have not included or mentioned all too briefly. Every discovery involves many students, postdocs, colleagues and collaborators, and at some level every scientific achievement is owed to a community. I apologise especially to anyone who played a role in the work I discuss here, but have not named. Through interviews with many scientists and my own reading of the original research I have sought to describe how advancements were made, but any one book can only tell part of a story. For that, I apologise in advance too. Finally, I have changed a few details in the medical stories I present in order to conceal some people's identities, but everything else of those stories is accurate and true.

Introduction

Imagine yourself as an alien with an exceptionally powerful telescope trying to understand what happens on Earth. You come across a soccer match, but your telescope isn't powerful enough to see the ball. You can make out a pitch with goals at each end, and players moving about, seemingly with some sort of organisation, but it's hard to understand what is happening precisely. You publish the observation in the *Alien Journal of Earth Science*. A few other aliens email you congratulations, but only a few.

In time, alien telescopes improve, and then occasionally you see one of the players in front of one of the goals fall over. Sometimes this is followed by the crowds of people around the pitch waving and cheering. It still doesn't make much sense, but leads to discussion at the bar during the Alien Congress of Earth Science, and your research funding is renewed. Eventually, when you are much older, a younger alien working with you notices something especially intriguing. When the player in front of the goal falls over, whether or not the crowd cheers seems to depend on one thing: whether or not the net bulges outwards. This leads your younger colleague to have a brilliant idea.

While others might have dismissed the observation without thinking very deeply about it, she wonders if there might be something there which causes the net to bulge – a ball – but it's just too small to see. At first you don't believe her, but the idea grows on you. With a ball, everything else starts to make sense: the movements of the players, the net, the cheers, the whole game, and in time other aliens agree, there has to be a ball there. Even though nobody can see the ball directly, everyone agrees it's there because so many things make sense if it is. You, your colleague and the alien who invented the super-powerful telescope collect many prizes, and everyone wants to be your friend.

Alien telescopes might improve again so that the ball is eventually seen. But equally, this might not happen. A heavy weight of evidence suggests the ball is there, but there may be no direct proof. At some level, it's debatable whether anything can ever be proven absolutely: there is no way of proving the sun will rise again tomorrow, just a heavy weight of evidence that says it will.

This tale of aliens and sport reflects how many discoveries are made. Take, for example, the discovery of the planet Neptune, first seen in 1846. The movement of another planet, Uranus, had been carefully tracked, and mathematical calculations showed that it didn't quite follow a simple orbit around the sun. This could be explained if an unseen planet was pulling on Uranus to influence its path. British and French astronomers calculated where such a planet would have to be located if it were to account for the distortion in the movement of Uranus. Then, with a telescope pointed precisely at the predicted place, the new planet was seen – Neptune. Today, a substance called dark matter and a force called dark energy are predicted to exist in order to explain the movement of stars and galaxies. As yet, both remain unseen.

Throughout almost all of history, most wonders of the human body have been hidden from view and barely imaginable. Some of our inner anatomy – bones, muscles and a few major organs – has always been available to scrutiny (albeit with a bit of delving beneath the skin), but the vast majority of our body's secrets have, until relatively recently, been the stuff of hypothesis and speculation. The discovery of cells made possible by the invention of the microscope in the late seventeenth century presaged the beginning of our modern understanding of human biology, and the discovery of the structure of DNA in the middle of the twentieth century was another gargantuan step forwards as it revealed how genetic information is stored and replicated. Most recently, however, a whole series of technological and scientific revolutions have taken place that are revealing hidden landscapes within the human body as never before – confirming some hypotheses, undermining others and, above all, leading to a whole new realm of possibilities, both theoretical and practical.

What we are learning is that the human body is a world full of other worlds. Every organ is a menagerie of cells, and each cell has its own inner cityscape of scaffolds, capsules and monorails, all fabricated from a bewildering array of biological building materials: proteins, sugars, fats and other chemicals. Our raw materials are nothing special – oxygen, carbon, hydrogen and a sprinkling of other elements – but, put together in an exceptional way, these raw elements create a body that is conscious, self-healing and capable of poetry. We know of nothing else quite like us in the universe; there may *be* nothing else like us in the universe. Surely nothing can be more profound or enlightening than understanding how we work. And new instruments and tools, from microscopes to complex data analytics, are providing this understanding by peeling back layers of the body like never before.

