PRAISE FOR *THE GENETIC AGE*

'Powerful gene technologies, long foreseen, are finally with us. Taking the measure of this daunting prospect calls for historical acumen, technical appreciation, and a clear-eyed view of human foibles. As this book attests, Matthew Cobb has all three'
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'A lucid and vigorously insightful account of the pitfalls and triumphs of the twenty-first century's most ethically challenging and potentially world-changing technology' Paul McAuley, author of *Fairyland*

'A superb account of genetic engineering in life and culture, in all its myriad anxieties and exhilarations' Adam Roberts, author of *It's the End of the World*

'A superb guide to the global history of the dreams, fears and science of genetic engineering, and why it matters for tomorrow'
Jon Agar, author of *Turing and the Universal Machine*

'[Matthew Cobb]'s riveting analysis warns that in a world beset by poverty, inequality and climate catastrophe, chasing apparently dazzling technofixes is rarely cost effective or morally justified'
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'A gripping, bawdy tale of science fiction morphing into business history … Exhaustively researched and beautifully written'
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'Rich, vivid and well-documented, this is a wonderful introduction to genetic technology, with the take-home message – just because we can, doesn't mean we should' Michel Morange, author of *A History of Molecular Biology*

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THE GENETIC AGE

OUR PERILOUS QUEST TO EDIT LIFE

Matthew Cobb

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In memory of my PhD co-supervisor, Barrie Burnet (1935–2020), Reader in Genetics at the University of Sheffield, and of my University of Manchester colleague, Roger Wood (1934–2021), who, like me, studied both insect genetics and the history of science.

INTRODUCTION

Ever since the early 1970s the world has been living through a scientific and technological revolution. New genetic techniques have transformed science, providing profound insights into the whole tree of life and allowing us to investigate a huge range of organisms with astonishing precision. These discoveries have been turned into novel technology with far-reaching implications, putting food in the fields and healing bodies. Vast fortunes have been made as whole sectors of the pharmaceutical industry have been transformed. To give just one example: if you take insulin, it was produced in a genetically engineered microbe.

Built upon dreams, genetic engineering has equally provoked nightmares throughout its history. The impact of the new genetics on popular culture and our global mindset over the last fifty years has mirrored the promises and doubts about nuclear power during the post-war decades. Nuclear physics lost its innocence in the searing white heat of Hiroshima and Nagasaki; genetic engineering has yet to suffer a similar fate but that is not for want of trying – from the very beginning, hidden from history, the new science has been used to create terrifying new weapons. The potential for the nightmares to become reality grows with our increasing mastery and our endless appetite for ever more audacious applications.

With every new development there have been promises of new sources of food or medicine, or new cures for diseases, which have been rapidly counterbalanced by fears of plagues, of genetically manipulated humans, or of the inadvertent or deliberate release of dangerous organisms. Genetically modified plants promised to transform agriculture, but opponents feared ecological catastrophe. Neither happened. The genetic dreams and nightmares have tended to recur: the promises are rarely fully realised, the worst fears never come to pass and after a while the whole issue subsides, only to re-emerge a few years later following new discoveries and applications.

This cycle has occurred repeatedly over the last half-century. Now, after a long period in which the technology began to appear commonplace, three recent developments have brought the dreams and nightmares back into our waking lives, providing amazing opportunities and raising the real possibility of catastrophe:

- In 2018 we stepped into the brave new world of heritable human genome editing when Chinese researcher He Jianqui used CRISPR gene editing in a botched experiment that mutated three healthy embryos, with unknown consequences for the resulting children. Despite a global outcry, there is no agreed way of preventing this from happening again.
- We can now transform whole ecosystems through a process known as a gene drive, which is essentially a genetic chain reaction. This could eradicate malaria mosquitoes, but as the scientists working on these systems have warned, it could also wreak havoc on the ecosystem.
- Well-meaning scientists trying to gain insight into the potential shape of future pandemics have deliberately produced new variants of lethal pathogens that are even more dangerous than before. These experiments were not behind the COVID-19 pandemic, but such research could inadvertently lead to an outbreak of a terrifying new disease.

These are not fantasies nor absurd predictions; this is where science has brought us.

My motivation in writing this book has been to explore my own fears about these three areas. Each of them worries me in different ways, but I recognise that many of my concerns are similar to those expressed by people faced with previous applications of genetic engineering, most of which turned out to be either exaggerated, or at least to be controllable by careful regulation and strict safety procedures. I needed to decide if these most recent developments of genetic engineering are truly novel and full of real threat, or if they, too, will turn out to be overblown in terms of both promise and peril. For the moment, I remain deeply concerned – we are indeed faced with new and serious threats and great care will be needed to negotiate the coming years. Above all, the key lesson I have learned is that to understand what these developments mean and how we should respond to them, we need to understand how we got here.

*

The history of nuclear power shows that dangerous technology can be used safely, despite its inherent potential for accidental or deliberate disaster. The rise and fall of the atom as a driver of culture and of popular anxiety also shows that as dangerous technology is safely employed, it loses some of its emotional power. Over recent years, that seems to have happened with genetic engineering too.

