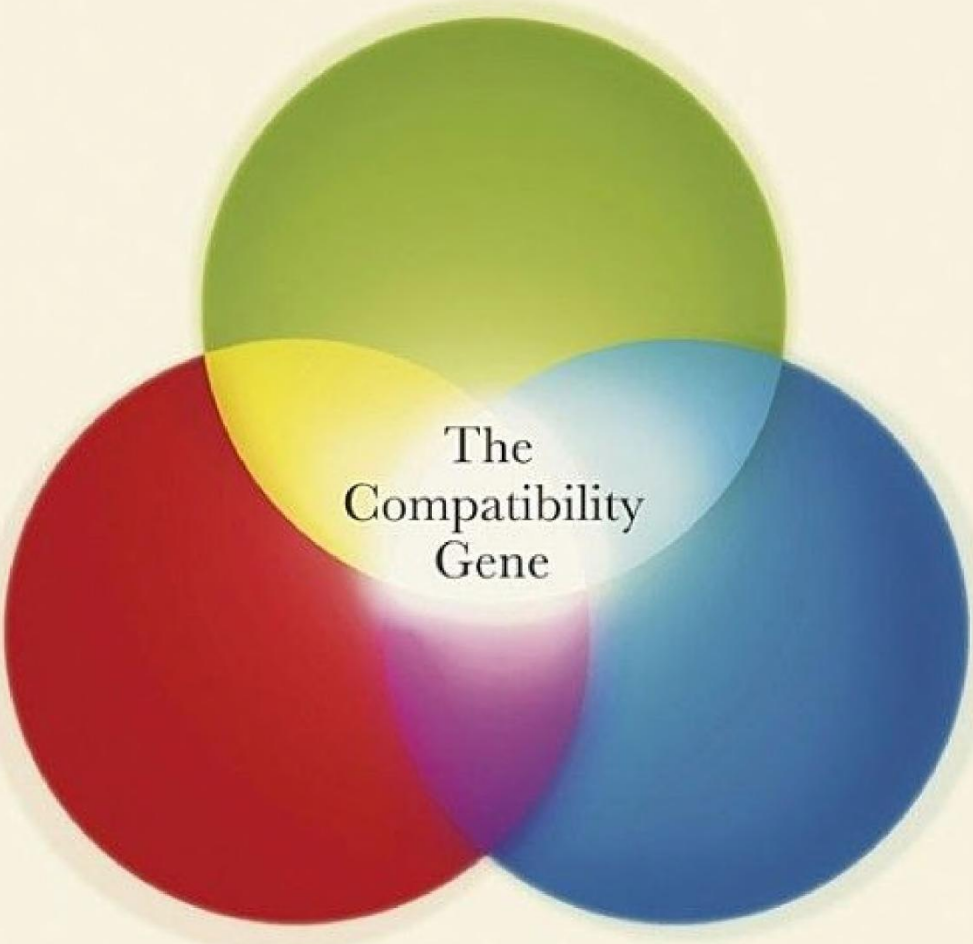
Daniel M. Davis



The Compatibility Gene

'Lab work has rarely been made to seem more interesting or heroic'
BILL BRYSON, *GUARDIAN* BOOKS OF THE YEAR

Daniel M. Davis

THE COMPATIBILITY GENE

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ABOUT THE AUTHOR

Daniel M. Davis is a Professor of Immunology at the University of Manchester and a visiting Professor at Imperial College, London. He previously carried out research about the immune system at Harvard University. He has published over 100 academic articles, including papers in *Nature*, *Science* and *Scientific American*. He won the Oxford University Press Science Writing Prize, has given numerous interviews for national and international media and was elected a Fellow of the Academy of Medical Sciences in 2011.

PENGUIN BOOKS

THE COMPATIBILITY GENE

'Dr. Davis's readable and informative book takes the reader into unexpectedly interesting corners of both the immune system and the lives of immunologists. It is packed with an insider's knowledge – not just of the field, but of where its bodies are buried' Nicholas Wade, *New York Times*

'Davis's book tells the story of the search for these compatibility genes, from the early days of blood transfusion to the cutting-edge science that has yet to appear in the textbooks' Tim Dowling, *Guardian*

'There aren't many stories of scientific endeavour that have never been told. This is one of them. Ostensibly about a set of genes that we all have and need, this book is really about the men and women who discovered them and worked out what they do. It's about brilliant insights and lucky guesses; the glory of being proved right and the paralysing fear of getting it wrong; the passion for cures and the lust for Nobels. It's a search for the essence of scientific greatness by a scientist who is headed that way himself' Armand Marie Leroi, author of 'Mutants'

'Davis ranges energetically through the research. Cultural references and anecdotes abound' *Nature*

'Davis makes the twists and turns all count' Peter Forbes, *Guardian*

'Genes help make us what we are, but in the often overstated claims of what DNA can actually say one crucial section of the double helix has largely been ignored. This book fills that gap.