Of course, all science has an ever-increasing impact on our lives, but nothing affects us as deeply or as directly as new revelations about the human body. There are any number of examples: analysis of our genes presents a new understanding of our individuality; the actions of brain cells give clues to how memories are stored; new structures found inside our cells lead to new ideas for medicine; molecules found to circulate in our blood change our view of mental health.

This book explores the recent breakthroughs in human biology that, I will argue, are vital to our future. Any number of frontiers can be considered important, but I will consider six which are unquestionably thrilling and especially impactful: the individual cell, the embryo, the body's organs and systems, the brain, the microbiome and the genome. Some of these topics you may have encountered before. If so, I hope to show how new details have recently come to light that are radically changing our understanding and capability. Other topics you may not have heard of, but are every bit as vital and game-changing as the ones that grab newspaper headlines. And at each frontier, I will show how new discoveries look set to change, or have already changed, our day-to-day lives, not to mention our overarching sensibilities and aspirations. By gathering them together in this way, I want to show that we are at the dawn of an enormous, sweeping sea

change in how we live our lives. It is not self-driving cars or robots that are going to have the biggest impact on us in the foreseeable future: it's new human biology.

More than this, what is occurring in the study of human biology is reminiscent of the revolution that took place in physics during the late nineteenth century. In 1887, the German scientist Heinrich Hertz found a way to produce 'mysterious electromagnetic waves that we cannot see with the naked eye'. Consistent with a theory developed earlier by James Clark Maxwell, Hertz showed that light is merely one type of electromagnetic wave, and there are others which we cannot see, which we now know include X-rays and radio waves. At the time, it was far from clear what the practical implications of this might be – or even if there were any. Hertz died in 1894, aged thirty-six. He could not have envisaged that his work would eventually lead to the radio, the TV and the Internet. Likewise, discoveries being made about the human body now are going to impact us, our children and grandchildren, in more ways than we can even imagine.

This book is also about *how* science reveals the body's secrets, in behind-the-scenes stories of people and technology driving everything forward. As we saw for the aliens, improvements in telescopes were vital for the discovery of the soccer ball. Likewise, disruptions and advances in the prevalent understanding of the human body are often brought about by the development of new technology. New scientific tools and instruments affect our lives in quieter but no less profound ways than mobile phones and social media.

Using a simple microscope in 1665, Robert Hooke saw minuscule compartments within slivers of cork, which he called cells. With today's microscopes, we can see cells shoot out protrusions, nets and packets of molecules; we see how they crawl about within our organs and tissues; and we witness the actions of enzymes and genes as they are turned on and off within them. Today's microscopes are in fact nano-scopes, capable of revealing the human body down to a few billionths of a metre.

As well as revealing new wonders about how cells work, these discoveries radically transform our ability to manipulate the body.

In my own laboratory, we have used these new kinds of microscope to watch how immune cells are able to detect cancer cells and then kill them. Watching these processes unfold at a molecular scale helps us understand how immune cells recognise cancer cells and, on the flip side, how cancer cells try to avoid being caught, all of which seeds new ideas for medicines. There are currently over 3,000 clinical trials in progress, testing new cancer medicines that work by switching on or boosting the body's immune cells. Our understanding of how different immune cells react to COVID-19, and how this varies from person to person, relies on these same tools and techniques. Indeed, if there is one realm of science moved centre-stage by the arrival of COVID-19, it is human biology. Everything discussed in this book, from understanding the immune system to the human mind, also relates to what needs to be known about this virus and the next one.