Many technologies have followed a similar arc, but in one extremely significant respect genetic engineering is unique. From the very outset, potential dangers led scientists to impose a temporary halt to experimentation while safety concerns were addressed.

No group of researchers, apart from geneticists, has ever voluntarily paused their work because they feared the consequences of what they might discover. Extraordinarily, this has happened not just once but four times – in 1971, in 1974, then again in 2012 and most recently in 2019.

There were some precedents for this. In the 1930s, Leo Szilard, who conceived the nuclear chain reaction, argued for the details to be kept secret; following the subsequent discovery of nuclear fission he

tried to persuade his colleagues to omit certain key bits of information from their publications to avoid helping Nazi Germany. Later, while working on the Manhattan Project, Szilard and other researchers opposed the continuing development of the atom bomb after the defeat of Germany in May 1945. But Szilard's protests were of limited effect and the result was the horror of Hiroshima and Nagasaki.

Geneticists have been more decisive in response to potential threats. In 1971, when the first experiment mixing two very different kinds of DNA – from a virus and a bacterium – was proposed, researchers raised fears that it might go horribly wrong, causing an outbreak of cancer. There were private discussions about the dangers and eventually some experiments were quietly abandoned by the handful of scientists involved. But new discoveries soon made the technique much simpler and within two years dozens of laboratories around the world could master it. The question of what might happen was posed once again, but this time on a global scale. That led to the first publicly declared research moratorium, which was announced in July 1974 and lasted about eight months while scientists argued about the issue.

The culmination of this process was a conference held in February 1975, at Asilomar in California, at which scientists came up with safe ways of performing their experiments but notably refused to consider the social or political consequences of what they were doing. Over the subsequent decades the self-regulation that was proposed at Asilomar has repeatedly been held up as an example of how science can act responsibly. And indeed, the great virtue of Asilomar was that the meeting took the potential dangers of genetic engineering very seriously indeed, thrashing out protocols that would protect researchers, the public and the environment and insisting that even with these safety measures, some experiments involving pathogens remained too dangerous to be carried out under any circumstances. But the debates were focused entirely on these biosecurity issues, with the sole objective of establishing safety criteria that would allow the moratorium to be lifted.

The organisers ruled out any discussion of moral issues, or of the potential military uses of what was known as recombinant DNA. And yet the political and social issues that have dogged the last

fifty years of the development and application of genetic engineering were precisely those that were ruled off the Asilomar agenda. Two key issues that shaped subsequent decades – the commercial exploitation of genetic engineering and the terrifying threat of new bioweapons made with recombinant DNA – were both being actively developed at the time of Asilomar but were not discussed. They were known to only a handful of privileged delegates, and no one was aware of both developments. Had there been an open debate about these matters, subsequently involving the whole world, later events might have turned out rather differently.

The reasons why molecular geneticists took this unprecedented step of halting their research until it could be made safe, while scientists in other controversial areas such as nuclear weapons research did not, probably lies as much in the people and the times as in the degree of existential threat. Genetic engineering was the right subject, in the right place, at the right time, with the right scientists involved, for such a stance to be taken.

Asilomar occurred in a period of doubt about science and its role in society, centred around the upheavals of 1968 and the long wave of global unrest and social uncertainty that surrounded those events, all of which was framed by the Cold War. Most of the organisers of Asilomar had been involved in campus protests against military research and against the US war in Vietnam and Cambodia. Furthermore, this was a field that involved a small number of scientists, working in groups of only a handful of researchers with no military or government involvement, which gave them a degree of autonomy.

The third pause in genetic engineering took place more recently, in 2012, when a few dozen scientists became alarmed at the direction being taken by their research on the extraordinarily dangerous H5N1 bird flu virus, which they were manipulating in order to prepare for future pandemics. That self-imposed moratorium lasted about eight months and, as at Asilomar, was similarly resolved through the adoption of new safety procedures, which arguably saved us from an accidental lab-leak pandemic that would have dwarfed COVID-19. However, those procedures were not globally binding – different countries have different biosecurity standards, some of which may lead to disaster in the future.

Both the recombinant DNA and the H5N1 research pauses were widely accepted and observed. The most recent call for a research moratorium, focused on heritable human gene editing, has not been met with such unanimity. In 2015 leading researchers and scientific authorities around the world declared it would be irresponsible to try and edit a human embryo using CRISPR, but there was no call for a pause on research. Indeed, those same researchers and authorities sought to chart what they called a 'prudent path' to heritable human genome editing. Then, in November 2018, He Jiankui announced to a stunned world that he had carried out such an experiment on three normal baby girls, with potentially disastrous results. A few weeks later, at the beginning of 2019, a group of leading geneticists called for a five-year moratorium on editing humans, but others, including Nobel Prize-winning leaders of the field, have rejected this approach. This time around, there is no consensus. Despite the widespread revulsion at the CRISPR babies experiment, there is no guarantee that it will not be repeated tomorrow.