The genes behind our system of diversity code for the clues that control tissue transplants, responses to infection and even sexual success. They are complex indeed but *The Compatibility Gene* cuts through the complexity to reveal the startling truth about perhaps the most important section of the molecule that defines what it means to be human' Steve Jones, author of 'Almost Like A Whale'

'What make us truly unique? Our personalities? Maybe, but more fundamental to the identity of each and every one of us is our spectrum of histocompatibility genes. Writing in a way that everyone can follow, Dan Davis tells this intriguing story' Peter C. Doherty, Winner of the Nobel Prize in Medicine for work on the immune system

'In a rollicking romp through immunology's first century, Dan Davis expounds on the extraordinary genes that determine compatibility of donor organs with recipient patients in clinical transplantation. By personalizing human immune systems, the compatibility genes have enabled individuals and populations to resist extinction by epidemic infections. If that were not enough, they also influence our brains, mate selection, and reproductive success. Boasting a particularly rare set of compatibility genes, Davis has a raw talent for evoking the thrill and thrall of scientific research' Peter Parham, Professor of Structural Biology & Microbiology and Immunology, Stanford University, author of *The Immune System*

'Davis describes his task simply: '[T]his is the story of a few human genes and how we discovered what these genes do.' However, his book is far more complex and rich than such an explanation might lead us to expect' *Publishers Weekly*

For Katie, Briony and Jack

A Brief Note to Professional Scientists

Immunology is a vast and complex science. In this book, I have sought to present some of the big ideas alongside the stories of individuals who have played a central role in gaining this knowledge. But I am acutely aware that there are a huge number of people who contributed to our understanding of the immune system and the relevant genetics, who are not explicitly named in this book or have been mentioned only superficially. I have made many ruthless omissions in my attempt to keep the narrative and the scientific ideas as clear as possible for the general reader. Quite simply, this is an extraordinarily rich story in which there have been many players, and it's impossible to catalogue everyone's contribution. Immunologists will notice that some details are covered more thoroughly than others; I have discussed class I genes far more than class II genes, for example. Rather than present a complete textbook-level description of the immune system, I wanted to focus on broad issues, such as the variation in human immune-system genes which can, for example, be illustrated equally well with class I or class II genes. I can only apologize to anyone whose discoveries I have not included or have mentioned all too briefly; *any one book can only tell part of a story*.

Introduction

There's a man, happy and minding his own business, who sees an open gate in the corner of the room where he is. He approaches the gate, wondering where it leads. But as he does so, he sees that it's being guarded. The guard – who looks powerful from a distance but appears unkempt close up – warns the man that nobody has ever been through this gate. He also mentions that beyond this gate there's another, with a guard who's even more powerful. So the man just backs away and spends his days – which turn into decades – in the room, occasionally wondering about the gate and where it leads to. Eventually, when the man is weak and knows his own death must be near, he realizes what he should ask the guard. He shuffles back and asks, 'In all the time I've been in this room, why has nobody ever been through the gate?' 'Because,' the guard replies, 'this gate was only meant for you ... but it's too late now.'

Written in 1914, Franz Kafka's parable 'Before the Law' has inspired me often. The version that I carry in my head now is slightly different from what Kafka actually wrote, or the way Anthony Hopkins tells it in the 1993 movie of *The Trial*. There are many interpretations of any great allegory; this one works for me on two levels. First, as a scientist, I want to open doors to where nobody has been before. Second, there is the simple, but all-too-easy-to-forget, truth that each of us really is unique, right down to the molecular detail of what our bodies are made of. My aim is for this book to work on these two levels. I want to tell some inspiring stories of men and women who have fought their way to new rooms of

knowledge and describe how, from the vantage point they reached, we see a fundamental importance for our own personal uniqueness.