But while new microscopes reveal all manner of details and opportunities, they also lead to an overarching problem. One type of microscope may capture detail best, but it takes a long time for such an accurate image to register, so another type of microscope is best for seeing movements of molecules, though it does so with less precision. A third type of microscope, meanwhile, sacrifices precision and movement in order to take a wider view – to see, for example, a slice of an organ rather than a minuscule area inside a single cell. Meanwhile, mathematical analyses and computer simulations offer a completely different perspective on the body altogether, as do analyses of gene activity or protein levels in individual cells and so on. Trying to understand the human body in this way is like trying to appreciate the *Mona Lisa* by careful examination of her left eye, or just a fragment of her brown iris. Wondrous as that is, it is not the whole *Mona Lisa*. Even the whole *Mona Lisa* is not the *whole Mona Lisa*: the painting's meaning shifts when you learn its monetary value, or about the life of Leonardo da Vinci, or how the painting deviates from other portraits from the sixteenth century. There are countless ways to understand the *Mona Lisa*, and there are countless ways to understand ourselves.

The complexity of the human body means it can only be revealed part by part, tool by tool. Just as an expert in the taste and colour of wine will gain much by being aware of the chemistry

that underlies those qualities, so each perspective on the body can potentially enhance the others. And yet every scientific tool, from microscopes to mathematics, and every aspect of the body, from the brain to the microbiome, requires such depth of expertise that this tends not to happen: we tend to study the human body in silos, each community insulated from the others by its own specialised vocabulary of symbols and acronyms necessary to communicate nuances. Research communities may be dedicated to one type of scientific tool or a specific component of the body, such as one type of cell. How different types of cell communicate with one another becomes its own specialist topic. Even simple forms of life on Earth such as an individual bacterium are now rarely studied as a whole, and the human body is manifestly much more complex. As long ago as 1890, *The Times* newspaper commented that knowledge 'had already become too vast to be manageable'. Today, nobody is an expert in the whole of anything.

Many books have examined one or other specialist topic about the human body. My hope for this book is that by bringing together six key areas of contemporary biological investigation that are normally dealt with separately, we might regain a sense of the whole body and begin to see not just what the new science shows, but what it all means.

This is hard. As knowledge has become so vast, we have had to come to terms with thinking about our own body in the same way that physicists have had to deal with light being described as waves, particles or mathematical symbols. Likewise, because the human body is more complex than words or diagrams can easily depict, almost everything in a textbook is an approximation or a fragment of the whole. The deeper we examine the body's cells, for example, the more difficult it is to establish what a cell really is. Cells can swap their genetic material, for example, or directly share their innards, and some can merge together to become super-cells. Where one cell ends and another begins becomes harder and harder to define. And if cells seem hard to define, then what looked like a simple rule – all life is made up from cells – also becomes less clear. Sometimes, greater knowledge of a part leads to a diminished understanding of the whole.

For the aliens to understand soccer, the discovery of the ball was only a starting place. There's so much more to the game: the different skills of players, the tactics they use, the offside rule, the offside trap, the penalty shoot-out, the league table, knock-out tournaments, the player transfer market, the sale of television rights, the way kids playing in a school playground are influenced by their sporting heroes, the knock-on effects of traffic jams after an important Premier League match. Everything has so much depth – soccer, the *Mona Lisa*, and especially us.

But we must try to embrace it all. Because research doesn't simply lead to ever-increasing detail in our knowledge of the body's mechanics, as might be depicted in increasingly complicated textbook diagrams. This knowledge also has a huge influence on how we think of ourselves and the narrative we give to our lives. It was once thought, for example, that the body was governed by four liquid humours – blood, yellow bile, black bile and phlegm – and that illness was a result of an imbalance of one humour over the others. The truth about disease is, of course, far more fantastical than this, but it was not until the 1860s that one of humankind's greatest discoveries, the discovery of germs, opened the way to our modern understanding. For anyone alive now it is very hard, if not impossible, to know what it *felt* like to be suffering from an imbalance of the humours, but we can be sure that people did. At one time, we interpreted someone hearing voices as relevant messages from supernatural entities or an act of sorcery; now, we tell a different story about the human brain and psychosis.