These examples show the singularity of genetic engineering in the history of science and technology – its strong connection with questions of social responsibility and a sense of doing the right thing. That is why, although this book surveys the last half-century and more, the central issues it addresses revolve around the current potential of the new science and how we can control it and prevent catastrophe. In a sense, the past, present and future of genetic engineering are on trial in these pages, and you are part of the jury.

*

To some readers, the term 'genetic engineering' will have a rather old-fashioned feel. This is partly because the name by which this technology is known has morphed and shifted down the decades. From genetic engineering, through recombinant DNA, gene stitching (that one did not catch on), gene cloning and gene splicing, to genetic modification and most recently gene editing, different terms have embodied various subtleties to both scientists and the public. Sometimes these names have been adopted because they present a new application of the science as somehow less threatening than

previous, contested versions (this is clearly the case with 'gene editing' which seems simple and rather domestic). Some terms refer to a much broader field – for example, 'biotechnology' or 'synthetic biology', both of which incorporate genetic engineering as a base technology but tend to have different ambitions and outlooks. What all these approaches have in common is the ability to deliberately and precisely introduce new changes into the genes of an organism – genetic engineering.

One of the key consequences of the new ability to manipulate genes that appeared in the 1970s was that, right from the outset, this technique was turned into a technology and was given practical application. This in turn led to fears and protests as new organisms made the transition from the laboratory to the factory or the field. These challenges form an integral part of the history of genetic engineering – they not only shaped public attitudes to the science, they also led to a series of regulations designed to assuage fears and to allow the safe application of the technology.

Nevertheless, faced with the ability to mix genes from wildly different species, many people continue to feel uneasy. Writing in 1997, as global suspicion of genetically modified (GM) crops was about to reach a paroxysm, pioneer molecular biologist François Jacob reached deep into our collective psyche to identify what he thought was the fundamental problem:

> The notion of recombinant DNA is tied to the mysterious and the supernatural. It rekindles the terror associated with the hidden meanings of monsters, the revulsion engendered by the notion of two beings merged in defiance of nature.[1]

The results of genetic engineering can be unsettling, and not simply because it can seem a bit weird when put starkly (for example, in my research I use flies that have genes from jellyfish in them, controlled by other genes from yeast). But a far greater problem than any unease we might feel is that, as with any technology, the outcome of genetic engineering is not guaranteed in advance. Its essence is the ability to produce inherited changes, and change may not always go in the direction we intend.

*

This book is not simply an account of how a revolution in science and technology has taken place – how brilliant men and women have developed theories, dreamed up experiments and imagined applications – and how the dangers have been perceived and countered. It also shows how those discoveries have formed part of a broader cultural, political and economic history, shaping our present day.

One significant feature of this story is the growing internationalisation of genetic engineering. In its earliest years it was largely US-based, now every continent is touched by this science and its application, and every inhabited continent is covered in the pages that follow. There is one specific change in the geographical focus of this story which is of fundamental importance and will increase in significance in the years to come – the growing influence of Chinese research. This is a product of both the growing economic and scientific power of China and the Chinese government's long-standing commitment to the application of genetic technology. China was the first country in the world to approve a GM crop and it now has the largest number of approved gene therapy protocols. And yet China is as vulnerable to genetic nightmares as anywhere else – the prospect of GM rice divides the Chinese Communist Party leadership and has led to a strikingly open debate in the country. Genetic engineering has the power to excite and disturb right across the planet.

Throughout its history, this technology has been intertwined with broader cultural and political changes – from the US counterculture of the 1960s and early 1970s, through the get-rich-quick deregulation years of the 1980s and 1990s, the collapse of the Soviet Union and the end of the Cold War, the growing opposition to globalisation around the turn of the century, the global responses to the 9/11 attacks, right up to the fears of a new pandemic which were tragically realised at the beginning of 2020. Genetic engineering and its applications have played a significant role in local, national and global politics, shaping and threatening our future as surely as the atom shaped the post-war world.

Although the pages that follow include plenty of experimental detail, this is not an academic account covering every conceivable

aspect of the subject. The impact of genetic engineering on virtually every part of biology over the last half-century has been so overwhelming that a book detailing those effects would turn into a history of modern biology itself. As a consequence, many scientific, technical and social developments that flowed from, or coincided with, the appearance of genetic engineering are deliberately not covered in any detail here – IVF, stem cell biology, embryo research, biotechnology, mammalian cloning, synthetic biology, genomics, DNA sequencing, transhumanism and many others. Some experts will undoubtedly find that their favourite technique, their favourite experiment or their favourite researcher has been missed out for reasons of space. My apologies for any disappointment, but rather than covering all the twists and turns of the history or every conceivable implication of the technology, I have preferred to focus on the key applications of genetic engineering and how it has acted as a cultural force, prompting creators to produce works that have inspired, stimulated and amused us.