Essentially, this is the story of a few human genes and how we discovered what these genes do. The knowledge we now possess of these genes reveals a great beauty in how we work at a microscopic – and macroscopic – level. We are not merely a more-or-less average blend of our parents; rather we gain specific traits and characteristics through the individual genes we inherit. As human beings we each have around 25,000 genes. To a large extent, we each have a very similar set of these genes but there are variations that provide us with individual characteristics such as hair and eye colour. Genetic variation also gives us more subtle – and superficially undetectable – differences. Crucially, the genes in this story are those that vary the *most* from person to person. These genes are, in effect, a molecular mark that distinguishes each of us as individuals.

It is this feature that led to their discovery. These genes – we'll call them our compatibility genes (though their unwieldy formal name is the *major histocompatibility complex* or MHC genes) – are not uniquely human and they were first discovered in mice. During the 1930s, scientists were trying to understand what determines the acceptance or rejection of skin cells transplanted from one mouse to another. They observed that transplanted cells were rejected when they had different compatibility genes; transplantation worked well when these genes were matched. In the 1950s and '60s, this was also found to be true for humans, and today, these are the genes that, when matched between donors and recipients, help provide the best chance of success in many types of organ transplantation. But the normal job for these genes can't be to make life difficult for transplant surgeons. What do these genes really do?

Decades of patient scientific inquiry and the occasional stroke of genius have unravelled the workings of our compatibility genes. This book charts this human endeavour – a global adventure spanning sixty years – tracing the history of transplants and immunology, leading to our eventual understanding of how and why compatibility genes are crucial to our health. This amounts to a scientific revolution, but not one that came from a single eureka moment; rather a revolution in our understanding of the human body that emerged from a swell of ground-breaking ideas and experiments happening in different places across the globe over decades.

We will see that a great many people made vital contributions – and that their characters do not fit any particular mould of scientist. Some collected data while others contributed more theoretically. Many classified and ordered the information, while others explored more like artists. Often one didn't appreciate another's approach. A picture of science emerges in which hundreds of researchers – each digging away in their own experiments and thoughts – individually uncover a fragment of the big picture.

The view we now have of what these few genes do reveals much about how your immune system works; how your body can detect what is not part of you, such as germs or transplanted organs from someone else. That is to say that these few genes help your body distinguish *self* from *non-self*. Practically – as a consequence of the way this system has evolved – we each have a different set of these genes. And it can really matter which versions you have inherited.

Each of our 25,000 genes can be ranked according to which are most important for our susceptibility or resistance to any given disease. The outcome is that compatibility genes come out top in influencing our susceptibility or resistance to an enormous array of illnesses: multiple sclerosis, rheumatoid

arthritis, type I diabetes, psoriasis, leprosy, ankylosing spondylitis and many others.[1]

Take one example: In 2003, Doug Robinson, forty-six, from Truro, Massachusetts, was infected with HIV. Yet, ten years on, his immune system has managed to keep it in check: the virus is almost undetectable in Doug's blood.[2] About 1 in 300 people infected with HIV do not progress to full-blown AIDS for seven years or more, because, like Doug, their immune system is able to fight the virus effectively. But what is so special about Doug's immune system that allows him to do this? Why is Doug so, *so* lucky? Doug's super-power turns out to be a version of compatibility gene that he inherited – one that appears to be particularly beneficial in fighting HIV.

For people infected with HIV, their rate of progression to AIDS depends on, amongst other things, which variants of compatibility genes they have inherited. Doug has a version designated as B*57 (said as B-fifty-seven), which happens to be one that protects most effectively against the progression of HIV to AIDS. Protection against disease is surely enough to warrant a book about how these genes work, but in fact, their importance stretches further. There is evidence that these very same genes are linked to whole other areas of human biology.

Radical and provocative research has suggested that finding a lover might be made simpler: as a 'scientific' process in which there's no need to waste time looking in bars or at parties. Just take a swab and run it along your inside cheek. Put it in an envelope and fill out the brief form – not forgetting to include your customer number. Send it off, wait a few days, then log in to your online account. Having analysed your DNA, your ideal partner will be selected from a company's database. Just go ahead and arrange a date. Marriage, happiness and wonderful kids are all assured, with minimal risk of either one of you ever cheating.

This highly controversial view of what's possible is based on experiments that suggest that you find others more or less sexy according to which type of compatibility genes they have. There have even been claims that women experience higher rates of orgasm if they choose partners with the right set of compatibility genes. The experiment that started this line of thinking used a very unusual protocol for scientific work.