More recently, we have been discovering that even germs do not account for all illness. Cancer comes about when cells in the body lose control and multiply excessively. This leads us to an awareness of all sorts of factors that we now know also contribute to ill health: excessive exposure to sunlight, radiation, chemical carcinogens and so on, which can start cells on the road to becoming cancerous. Allergies, too, have little to do with germs. Thinking about allergies has led us to other ideas about health and disease, such as the idea that some level of childhood exposure to microbes might be important in training our immune system for health: the so-called hygiene hypothesis. Understanding these

causes of different kinds of disease most obviously gives us new ideas for medicine, but it also shifts the way we feel about our body and our environment: the feeling of sunlight on our skin or of growing up on a farm has been changed by the relatively recent discovery that one can be damaging and the other might be beneficial.

The effects of science on our lives also extend far beyond illness and medicine. For example, understanding evolution led to a profound alteration in our sense of origin. The fact that we share a huge fraction of our DNA with chimpanzees, and even a fruit fly, connects us in a profound way to all life on Earth. More practically, understanding hormones shapes our attitudes to teenagers, and knowing about the effects of trauma and deprivation influences how we tackle crime. There is almost no aspect of our lives that isn't framed by science's description of what's happening deep down.

Alice (that's not her real name) lost her mother when she was five years old. Her mother had died suddenly from a heart attack. Growing up in the 1980s and 1990s, Alice was bombarded with adverts promoting all kinds of products which could supposedly help keep cholesterol low, to avoid a heart attack. Alice was already anxious that she might die young, and the adverts didn't help.

One day, a letter arrived from a hospital she had never been to. The letter discussed another relative's medical situation. This relative had recently had a heart attack, and thankfully survived. But because two heart attacks in young people within the same family are very rare, doctors studied the possible causes closely. It became apparent that the two heart attacks, and other medical issues in the family, were almost certainly related to a genetic variation. By analysing blood from Alice's relative, a specific mutation had been found. The letter asked Alice if she wanted to find out whether or not she had inherited the problem.

Making a decision was especially difficult for Alice because the scientific details were vague (and they still are). The precise level of risk caused by her family's genetics was not clear. Several different mutations within the gene in question had been found in

people with heart problems, but the relative risk of each – some were bound to be more dangerous than others – was not yet clear. Despite all the uncertainty, Alice went ahead with a genetic test. A few days after giving blood at her local surgery, she phoned to get the results. All of a sudden, a huge restraint on her life evaporated; she was fine, very unlikely to be at an increased risk of suffering her mother's fate. And from this, Alice's life story suddenly shifted. Day to day, she worried less about what she should or shouldn't eat. More importantly, the way she related to her parents and her family at large changed, and what she thought about having children herself. By now she was already middle-aged. Who knows what life decisions she might have made differently had this all been known earlier?

Inevitably, this kind of situation – new science shifting the way we see our lives – will arise more and more. Right now, however, a lot of that is hidden away, only discussed in detail in research labs or at the hotel bar of a scientific conference. This book will, I hope, bring the most important of that science out into public view.

To take one example, which will be explored fully in Chapter Three, let's consider again one of the new discoveries about cells. Perhaps on the face of it, basic research about the fundamental nature of cells might seem unlikely to raise any important or difficult dilemmas for our lives or for society. But I think it will.

A nerve cell is evidently different from an immune cell, and both of these are different from a kidney cell or a heart cell. But all these types of cells – nerve, immune, heart and kidney cells – are only very coarse descriptors. A fascinating new area of cell biology builds upon the idea that, on a subtle level, every single cell has its own uniqueness, influenced by its location, its age, its state of activation, its history in the body and what other cells are interacting with it. A huge global endeavour every bit as ambitious as the Human Genome Project is now under way – the Human Cell Atlas project – in which over 10,000 scientists have come together to identify and classify all 37 trillion cells of the human body. By comparing individual cells in depth – by analysing the level to which genes are activated in them, how many copies of each protein is present in them, and so on – we can classify single cells with unprecedented detail. Some of those overseeing the project

hope that by scrutinising the body's cells at this scale, we could establish a periodic table for human cells – a way of organising every cell's differences in one chart that makes sense of their variety. Whether or not this particular aim pans out, everyone agrees that the project will lead to a deeper understanding of the way tissues and organs are constructed, which cells derive from which other cells in the body, and what goes wrong in disease. Excitingly, the project has already found previously unknown cells in the human body: a new type of immune cell and a new cell in the lining of the lung.