In some cases, these creations have proved so powerful that they have almost replaced the old references to *Frankenstein*. Like Mary Shelley's influential book, many of these works – from *Jurassic Park* to untold numbers of B-movies, from high-concept novels by Nobel Prize winners to clunky thrillers, from pop songs and comic books to sculptures and pieces of conceptual art – focus on the nightmares, shaping attitudes to the scientific and technological moments we have been living through for the last few decades. Like news media, TV and radio programmes, cultural and artistic artefacts have their place in the story of genetic engineering as they have refracted the science and politics of our times and left lasting traces. This broad focus makes this book much more than an inward-looking history of science.

*

Nevertheless, there is quite a bit of science in this history. I have tried to keep the technicalities to a minimum and to explain each step only as much as is strictly necessary, but if you are unsure about the basics of genetics, the following three paragraphs will give you the key information you need to begin (there is also a glossary at the back).

Our genes are made of DNA, a molecule that has two strands – the famous double helix. Each strand carries a sequence of four chemical structures called bases, which are known by their initials, A, C, G and T. The shape of these bases means that the two strands of DNA are complementary – if there is an A on one strand, the base on the opposite strand has to be a T, and vice versa. The same is true of the C and G bases. Genes consist of unique sequences of bases and, in general, a gene codes for a protein (a string of amino acids), which is produced by the cell following the instructions in the gene. Each group of three bases, called a codon, corresponds to an amino acid. Amino acids are strung together by the cell to form proteins, which can do an infinite variety of things in the organism – in particular they can be structural (for example, hair) or they can alter physiology (for example, enzymes or hormones).

When a gene is activated, the double helix is unravelled by enzymes in the cell and the gene is transcribed: the DNA on the strand that carries the gene is used to produce a molecule called messenger RNA (mRNA), which is a complementary copy of the gene, just like the DNA on the other strand, except that in RNA the T base is replaced by another base called U. This mRNA molecule is then used by cellular structures called ribosomes to turn the genetic message into a protein. Each three-base codon is read by the ribosome, and the corresponding amino acid is found within the cell and brought to the ribosome by transfer RNA (tRNA) molecules, where it is attached to the amino acid preceding it to form a protein. Ribosomes are made of RNA and protein; like everything else, they are encoded by genes. In some cases, RNA or protein produced from a gene's DNA is used by the cell to control the activity of other genes.

Viruses have played a key role in genetic engineering. They are replicating parasitic molecules, made of either DNA or RNA, concealed in a protein coat (the instructions to make that coat are encoded in the virus's DNA or RNA). The sole function of a virus is to penetrate a cell and hijack its internal mechanisms, using the cell's biochemistry to reproduce copies of the virus's DNA or RNA, and then to turn that into more viruses. There are untold numbers of different kinds of virus on the planet; most are harmless, some are

lethal. The beginning of the genetic engineering revolution occurred when scientists set out to harness the ability of viruses to introduce DNA into a cell. Their ultimate objective was to alter a virus so that it carried well-understood bacterial DNA and to transfer that DNA into a mammalian cell, thereby shedding light on the mysteries of gene function in multicellular organisms.

That is all you really need to know to start reading.* You will know a lot more by the time you have finished.

*

This book takes you through the changing science of genetic engineering, explaining the links between science and politics, ethics, business and culture, rooting our developing knowledge in the changing world of the last half-century and showing how fears and protests have been there from the very outset. This history carries lessons for all branches of science where discoveries might produce dangers, perpetuate inequalities or otherwise damage society. It highlights the importance of the general population being informed about and involved in decisions about science and its application from the very beginning.

Such social questions are not an optional add-on, something that can be left at the door of the laboratory. They are there, in embryo, in every genetic engineering experiment. They are part of the politics implicit in this revolutionary technique which has transformed science, medicine and agriculture. These issues are present in genetic engineering in a way that is not the case in other branches of genetics because, as my good friend the historian of science Michel Morange has put it, the whole point of the field is to transform molecular biology 'from a science of observation into a science of intervention and action'. When you intervene and act upon the world, rather than simply observing, when you create things that have never existed before, you run the risk of things happening that you did not intend,

*If you want to know how we discovered all this, I would immodestly recommend my 2015 book, *Life's Greatest Secret: The Race to Crack the Genetic Code* (London, Profile).

or which you may desire but others do not. Resolving these issues is a political question – science and society are intertwined.

This interventionist, creative aspect of genetic engineering was first imagined centuries ago, long before the discovery of genetics. When he died in 1626, the English thinker Sir Francis Bacon left an unfinished fragment of fiction known as *The New Atlantis*, which purported to be an account of life on the imaginary island of Bansalem, somewhere in the Pacific Ocean. A key feature of the island was Salomon's House, a kind of research institute that investigated all aspects of the natural world with a view to 'enlarging the bounds of human empire', developing not just knowledge, but also application and control. At a time when heredity was so profound a mystery that the word had no biological meaning, Bacon's fictional institute was able to manipulate plants and animals in a precise and desired way, mixing different species and creating new organisms for the benefit of all:

> We finde Meanes to make Commixtures and Copulations of diverse Kindes; which have produced New Kindes, and them not Barren, as the generall Opinion is. We make a Number of Kindes, of Serpents, Wormes, Flies, Fishes, of Putrefaction; Wheroff some are advanced (in effect) to be Perfect Creatures, like Beastes or Birds; And have Sexes, and doe Propagate.[2]

Despite the weird spelling and understandable lack of detail, Bacon was describing our world. Four centuries later, we have exactly the kind of power over nature that Bacon dreamed of. The idea of mixing the characteristics of different species goes deep into mythology – half-human, half-animal creatures are a common feature of many cultures – but Bacon's proposal that we might deliberately create such hybrids to exploit their characteristics was both novel and profoundly significant, heralding the shift in attitudes to the natural world that took place with the development of science, technology and industry over subsequent centuries. In a way, this book is about the realisation of Bacon's dream.