Women were to refrain from sex for two days, use a nasal spray to keep their nostrils clear, read Patrick Süskind's novel *Perfume* – a book about a man with olfactory hypersensitivity who is obsessed with people's smells – and then come into the lab to smell a collection of T-shirts worn by men who hadn't showered for two days. The experiment yielded an astonishing result: T-shirts worn by people with *different* compatibility genes smelt the sexiest. The big idea that follows from this research is that we subconsciously favour sexual partners who have different compatibility genes from ourselves. Profoundly personal, life-forming and life-changing decisions can, it appears, be reduced to the actions of a few inherited genes.

Is this true? How and why could it possibly work? We each spend a great deal of effort defining our personalities by choosing the things we like or dislike, and form friendships with people who have similar tastes. Many of us spend a great deal of our lives in the quest for a soul-mate. The idea of genes pervades our culture, and we have no problem accepting that our physical characteristics – hair and eye colour, for example – are dictated by our genetic make-up. But can something that feels as intimate as choosing a partner be similarly influenced by our genetic inheritance? There's no short answer to this question; the subject is contentious.

Controversy surrounding compatibility genes doesn't stop there. Other research suggests these genes might also influence parts of our brain. Specifically, the wiring between some neurons may be kept or broken according to the activity of compatibility genes. Most recently, evidence has emerged to suggest that compatibility genes are also able to influence the chance that two people have a successful pregnancy.

Quite simply, it seems that these few genes can affect who's born and who dies – at many levels. This multi-functionality of compatibility genes suggests that all of these different aspects of us could be fundamentally connected. And if so, then a shocking amount of who we are and what we do is directly influenced by the way we have evolved to survive disease.

Understanding this in depth – resolving the controversies – is not simply a matter of academic interest. Given, for example, that we each respond slightly differently to any particular disease, it can be expected that we also respond slightly differently to any given medicine. In the not-too-distant future, we can anticipate that vaccines or a choice of therapeutic drugs might be tailored to match our compatibility genes. Unlocking the secrets of our compatibility genes is undoubtedly important for medical practice in the twenty-first century.

Other sorts of issues also arise from these discoveries. The possibility is already available to seek a partner according to compatibility genes,[3] and disease treatments tailored to our gene types are just around the corner. But how much of this is where we want to go? Governments and the pharmaceutical industry must move forward mindfully, so that we don't end up in a Brave New World. We must each make our own personal decisions, fully informed about how

this wondrous system works within each of us and across us all.

As I mentioned, there are many interpretations of any great allegory. In Kafka's 'Before the Law', the man and guard might be one and the same; there's an internal struggle in anyone stepping forward somewhere new. More importantly, it is surely impossible that a gate will be opened and closed to fit the term of one person's life. More likely, once a new room has been seen, its guard will not actually be able to shut the gate.

Part One

THE SCIENTIFIC REVOLUTION IN COMPATIBILITY

1

Frankenstein's Holy Trinity

You can always find stories that make any person look good or bad – with the exception of Peter Medawar. Anecdotes about Medawar always cast him as a hero, and his story is a scientific legend forged from his Nobel-Prize-winning discoveries in transplantation. His work helped reveal how the human body is able to sense its own cells and tissue. Concerned with the difficulties in medical transplantation, he studied how the body is able to accept its own tissue as *self*, yet reacts against alien tissue from somebody else – as *non-self*. His work helped uncover that this happens because a handful of human genes provide a molecular mark of our individuality – 'the uniqueness of the individual', as he called it. These genes are, in effect, hallmarks etched on all our cells which can be recognized by our immune system. Medawar's discoveries are a good place to begin this sixty-year-long scientific adventure to understand how the immune system works, which culminates in recent discoveries indicating that our immune system impacts many aspects of human biology. This journey to understand the importance of our compatibility genes – and Medawar's legend – starts with a plane crash in Oxford in the summer of 1940.

It was a hot Sunday afternoon when Medawar, then twenty-five, enjoying garden life in Oxford with his wife Jean and eldest daughter Caroline, was startled by the sight and noise of a bomber flying low towards them. Jean scrambled

with Caroline to a shelter and the plane crashed violently in a garden 200 metres away. It was a British plane and the pilot survived but suffered horrific burns. The sight of such agony marked an epiphany for Medawar: from that moment, his work ceased to be a purely intellectual exercise. 'A scientist who wants to do something original and important must experience, as I did, some kind of shock that forces upon his intention the kind of problem that it should be his duty and will become his pleasure to investigate,' he said later.[1]

Medawar had trained as a zoologist, but his recent research had been to find out which antibiotics were best at treating burns. For the pilot who had just crashed, doctors were at their wits' end in deciding the right medication and asked Medawar to help. They asked him to come and look at the patient, and the visceral shock of pacing the war wounds hospital spurred the young Medawar to think and work to a degree of intensity that he hadn't known he was capable of; Jean said that from then on, 'he worked like a demon'.[2] He saw airmen with much of their skin incinerated, lying in agony: while their lives could be prolonged by new medical advances – blood transfusions and antibiotics – there was no way of treating these horrific burns.