Currently a person's health is often assessed by a blood count – a simple count of how many platelets, red or white cells are present in the blood. But soon, building on the Human Cell Atlas project and related research, we will be able to assess in great detail the types, status and history of a person's blood cells. This is especially important for white blood cells, a catch-all term for countless different types of immune cells, which we already know can vary hugely between people in their specific characteristics. At the same time, the 150-year-old technique of staining tissue biopsies to categorise disease, routinely done in a hospital histopathology lab, is likely to be replaced by a far more in-depth molecular-level profiling. Taken together, these analyses will allow us to diagnose disease states to an unprecedented degree which, it is hoped, will allow us to predict whether or not a particular medicine is likely to work or could lead to toxic side-effects.

On the face of it, this is all very good news, but the implications of scrutinising the vast diversity of the body's cells reach far beyond the medical sphere. As we learn about the composition and status of the body's cells in large numbers of people, this will inevitably establish streams of new metrics by which to measure our health. Which is where things become unsettling. Inevitably, the medical profession will be asked to define what constitutes a 'normal' range for the prevalence and properties of these cells, which must in turn lead to those of us whose cells fall outside that range being categorised as 'abnormal'. We are already familiar with the idea of the body-mass index, a value derived from a person's weight and height, being used to categorise us as underweight, normal weight, overweight or obese. With the

advent of new metrics by which to define a person's state of health, a whole host of new ways will arise to categorise us as normal or abnormal. Everyone will fall short in some way if enough things are measured. There are obvious implications here for health insurance premiums and, more importantly, for our psychology: such categorisation can be deeply troubling, both for an individual person's sense of self and for society's view of human diversity.

It may be that we become blasé about metrics of well-being, but so far we haven't seen any sign that this will happen. To the contrary, many people suffer from the baggage that comes with being labelled obese, for example. Somehow, being thin has come to imply attractiveness, self-control and even a kind of superiority. As we discover more and more about what makes each of us different, it becomes increasingly difficult to see what is and isn't a useful label on a person's health. Or what warrants medical intervention and what shouldn't. Many diseases are already hard to define. A person showing a set of particular behavioural traits can lead to a diagnosis of schizophrenia or autism, for example, but there is no clear-cut delineation that allows us to assess a person's behaviour and be able to state categorically that this side of the line is normal and that side is abnormal.

Just as physicists who set out to study the nature of atoms unwittingly changed the nature of bombs, so anyone working on basic science projects about the human body is likely to change society, whether they intend to or not. Which is not to say that the research should stop, or that scientists involved in this endeavour, myself included, are directly involved in something destructive; rather that, as big new concepts are opening up about how the human body works, the implications are huge, potentially explosive, and will continue to be so for some time to come.

In this book, I want us to take stock of where we're at: to immerse ourselves in the splendour of it all and to understand how we've achieved all we know – but also to think deeply about what all these new discoveries mean for our lives. I will not be afraid to speculate where they might lead and, where necessary, to challenge their direction.

in endlessly, because of the way light spreads out and bends around small objects: a feature called diffraction. The highest resolution any microscope could achieve would be about half the wavelength of light, roughly 200 nanometres (200 x 10^{-9} metres), or about 1,000 times less than the width of a human hair.[6] It's hard for us to imagine such a minuscule distance, but all sorts of wondrous and important things are smaller than this, from the structures within a butterfly's wing that provide their iridescent colouring to the HIV virus that has killed 35 million people. Other scientific instruments allow us to detect these things, albeit with difficulty, but crucially none works with living specimens. An electron microscope, for example, requires its specimen to be bathed in chemicals and then placed in a vacuum chamber.[7] Only a light-operated microscope lets us witness processes in a living cell directly, and Abbe's law seemed an insurmountable barrier to doing so beyond a certain point. On a memorial to Abbe in Jena, Germany, where he lived and worked, his law, given in mathematical notation, is literally written in stone.

And yet now, thanks to a series of discoveries so ingenious and circumstances so unlikely that they would be dismissed as ridiculous were they not the truth, we are able to see at magnitudes at least ten times smaller than Abbe predicted possible. As a result, the discovery of new human anatomy on a minuscule scale is enjoying a global renaissance, to the extent that we have had to rethink what the fundamental unit of biology – the cell – really is.