I hope you will be enthralled, amused, moved and alarmed by what you read here – I did not know all of this history and there were

things that I discovered that made my blood run cold. Above all, you should be informed – decisions on using the latest versions of this technology need to be in the hands of every citizen on the planet. By understanding the past and the present we can be more confident in our ability to control the future, or at least to limit the damage that might occur there. As you will see, this is too important to be left to the scientists.

Four hundred years ago, Francis Bacon hoped we would enlarge the bounds of human empire, subduing the forces of nature. To an extent, genetic engineering has helped us do that. But technology is not neutral – it changes the way we behave. In 1872 the German philosopher-revolutionary, businessman and honorary Mancunian Friedrich Engels explored the consequences of our mastery of the forces of nature through technology. As he put it, those forces avenge themselves by imposing a veritable despotism upon us. In other words, technology shapes our social organisation, it requires us to behave in a particular way. In the case of genetic engineering, this has shaped our view of life itself – some organisms have become pieces of machinery that can apparently be controlled and their behaviour predicted. But sometimes, our predictions are poor, our control is inadequate and discovery creates danger.

There is no way of unlearning what we have found out, and equally we cannot escape the implications of what we have created – we have to meet the potential threats that we now face. To do that, we must first understand them. As Francis Bacon also said, 'knowledge is power'. That is the point of this book.

Manchester, March 2022

– ONE –

PRELUDE

Humans have been changing genomes for millennia. From our earliest days in Africa, hundreds of thousands of years ago, we have inadvertently altered the genes of the animals and plants we eat, acting as a force of natural selection just like other predators. Some animals and plants were able to adapt to our attentions; others could not and went extinct, in particular the megafauna – mammoths, woolly rhinoceroses, giant sloths and so on. Then, with the slow development of agriculture around 10,000 years ago, we began to systematically domesticate animals and plants, deliberately breeding those types that suited our needs.

The results could be dramatic. Genomic analysis shows that all modern horses are descended from a small group of animals that were domesticated in the Western Eurasian steppes around 4,000 years ago.[1] Strong and docile, they rapidly replaced the other breeds of horses that we had tamed. We can see this process in the horse genome – our ancestors selected for behavioural and physiological characteristics that allowed the animals to be ridden for long distances and made them more placid, but underlying this process were unseen molecular genetic changes that we can now understand. It is even possible that, over hundreds of thousands of years,

we domesticated ourselves, intuitively selecting against aggressive behaviour and in favour of all sorts of cooperative characteristics. With the development of agriculture, we also began to use the simplest form of biotechnology, unwittingly harnessing the activity of microbes to make bread, cheese, beer and wine, inadvertently selecting the varieties that best suited our purpose.[2]

That activity has also led to insight – understanding mating and pollination became of great importance once agriculture had begun. There is a rough synchronicity between when people around the world realised how reproduction works and when they domesticated plants and animals: the growth in our knowledge of the natural world and our increasingly detailed attempts to assert control over it have gone hand in hand.[3]

Despite this deep history, 1972 marked a real qualitative change in our ability to change genes – blind tinkering became precise and deliberate manipulation. This happened through the publication of the work of a group of researchers at Stanford University in Palo Alto, California, in what is now known as Silicon Valley (not much of a valley, to be honest). The researchers, led by 45-year-old Paul Berg, took a mammalian virus called SV40 and added to it DNA from a bacterium, *Escherichia coli*. Berg's idea was to use the virus to introduce the well-understood genetic material from *E. coli* into a mammalian cell and thereby gain the first insight into how genes work in multicellular organisms. The following year the approach was simplified, allowing the fusion of DNA from virtually any organisms. Once the procedures were shown to be safe and controllable, this ability to produce what was called recombinant DNA led to the explosion of the biotechnology industry, the development of GM crops and gene therapy, massive advances in our scientific understanding of the whole of biology and, ultimately, the current excitement over CRISPR gene editing.

The techniques used during this revolution have changed – Berg's pioneering but primitive genetic engineering and today's gene editing are radically different in their detail – but in outlook and in underlying approach all the methods used over the last half-century trace their origin back to Stanford in 1972. As with any revolution, to understand the key moment and the events it unleashed, we need

to explore what came before and what came afterwards. We need to begin, not at the beginning, but before the beginning. And before there was fact, fiction could outline what might be possible, enabling thinkers to explore both the promise and the perils of future developments centuries before science could make them a reality.