The research that Medawar would carry out in response to this shock marked the beginning of modern transplantation. Even so, it's been said by one of his many protégés, Avrion Mitchison, that his smartest achievement was actually to marry Jean, three years before the formative plane crash.[3] Peter and Jean met as undergraduates in Oxford in 1935, on Peter's twentieth birthday, and they would be married for fifty years, until Peter's death. Physically attractive and charming, Peter was 6 feet 5 inches tall; you 'sensed that you were in the presence of a giant', as one colleague wrote about him.[4] He was vibrant and sharp and had a gift for inspiring those around him. Highly talented, multilingual and also

physically attractive herself, Jean was nevertheless in awe of Peter's intellect and charisma.

Peter and Jean's wedding reception was a low-key sherry party in their Oxford flat, the day before Peter's twenty-second birthday. Jean, already twenty-three, had bought her own wedding ring 'to save him time', and their relationship was to remain somewhat unconventional. Once, Jean asked Peter directly if he could spend less time in his lab, to which he replied, 'You have first claim on my love, but not on my time.' Jean thought to argue back – love needs shared time – but she kept quiet. They came to an arrangement in which Peter's time for thinking and working was treasured and protected.[5]

Peter forever remained detached from any emotional problems that might otherwise take up his time and energy, and was generally dismissive of any problems at home. Living frugally during the war years took time and energy and Jean understood this to be her job – leaving Peter to work ferociously. When Peter looked as though he was thinking deeply, Jean would ask 'Are you thinking?' before starting any discussion. If he was, she wouldn't continue.[6] Peter also told Jean that he was happy for theirs to be an open marriage. Peter's discoveries were hard-won, and home life could not have been the bliss it was made out to be in the autobiographies by himself and his wife. He devoted himself fully to solving the transplantation problem.

Skin transplants, or grafts, were needed to treat such extensive burns, but when doctors transplanted skin from one person to the next, it was destroyed two to three weeks later. At the time, doctors didn't think there was any fundamental biological problem to transplantation, only that the actual practicalities had to be perfected; the cutting and sewing. Still, they did know that grafts using skin taken from elsewhere on the same patient worked far better. Why was

that? Isn't everybody's skin – human tissue – essentially the same? How could one person's skin differ from that of another? Stranger still, how does your body know the difference?

Medawar's work would help show that transplant rejection is the result of a reaction from immune cells and, crucially, he went on to lead a team that found a way to circumvent transplant incompatibility. In doing so, he went down in scientific history and, aged forty-five, won the Nobel Prize in 1960 for a plethora of crucial experiments. While the medical need for transplantation was made acute by the war, his discoveries answered questions that were not new at all, but ancient.

The basic idea of skin transplantation stretches back for millennia. The renowned Hindu medical text the *Sushruta Samhita* discusses how to extend a short earlobe with skin taken from the patient's cheek or neck.[7] It's not entirely clear where or when Sushruta lived, perhaps between 600 and 400 BCE, and he may have been a contemporary of Buddha. Nor is it clear when this ancient Sanskrit text was written: the version we have now is likely the collective work of many ancient Indian medical practitioners. Nevertheless, this text describes fifteen specific procedures for fixing earlobes, from reconstructing earlobes shortened by a blow, to helping anyone born with short or malformed earlobes who simply wanted enlargements.

Another notable ancient case of transplantation is a third-century CE story of Christian Saints Cosmas and Damian, depicted in a fifteenth-century Spanish iconographic painting held by the Wellcome Trust in London. The most famous miraculous procedure these two early Arabian physicians performed was the replacement of a church official's ulcerated leg with one from a dead Ethiopian. In the painting, their patient is at peace – remarkably so given that his own

side from falling against her gas fire.[10] The burns were cleaned and a month later she had a blood transfusion but she remained poorly, her wounds still not healed. If her condition had been better, Medawar and Gibson would have grafted large pieces of her own skin to cover the wound, but they decided instead to try several small squares of skin, with the hope that these would grow to cover the whole burnt area. One area of her wound was covered with fifty-two small discs of skin from her thigh and another area with fifty discs of skin taken from her brother's thigh.