The story of this remarkable feat begins with a Japanese scientist named Osamu Shimomura and his fascination with jellyfish.

Osamu Shimomura was 'a quiet and brilliant researcher'[8] working at Princeton University with his wife Akemi in the 1960s. Nearly every summer they travelled to Friday Harbor on the San Juan Islands, around ninety miles north of Seattle, to collect jellyfish.

> We collected jellyfish from 6 a.m. to 8 a.m., then after a quick breakfast we would cut rings from the jellyfish until noon. We devoted all afternoon to the extraction. After

> dinner, we again collected jellyfish from 7 p.m. to 9 p.m., and the catch was kept in an aquarium for the next day.[9]

His children Tsutomu and Sachi helped, but they weren't usually up as early as their parents.[10] Locals sometimes wondered what the family were up to with their nets and buckets, scooping up so many jellyfish; they often asked, 'How do you cook them?'

In 1955, these jellyfish had been observed to emit a green glow at the rim of their umbrella-shaped bodies.[11] Shimomura wanted to understand the biological process that made them glow. At least initially, he didn't have any practical application in mind for his work. He was simply fascinated by the way some animals glow. All kinds of life – including fireflies, worms and deep-sea fish – use light to attract mates, warn off predators and communicate in ways we hardly appreciate. Life continues to surprise us with its colour: flying squirrels have recently been found to shine pink under UV light, and nobody knows how or why.[12] Shimomura wanted to understand the basic principles of how this happens.[13]

Shimomura's success was partly owing to his characteristic approach to solving problems. Rather than foraging through books and scientific papers to find a suitable method, he would devise his own procedure from scratch with unusual resourcefulness. Instead of using one of the filters that happened to be available from the lab supply store, for example, he would think about the kind of the fabric that would work best and seek that out, wherever it was to be found. His daughter Sachi recalls how her father would often wander around a hardware store looking for things he could repurpose in the lab. He used dental floss to sew netting onto metal wire frames to make the shallow dip-nets his family used to collect the jellyfish. His jellyfish-cutting machine was essentially made from a juice blender.[14] Shimomura would often emphasise this as an important ethos: that young scientists need to learn how to learn, and inventing one's own procedures is an important way of doing so.

This approach to science came from his upbringing. His family moved homes several times, and his father, an army captain, was away a lot. Shimomura's school education was frequently disrupted by military exercises and later abandoned entirely. At

sixteen, he was at work in a factory just 15km away from Nagasaki when the atomic bomb was dropped. He witnessed two B-29 planes drop parachutes without any people hanging from them and, as he recalls in his autobiography, 'a powerful flash of light hit us through the small window. Then, maybe forty seconds after the flash, we heard a loud sound and felt a sudden change of air pressure.'[15] On his way home that day, a black rain fell. His grandmother gave him a bath as soon as he got in, which probably saved him from radiation poisoning.[16] Growing up in Japan during the Second World War taught Shimomura to be strong, independent and resourceful.[17]

Ultimately, by comparing extracts from the jellyfish cells, seeking any that showed optical activity, Shimomura identified two types of protein molecule that make jellyfish cells glow. One emits blue light in the presence of calcium and a second takes up the blue light and emits green light.[18] It was this second protein, later named green fluorescent protein or GFP, that was to play such a crucial role in microscopy.[19]

It was not until years later, though – at just after noon on Tuesday, 25 April 1989, to be precise – that Chicago-born Martin Chalfie, working at Columbia University, New York, happened to sit in on a talk which mentioned Shimomura's work, and a new chapter in the story of GFP began.[20] Immediately, Chalfie began to fantasise about how this green-glowing protein might be used inside cells of other animals – specifically a small worm that he was studying – to highlight the location of specific types of cell or even certain molecules within cells.[21] In an era before Google and Wikipedia, he spent the next day phoning people in order to find out all he could about it.[22]

One person he was led to call was Douglas Prasher, then at the Woods Hole Oceanographic Institution, who was working to identify the gene which carried the instructions for the production of GFP. Prasher agreed to send Chalfie the gene once he had isolated it, but soon afterwards they lost touch. In time, Chalfie went on a sabbatical. Unable to reach him, Prasher assumed he had left science altogether. And when Chalfie never heard from Prasher, he assumed Prasher had never isolated the gene. It was not until 1992 that Chalfie stumbled upon a scientific paper by

Prasher saying that he had.[23] Chalfie got back in touch, and Prasher sent him the gene.