*

The most powerful fictional portrayal of the dangers of science is surely *Frankenstein*, written by the teenager Mary Shelley in 1816 and published two years later.[4] Influenced by Greek mythology and the story of Prometheus, the Greek god who gave humanity fire and suffered terribly as a consequence ('The New Prometheus' is the subtitle of the book), by the Jewish myth of the Golem – a man-made creature that would do its creator's bidding – and by the German story of Faust and his pact with the Devil, Shelley's book has been taken as a warning tale about the potential dangers of the new way of knowing – science – and in particular the risks of creating something profoundly unnatural.

Towards the end of the nineteenth century, the slow discovery of the mechanisms of heredity led to this new phenomenon becoming the focus of fiction. H. G. Wells conjured the horror that might occur if modern medicine were able to create grotesque hybrid animals through vivisection in his 1896 novel *The Island of Doctor Moreau*. Eight years later, Wells imagined what would happen if food additives changed our heredity. In his now-forgotten novel *The Food of the Gods*, farm animals and children grow to giant size after consuming a substance known as Boomfood; most significantly, they pass their gigantism to their offspring, with terrible social and political consequences. *The Food of the Gods* was published three years after the rediscovery of Mendel's laws of genetics, which were first established in 1865.

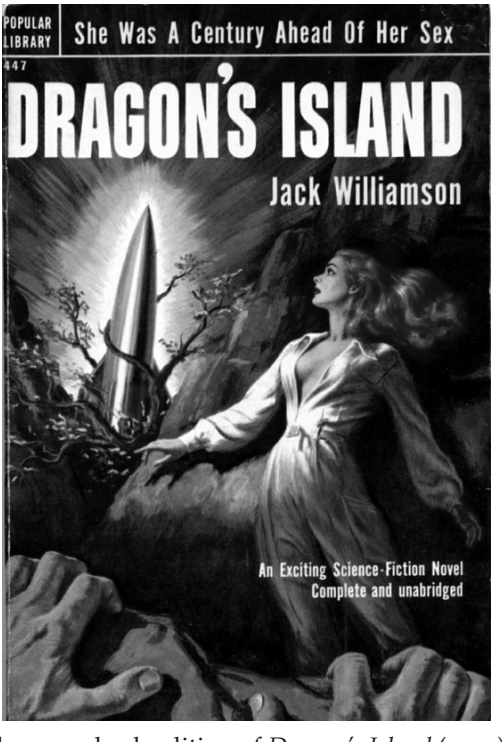
The twentieth century was the century of genetics. For its first few decades, it was also the century of eugenics – the desire to deliberately manipulate human genes by selective breeding. This was widely applied, notably in the United States and Sweden, mainly by sterilising those who were deemed unfit – in particular

the poor and the disabled. This reached its foul culmination in Nazi Germany, where selective breeding became systematic murder.[5] The most influential fictional account of the consequences of eugenics is Aldous Huxley's 1932 novel *Brave New World*, in which humans are bred in artificial wombs using Podsnap's technique and Bokanovsky's process and have a genetically determined role in society. Although Huxley made up the sciencey-sounding genetic technology employed in his dystopia, he did not have to imagine what eugenics might look like – it was around him, infesting society, irrespective of politics (the socialist Wells was one of many left-leaning eugenicists).

The horror of the Holocaust dampened the appetite for eugenics in the post-war world but growing scientific interest in the nature of genetic material and what might be done with it percolated into fiction. In 1951, the pulp science fiction writer Jack Williamson published an unremarkable novel, *Dragon's Island*, which revolved around the fictional science of what he called genetic engineering – 'a process for creating new varieties and species at will' by 'directing mutation'.[6] The result was the appearance of 'Not-men' – 'superhuman monsters … Hiding among mankind, and waiting to overwhelm us.'[7] By the end of the story the protagonists prophetically decide to set up a company to spread the benefits of the new technology and make pots of money.*

Williamson might have written a clunker (in best pulp tradition, the dramatic title and the lurid cover had little to do with the story), but he had detected the glimmer of scientific and pecuniary potential contained in a discovery that had been made in 1944 by Oswald

*Although Williamson believed he had coined the term 'genetic engineering', the phrase had already appeared in *Science* in 1949 referring to genetic counselling and eugenics. Furthermore, an earlier usage, closer to today's meaning, was made in 1934 by Nikolaj Timoféeff-Ressovky, who described the creation of mutations by radiation as a type of genetic engineering. Two years before that, a talk entitled 'Genetical Engineering', referring to the selective breeding of crops and farm animals, was given at the Sixth International Congress of Genetics. Nevertheless, Williamson was the first to use the term to describe deliberate, directed mutations. Stern, K. (1949), *Science* 110:201–8; Timoféeff-Ressovky, N. (1934), *Biological Reviews* 9:411–57; Crowe, J. (1992), *Genetics* 131:761–8.



The paperback edition of *Dragon's Island* (1952).