Over the following days, the two sets of grafts were studied and biopsies taken for closer examination under a microscope. At first, both grafts looked identical: this was significant as it showed that initially each graft healed properly. But then, a few days later, the microscope revealed that Mrs McK's immune cells had invaded the skin grafts taken from her brother. Between fifteen and twenty-three days after the transplant, the brother's grafts degenerated: Mrs McK's body had rejected them. Her immune cells had seemingly caused the graft rejection, but the evidence was weak: the immune cells were at the scene – but did they do the killing? Medawar and Gibson knew all too well that there were several theories as to what caused transplant rejection and that they would need more than just this circumstantial evidence.

Crucially, Gibson happened to mention to Medawar his suspicion that, in his experience, a second set of skin grafts often degenerated even faster. Medawar recognized this faster reaction second time around as the hallmark of an immune response, and so together they realized that they should systematically test whether or not Gibson's impression was true. To do this, they decided that a second set of discs of her brother's skin should be grafted on Mrs McK. This time, the brother's skin degenerated in about half the time the first

skin grafts had lasted. It seemed to bear out Gibson's hunch and was strong evidence that the grafts were rejected because of a reaction involving cells from Mrs McK's immune system. With that, the surgery of transplantation became linked with a scientific realm that was more respectable at the time – understanding the immune system.

Although this was a pivotal observation, it came from only one patient. Medawar knew that an experiment with one patient couldn't be counted as definitive proof of any general principle; he needed large amounts of data – and to get this, he needed to use animals. Back in Oxford, Medawar chose the rabbit – 'more for its size and ease of supply than for any intrinsic merit', he explained to the War Wounds Committee.[11] Taking twenty-five rabbits, he grafted pieces of skin from each one onto every other rabbit in the group. For so many grafts between rabbits, he devised his own methods that are basically still used today – published across two very long papers in 1944 and 1945[12] – and he then stained, examined and photographed hundreds of rabbit-skin samples under the microscope. He also cared for the rabbits himself, looking after their food and their cages and carrying them back and forth for the experiments. If you've ever wondered what it might take to win a Nobel Prize, this one starts here: with an important hypothesis tested by 625 operations on 25 rabbits (25 × 25 individual skin grafts).

The experiments were tough – the hardest work of his life, Medawar later recalled. Sometimes he didn't get home until 11.30 p.m., with a briefcase full of papers to read by morning;[13] he exhausted himself but was spurred on by the thought that it was the least he could do for those actually fighting the war. Medawar was also motivated by ideas: fundamental ideas about the way the world worked and the way that we work. Unlike some great scientists – Einstein, for example, who famously used 'thought experiments' or

Gedankenexperiments – Medawar's ideas came to him when pondering his experimental results rather than by thinking about abstract concepts alone. Even much later, when he became the head of the UK's National Institute of Medical Research (working in a building used as the fictitious psychiatric hospital Arkham Asylum in the 2005 movie *Batman Begins*), Medawar always sustained his data-driven perspective, setting aside two weekdays and Saturday morning for doing experiments, and never allowing the demands of policy and administration to dominate him.

The outcome of Medawar's meticulous work in the early–mid-1940s was confirmation that skin could not be permanently grafted from genetically different rabbits; as with the grafts from Mrs McK's brother, they lasted a few weeks at best. His experiments also revealed that, in a second round of grafts, rejection happened more quickly. Again, this was exactly what he and Tom Gibson had observed in the Glasgow Infirmary with Mrs McK: the signature of an immune cell response. But, tinkering with the conditions of the rabbit experiments, Medawar now made two other key observations.

First, larger skin grafts were destroyed more rapidly than smaller ones. This feels counter-intuitive: it might be expected that a larger skin graft would simply take longer to be destroyed, given that there's more of it to get rid of. Yet the fact that a larger skin graft was actually destroyed more rapidly indicates an immune response because immune cells would be expected to mount an attack in proportion to the level of threat. A larger graft would, in this view, be attacked more ferociously and destroyed more quickly.

Most importantly, however, Medawar also found that the rate of rejection second time around depended on the relationship between the two grafts. That is, if the second skin graft was taken from a different rabbit from the first, it

In these few pages Medawar established a way to solve the problem of transplantation. That is, he found a way to transplant skin from one animal to another so that it would not be rejected – there would be no immune reaction at all – even if the animals were unrelated. The way in which he solved the problem built upon an observation made many years earlier. In science, in general, bolts from the blue can occur – like the discovery of radioactivity by Marie and Pierre Curie and Henri Becquerel in the late 1890s – but these are exceptionally rare. Even with radioactivity, understanding the initial observation certainly didn't come in a flash of inspiration but required a long, hard slog. In Medawar's case, the important foundation for his seminal three and a half pages in 1953 was a paper published eight years earlier by Ray Owen at Wisconsin University in the US.[16] Owen's work was initially ignored by most, and indeed Medawar was unaware of it until he read a paper published in 1949, by Australians Macfarlane Burnet and Frank Fenner, which quoted Owen's research.