In Chalfie's lab, they found that the jellyfish gene could indeed be re-deployed to make bacteria or worms glow green.[24] It was a PhD student, twenty-six-year-old Ghia Euskirchen, who was the first person ever to see this. The bacteria's green glow was so faint that Chalfie's lab microscope couldn't detect it. Luckily, she double-checked on a microscope in another lab and discovered that her experiment had worked.

It was already well established that genes could be transferred between species – because the basic chemistry of genes is the same in all life on Earth – but the fact that it took only a single gene to make an organism glow green was a vital revelation: it could have easily been the case that GFP would only work in concert with a suite of other proteins that were only found in those particular jellyfish. Chalfie's lab first described these results in the October 1993 issue of *Worm Breeder's Gazette* – not a widely read publication, and certainly not a usual source for paradigm-shifting new technology.[25] 'We have lots of ideas of how GFP might be used and imagine that other people will have many more,' they wrote. 'If you are interested in obtaining [the GFP gene], please write ... we'd like to know what you are interested in doing, but that's not essential.' Soon after, in February 1994, they published their work in the pre-eminent journal *Science*.[26]

Eventually, the green jellyfish protein would be used in a vast array of experiments to study all kinds of life, from yeast to humans, but when Chalfie first talked to others in his university department about it, few grasped its potential. He thinks this is probably because it's hard to realise the full importance of anything new the first time you hear about it.[27] But one person who did appreciate the work very early on – and she undoubtedly heard about it far more than once – was his wife, Tulle Hazelrigg, also a professor at Columbia. It was in Hazelrigg's lab that the major step was taken that turned GFP into such a useful device: her team attached GFP to another protein by fusing together the two genes that encoded for them, allowing scientists to 'tag' that protein with GFP and thereby detect its location inside a cell. With this, Chalfie's fantasy had come true: the green-glowing jellyfish


image
not
available

lot less comfortable than Hess's living room. It worked. They quickly found that they could locate molecules in living cells with unprecedented accuracy.[49]

It took six months from the moment they started building the instrument to proving it worked and getting enough data to earn a Nobel Prize. 'We knew we had to work fast because this idea was going to be ripe and in the air,' Betzig recalls.[50] They were right to hurry. Xiaowei Zhuang at Harvard University – who had been educated in China in a special programme for gifted children – developed a very similar type of microscopy, except that she used a chemical dye, rather than the jellyfish protein, as a label.[51] Zhuang demonstrated how well her microscope worked by looking at dyes along strands of isolated DNA. Her work was formally published one day before Betzig and Hess's.[52] A third team, at the University of Maine, also developed a similar microscope.[53]

Stefan Hell, working at the Max Planck Institute for Biophysical Chemistry in Göttingen, Germany, also developed a new kind of microscope that smashed Abbe's law, but his method was completely different. Born and raised in Romania, Hell moved with his family to Germany in 1978, when he was aged fifteen. As an only child, he spent a lot of time with books, enjoyed science fiction thrillers on TV, and knew from a young age that he wanted to be a scientist. He later wrote that while he was growing up in Communist Romania, a feeling took root which would prove prescient: 'Things which are publicly asserted and constantly repeated aren't necessarily true.'[54]

Hell was attracted to working in theoretical physics, but because his parents struggled when they moved to Germany – his father's job was uncertain and his mother was diagnosed with a serious illness – he thought he should work on something more vocational. So for his doctoral research, he worked in a small start-up company developing microscopes to help with the production of computer chips. The work was practical, as Hell had wanted, but also boring. He felt that the physics of microscopes was the physics of the nineteenth century. He was trapped between the need to earn a living and the desire to work on something scientifically challenging. Seeking a way out, he wondered whether there might

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