Avery at the Rockefeller Institute in New York. Avery showed that pneumonia bacteria could be transformed from infectious to benign, and vice versa, by adding an extract of the other kind of microbe. The earliest interpretation of Avery's work suggested that transformation induced a mutation in the receiving bacteria – it looked as though the process produced a specific genetic change. [8] This would have been revolutionary – existing methods of creating mutations with X-rays or chemicals were essentially random, while selective breeding, which had been the basis of agriculture for millennia, was a slow, hit-and-miss process.

But this interpretation was wrong. Avery and his colleagues had in fact discovered something much more fundamental: the nature of the genetic material itself. To their surprise, the material they transferred between bacteria – they called it the transforming principle – turned out to be made of deoxyribonucleic acid, or DNA.

This substance had been thought to have a purely structural role in chromosomes, which carry genes – it was seen as a kind of scaffold, while genes were generally assumed to be made of proteins. Through a series of careful experiments, Avery and his colleagues, Colin MacLeod and Maclyn McCarty showed that, in bacteria at least, genes were made of DNA. This opened the road to decades of discoveries in molecular biology, the great new science of the second half of the twentieth century.

During the 1950s, speculation about transferring DNA from one organism to another, or using enzymes to change DNA sequences, moved from science fiction into science itself. In December 1958, Ed Tatum gave a lecture in Stockholm, to mark his share in half of the 1958 Nobel Prize in Physiology or Medicine for showing with George Beadle that genes can produce enzymes (the other half of the prize had gone to Joshua Lederberg, who had turned to bacterial genetics after reading Avery's 1944 paper on DNA). Tatum was speaking a little over five years after Jim Watson and Francis Crick, using data from Rosalind Franklin and from Maurice Wilkins, had proposed that DNA has a double-helix structure. At this time the role of DNA as the hereditary material in all life was still no more than a working hypothesis. It had taken over a decade for Avery's discovery to be widely accepted, and there was still no decisive proof that all genes were made of DNA. Scientists could be reasonably sure of the genetic function of DNA only in bacteria and viruses; the situation in more complex organisms remained unclear until the late 1960s.[9]

The closing part of Tatum's speech – a mere 400 words entitled 'Predictions' – looked into the future and foresaw our present:

> Perhaps within the lifetime of some of us, the code of life processes tied up in the molecular structure of proteins and nucleic acids will be broken. This may permit the improvement of all living organisms by processes which we might call biological engineering.[10]

The kind of engineering Tatum had in mind involved synthesising DNA molecules with desired characteristics and introducing these molecules into an organism by injection or by using engineered

viruses. The aim of this work, he argued, would be to cure genetic defects and to create more productive and disease-resistant animals and plants. He predicted that a full understanding of the interplay of nature and nurture would lead to a new Renaissance 'in which the major sociological problems will be solved and mankind will take a big stride towards the state of world brotherhood and mutual trust and well-being envisaged by Alfred Nobel'.

Although Tatum's description of the direction of science was remarkably accurate, you may have noticed that it did not lead to his utopia. Tatum, like many who predict the future, underestimated the difficulties in applying scientific discoveries. Understanding needs to be turned into reliable and scalable technology and there must be cultural acceptance of both the techniques involved and their application. That acceptance can be affected by all sorts of contingent factors: in the years that followed Tatum's speech, political and social developments profoundly altered global views on science, building on a growing suspicion of the power of the atom that dominated the Cold War world of the 1950s. By the end of the 1960s a new, pessimistic attitude crystallised, colouring and shaping responses to the coming revolution in genetics.

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In January 1960, *Time* magazine named US scientists as its 'Men of the Year'.[11] The fifteen men who represented the profession were mainly physicists, but there were two molecular geneticists on the list – Beadle and Lederberg – and the *Time* article hailed the 'glittering opportunities' of molecular biology, in particular the hope that in the near future 'it should become possible to treat and correct genetic diseases, now mostly incurable'. For *Time*, science was 'at the apogee of its power for good or evil'.

A mere twelve months later the balance seemed to have shifted towards the negative. In January 1961, as President Eisenhower handed over power to his successor, John F. Kennedy, the old soldier broadcast to the nation, alerting the American people to the growing influence of the military-industrial complex, criticising the links between science and government, and predicting that 'public policy

could itself become the captive of a scientific-technological elite'. Eisenhower's gnomic warning – soon amplified by fears of nuclear annihilation during the Cuban Missile Crisis of October 1962 – connected to a slow growth in pessimism about science that was taking place across Western societies.[12]

These doubts and suspicions were principally driven by the menace of nuclear weapons, and focused not only on the immediate threat of thermonuclear annihilation, but also on the danger of radioactive fallout from nuclear tests that was increasingly recognised as a potential trigger for a possible epidemic of cancers and mutations. In 1954, US nuclear tests on Bikini Atoll caused a scandal when they produced unexpectedly high levels of fallout, which affected hundreds of people on nearby islands and on a Japanese fishing boat. In Nevil Shute's best-selling 1957 novel *On the Beach,* which was made into a film two years later, nuclear weapons cause the death of humanity through a massive cloud of fallout that rolls around the planet. By the mid-1950s there were alarming numbers of atmospheric tests (over 250 had taken place by 1958) and calls grew for a ban on atmospheric and undersea tests. Eisenhower was initially supportive of a 'moratorium' on tests – this term became widespread with regard to nuclear weapons and would eventually be used repeatedly down the decades in debates about the dangers of genetic engineering.