Owen discovered that the blood of non-identical cattle twins contained cells in common, presumably coming from the shared placenta. It would be easy to dismiss this as just vaguely interesting; an anecdote of anatomy. But in the context of transplantation, the observation was startling because it meant that each twin of a non-identical pair would not react adversely to cells from the other, even though they were genetically different. The importance of Owen's finding was that this showed that it was at least possible for cells from one animal to exist in another without any reaction occurring: the holy grail for solving the transplantation problem. Inspired, Medawar set out to try to artificially recreate this natural situation in the lab, and this put him on the right track for solving the transplantation problem, and producing his three-and-a-half-page masterpiece.

Thankfully, Brent's parents knew the director of a Jewish boys' orphanage in Berlin, Kurt Crohn, who had left Köslin when young. One day, in the winter of 1936, Brent went by train to the orphanage, where it turned out that many Jewish boys – even those with parents – had been sent under similar circumstances.

However, the orphanage would offer only a temporary sanctuary. In 1938 it was ransacked by a mob while the thirteen-year-old Brent hid under the roof rafters with a friend. 'There we stayed with beating hearts,' he later recalled, 'until everything became eerily quiet.'[21] Shortly after, on 1 December 1938, a few weeks after *Kristallnacht*, his life was saved by being transported to England, in the Refugee Children's Movement, or *Kindertransport*, programme. Crohn, the orphanage head, had nominated him to be one of the first to travel. Brent remembers how, when they reached Holland, en route to England, they finally 'seemed to have been relieved of [their] role as scapegoats, villains and victims'.[22] Many other boys in the orphanage were not so lucky: they were later rounded up and sent to concentration camps. Crohn himself was killed in Auschwitz in September 1944.

At Dovercourt Reception Camp in Essex – a Butlin's seaside holiday camp used as temporary accommodation for refugee children in 1938–9 – Brent was introduced to English culture and, appearing on a BBC TV documentary aimed at encouraging British couples to take in these new immigrant children, he said he wanted to become a cook. Transferred to a boarding school, he spent his holidays with various families, and, when he was sixteen, a secretary of the Refugee Children's Movement found him a job as a laboratory assistant at Birmingham University. Army service followed. He was in the British infantry from January 1944 to autumn 1947, and it was during this time that he chose his name to be Leslie Brent – Leslie after the actor Leslie Howard and Brent

just chosen from telephone directory to have the same initials as the name his parents gave him. He was told that his real name sounded too Jewish/German, which could be fatal: if captured, he could be killed for being either a German traitor or Jewish. The army made him 'confident, self-reliant and with a sense of belief in [himself]'.[23] Because he entered a training programme to be an officer, he wasn't sent to the front during the war but was stationed in Germany in 1946 and later served in Northern Ireland.

On VE day, 13 May 1945, he was at the celebrations in central London but couldn't join in, feeling 'horrendously oppressed',[24] not knowing the fate of his family. The following year he accessed official files in Berlin, which noted that his parents and sister had been 'sent east'. He mistakenly took that to mean that they were killed in Auschwitz and he uncontrollably burst into tears visiting the concentration camp decades later in 1976. Eventually, he discovered their actual fate: in October 1942 they had been taken on a crowded three-day train journey from Berlin to Riga, the largest city in Latvia, led into the woods and shot.[25]

After the army, in 1947, Brent returned to Birmingham and, as an undergraduate student in zoology, began research with Medawar. Already in the lab, Billingham, four years older than Brent, had been Medawar's first graduate student at Oxford after returning from active service in the navy. Impressed by the military rigour that Billingham brought to his planning and performing of experiments, Medawar obtained a position for him so that the two could move together from Oxford to Birmingham in 1947. Billingham came from a non-academic background – his father owned a fish and chip shop – and in general he was more down-to-earth, less of a philosopher, than Medawar. But Billingham's role in the team is not to be underestimated; he was ingenious at getting experiments to work technically and,

Brent recalls, he had a 'single-minded dedication to his career'.[26]