Eventually, after a great deal of politicking on both sides of the Iron Curtain and a lot of campaigning by protestors, including chemist Linus Pauling, who won the Nobel Peace Prize in 1962 for his role, the Partial Test Ban Treaty came into effect at the end of 1963. That did not mean that the threat of fallout went away. In the United States there were repeated attempts to develop the peaceful use of nuclear weapons through Project Plowshare, in which nuclear bombs would gouge out new harbours in Alaska and Australia or even blast a new sea-level Panama Canal that would directly link the Atlantic and Pacific Oceans (this would have required anywhere between 185 and 925 explosions, depending on the route).[13] Devised by Manhattan Project veteran and 'father of the hydrogen bomb' Edward Teller, Project Plowshare carried out twenty-seven test detonations between 1957 and 1973 (it was finally defunded in 1975), leaving

100-metre-deep craters and ejecting debris nearly five kilometres into the atmosphere. From the outset, the project was dogged by hubris, as grandiose plans turned out to be unfeasible, unwanted or hideously expensive, while there was repeated opposition from the public and from local authorities who were concerned that underground explosions might produce dangerous levels of fallout. Which is what happened. Radioactive isotopes were repeatedly found in the environment – including in neighbouring towns and on farmland, causing widespread protest and weakening governmental support for a project that looked increasingly out of step with reality.

Hollywood picked up on these fallout fears in the crudest way – 1954 saw the release of *Them!*, a monster movie in which radiation from atomic tests led to the appearance of two-metre-long giant ants that threatened Los Angeles. When the ants were finally defeated by conventional weaponry, one of the scientists concluded: 'When Man entered the Atomic Age, he opened the door to a new world. What we may eventually find in that new world, nobody can predict.' The power of the atom and the power of the gene became intertwined in the popular imagination. Media aimed at the younger generation was particularly interested in the question – key Marvel Comics characters created in the early 1960s, such as the Hulk, Spider-Man and the X-Men, derived their superpowers from the effects of radioactivity on their DNA.* Similarly, when the Daleks, the iconic baddies in the BBC TV science fiction series *Doctor Who*, first appeared in 1963

*Despite its apparent triviality, the changing origin story of the X-Men nicely illustrates one of the themes of this book – the shift in public fears from radiation to genetic engineering and how these were reflected in culture at all levels. At their creation, the X-Men gained their powers through mutations that were implicitly caused by radiation, with this link being explicit in the case of The Beast (his father was a nuclear engineer, as explained in *X-Men* #15, from 1965). But in 1980, as fears of radiation receded and worries about the power of genetics grew, a new layer of Marvel mythology was added, involving hokey von Däniken-esque aliens known as the Celestials. According to the new origin backstory, a million years ago the Celestials visited the Earth and carried out a series of genetic engineering experiments on pre-humans (*What If…* #23). One experiment, carried out by a Celestial called Oneg the Prober, produced the human lineage, replete with a 'latent gene' that when mutated would later produce superpowered individuals.

they were revealed to be mutants created by a centuries-long atomic war on the planet Skaro.

Both the bomb test moratorium and the test ban treaty required the public to trust their political and military leaders at a time when confidence in authority – including in science – was becoming increasingly fragile. Intellectuals began to question science's claims to authoritative knowledge, in particular following the publication of Thomas Kuhn's *The Structure of Scientific Revolutions* in 1962. Kuhn explored how scientific disputes were also struggles for power within science; to his dismay, some readers concluded that truth was a purely relative thing and that ultimately science was just another story. More concretely, there were growing worries about the inadvertent effects of chemicals, as highlighted by the thalidomide scandal, when a drug prescribed to relieve morning sickness caused tens of thousands of children to be born with deformities. The side effects of chemicals were also at the heart of Rachel Carson's prophetic 1962 book *Silent Spring*, which described the unintended environmental effects of insecticides. Meanwhile, the fallibility of technology and the potential for a technical incident to produce annihilation were portrayed with savage black humour in Stanley Kubrick's 1964 film, *Doctor Strangelove*.

The creeping American involvement in Vietnam was a key contributory factor to a growing mistrust of government in the United States.[14] Gradual awareness of the use of chemical weapons such as napalm, Agent Orange and dioxin in Vietnam reinforced widespread suspicions about the involvement of scientists in government-sponsored projects.[15] * Throughout the 1950s and 1960s, fiction writers explored the inadvertent consequences of chemical and microbial research, for example in John Christopher's novel *The Death of Grass* (1956), in which a pesticide causes a virus to mutate and kill all grasses and related plants, leading to a global famine. In the United Kingdom, concerns about bioweapons were amplified in 1962 when a scientist at the Microbiological Research Establishment at Porton Down died after being accidentally infected with bubonic plague.

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* Ironically, leading scientists, such as the pioneer molecular geneticist Matthew Meselson, played a key role in exposing the use of these weapons.