In Birmingham, initially ignorant of Owen's earlier research, Medawar and Billingham performed experiments to test whether or not skin grafts could have a practical use in determining whether cattle twins were identical or non-identical. They did this as a small side project to give some immediate relevance to their work, since such a test would have particular significance for farmers in identifying female calves (called freemartins) that had become masculinized and sterile by being exposed to hormones from a non-identical male twin. Medawar and Billingham's test involved simply grafting skin from one animal to another and observing the outcome. They predicted that non-identical twins would reject grafts from each other, while identical twins would readily accept grafts. However, they were stunned to find out that cattle twins always accepted grafts from each other, no matter whether they were identical or not. The penny dropped when they eventually read Owen's earlier research, which had demonstrated that even non-identical cattle twins shared blood cells, presumably through a shared placenta. Transplants *could* work between genetically different animals, and from their experiments and Owen's earlier study, the trick seemed to be that, when animals shared tissue as a foetus, they could later in life still accept transplants from each other.

So the team of Billingham, Brent and Medawar – together in their new lab in London, 1951 – discussed a specific experimental plan that could test this idea. They decided that they could use inbred mice, which have defined genetic traits obtained by mating siblings many times. They injected cells from one inbred mouse strain directly into unborn foetal mice of another, non-identical, strain. They discovered that after birth, when tested as adults, the injected mice were able

to accept skin from the unrelated mouse strain whose cells had been injected. These were startling, ground-breaking results – a solution to the ancient problem of transplantation. Jean dubbed the treated mice 'super-mice'.

The super-mice had become tolerant to skin grafts from unrelated mice whose cells they had been exposed to when foetuses. This was not the bolt from the blue that radioactivity was, for example – the trio had planned and carried out a specific experiment to test a hypothesis – but, as with radioactivity, it cannot be over-emphasized how important their discovery was; as with radioactivity, nothing in our everyday experience hints at the fact they discovered.

Key to their success as a team, all three were trained in zoology, so they spoke the same scientific language and, perhaps most important of all, they were all dedicated workaholics. Although this might read as though the breakthrough happened smoothly and simply, in practice the team had to go back and forth with variations in the conditions of the experiment to get things to work out. And in the midst of it all there was, of course, no guarantee it was ever going to work out. Doing science is like playing snakes and ladders: you can be five squares from glory, but the die rolls to four, lands you on a snake and you're back at square one. To win, the team worked long and hard.

They then went on to verify that the process was also true for other species – doing similar, but less extensive, experiments with chicken chicks. The transplantation problem had been solved, but in laboratory conditions, and using animals rather than humans. The team were acutely aware that this was not yet a practical medical advance: it would be impractical to inject cells into a human foetus. But their experiments had nevertheless revealed a solution to a problem previously thought insoluble. They had shown that it is, after all, possible to breach the natural barrier for

statement of how important Billingham and Brent were, Medawar shared the prize money with them. In a personal letter to Brent's wife, Joanne, Medawar wrote that 'I wish to make it absolutely clear that it [a share of the prize money] is no way a present but comes to Leslie as of *right*.'[33]

Medawar was also generous to Ray Owen, who had made the early ground-breaking observation that blood cells can be transferred between non-identical cattle twins. Medawar wrote to Owen: 'Of the five or six hundred letters I have had about the Nobel Prize, yours is the one I most wanted to receive. I think it is very wrong that you are not sharing in this prize ... you started it all.'[34]

It is not simply winning a Nobel Prize that makes Medawar's name endure, it is also the brilliance of his essays and books, which remain influential; the eminent biologist and writer Richard Dawkins takes inspiration from Medawar as the 'wittiest scientist ever'.[35] An example of Medawar's incisive writing and clear thinking comes across well in his critique of a book, *The Phenomenon of Man* by French philosopher Pierre Teilhard de Chardin, published in 1955. The book, hugely influential at the time, used flowery language to present wild speculations about the process of evolution. 'It is the style [of the book],' Medawar wrote, 'that creates the illusion of content ... The greater part of it ... is nonsense, tricked out with a variety of tedious metaphysical conceits, and its author can be excused of dishonesty only on the grounds that before deceiving others he has taken great pains to deceive himself.'[36]

A year after Medawar's Nobel Prize came the death of another pioneering London-based transplantation scientist, Peter Gorer. Medawar wrote a memoir of him for the Royal Society. While Medawar's research linked transplantation to the body's immune response, Gorer's research had earlier connected transplantation to our compatibility genes, and

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