– ONE –

GENES BEFORE DNA

In the early decades of the nineteenth century, the leaders of the wool industry in the central European state of Moravia were keen to improve the fleeces produced by their sheep. Half a century earlier, a British businessman farmer called Robert Bakewell had used selective breeding to increase the meat yield of his flocks; now the Moravian wool merchants wanted to emulate his success. In 1837 the Sheep Breeders' Society organised a meeting to discuss how they could produce more wool. One of the speakers was the new Abbot of the monastery at Brnö, a city that was at the heart of the country's wool production. Abbot Napp was intensely interested in the question of heredity and how it could be used to improve animal breeds, fruit crops and vines; this was not simply a hobby – the monastery was also a major landowner. At the meeting, Napp argued that the best way to increase wool production through breeding would be to address the fundamental underlying issue. As he put it impatiently: 'What we should have been dealing with is not the theory and process of breeding. But the question should be: *what is inherited and how*?'[1]

This question, which looks so straightforward to us, was at the cutting edge of human knowledge, as the words 'heredity' and 'inheritance' had only recently taken on biological meanings.[2]

Despite the centuries-old practical knowledge of animal breeders, and the popular conviction that 'like breeds like', all attempts to work out the reasons behind the various resemblances between parents and offspring had foundered when faced with the range of effects that could be seen in human families: skin colour, eye colour and sex all show different patterns of similarity across the generations. A child's skin colour tends to be a blend of the parental shades, their eye colour can sometimes be different from both parents, and in all except a handful of cases the sex of the child is the same as only one parent. These mysterious and mutually contradictory patterns – all of which were considered by the seventeenth-century physician William Harvey, one of the first people to think hard about the question – made it impossible to come up with any overall explanation using the tools of the time.[3] Because of these problems it took humanity centuries to realise that something involved in determining the characteristics of an organism was passed from parents to offspring. In the eighteenth and early nineteenth centuries, the tracing of human characteristics such as polydactyly (extra fingers) and Bakewell's selective breeding had finally convinced thinkers that there was a force at work, which was termed 'heredity'.[4] The problem was now to discover the answer to Napp's question – what is inherited and how?

Napp had not made this conceptual breakthrough alone: other thinkers such as Christian André and Count Emmerich Festetics had been exploring what Festetics called 'the genetic laws of nature'. But unlike them, Napp was able to organise and encourage a cohort of bright intellectuals in his monastery to explore the question, a bit like a modern university department focuses on a particular topic. This research programme reached its conclusion in 1865, when Napp's protégé, a monk named Gregor Mendel, gave two lectures in which he showed that, in pea plants, inheritance was based on factors that were passed down the generations. Mendel's discovery, which was published in the following year, had little impact and Mendel did no further work on the subject; Napp died shortly afterwards, and Mendel devoted all his time to running the monastery until his death in 1884. The significance of his discovery was not appreciated, and for nearly two decades his work was forgotten.[5] But in 1900 three

European scientists – Carl Correns, Hugo de Vries and Erich von Tschermak – either repeated Mendel's experiments or read his paper and publicised his findings.[6]

The century of genetics had begun.

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The rediscovery of Mendel's work led to great excitement, because it complemented and explained some recent observations. In the 1880s, August Weismann and Hugo de Vries had suggested that, in animals, heredity was carried by what Weismann called the germ line – the sex cells, or egg and sperm. Microscopists had used newly discovered stains to reveal the presence of structures inside cells called chromosomes (the word means 'coloured body') – Theodor Boveri and Oscar Hertwig had shown that these structures copied themselves before cell division. In 1902, Walter Sutton, a PhD student at Columbia University in New York, published a paper on the grasshopper in which he used his own data and Boveri's observations to audaciously suggest that the chromosomes 'may constitute the physical basis of the Mendelian law of heredity'.[7] As he put it in a second paper, four months later: 'we should be able to find an exact correspondence between the behaviour in inheritance of any chromosome and that of the characters associated with it in the organism'.[8]

Sutton's insight – which Boveri soon claimed he had at the same time – was not immediately accepted.[9] First there was a long tussle over whether Mendel's theory applied to all patterns of heredity, and then people argued over whether there truly was a link with the behaviour of chromosomes.[10] In 1909, Wilhelm Johannsen coined the term 'gene' to refer to a factor that determines hereditary characters, but he explicitly rejected the idea that the gene was some kind of physical structure or particle. Instead he argued that some characters were determined by an organised predisposition (writing in German, he used the nearly untranslatable word *Anlagen*) contained in the egg and sperm, and that these *Anlagen* were what he called genes.[11]

One scientist who was initially hostile to the new science of what was soon known as 'genetics' was Thomas Hunt Morgan, who

also worked at Columbia (by this time Sutton had returned to medical school; he never completed his PhD).[12] Morgan had obtained his PhD in marine biology, investigating the development of pycnogonids or sea spiders, but he had recently begun studying evolution, using the tiny red-eyed vinegar fly, *Drosophila*.[13] Morgan subjected his hapless insects to various environmental stresses – extreme temperatures, centrifugal force, altered lighting conditions – in the vain hope of causing a change that could be the basis of future evolution. Some minor mutations did appear in his fly stocks, but they were all difficult to observe. In 1910, Morgan was on the point of giving up when he found a white-eyed fly in his laboratory stocks. Within weeks, new mutants followed and by the summer there were six clearly defined mutations to study, a number of which, like the white-eyed mutant, seemed to be expressed more often in males than in females. Morgan's early doubts about genetics were swept away by the excitement of discovery.

By 1912, Morgan had shown that the white-eyed character was controlled by a genetic factor on the 'X' sex chromosome, thereby providing an experimental proof of the chromosomal theory of heredity. Equally importantly, he had shown that the shifting patterns of inheritance of groups of genes was related to the frequency with which pairs of chromosomes exchanged their parts ('crossing over') during the formation of egg and sperm.[14] Characters that tended to be inherited together were interpreted as being produced by genes that were physically close together on the chromosome – they were less likely to be separated during crossing over. Conversely, characters that could easily be separated when they were crossed were interpreted as being produced by genes that were further apart on the chromosome. This method enabled Morgan and his students – principally Alfred Sturtevant, Calvin Bridges and Hermann Muller – to create maps of the locations of genes on the fly's four pairs of chromosomes. These maps showed that genes are arranged linearly in a one-dimensional structure along the length of the chromosome.[15] By the 1930s, Morgan's maps had become extremely detailed, as new staining techniques revealed the presence of hundreds of bands on each chromosome. As Sutton had predicted, the patterns of these bands could be linked to the patterns with which mutations were

inherited, so particular genes could be localised to minute fragments of the chromosome.

As to what genes were made of, that remained a complete mystery. In 1919, Morgan discussed two alternatives, neither of which satisfied him. A gene might be a 'chemical molecule', he wrote, in which case 'it is not evident how it could change except by altering its chemical constitution'. The other possibility was that a gene was 'a fluctuating amount of something' that differed between individuals and could change over time. Although this second model provided an explanation of both individual differences and the way in which organisms develop, the few results that were available suggested that it was not correct. Morgan's conclusion was to shrug his shoulders: 'I see at present no way of deciding', he told his readers.[16]

Even fourteen years later, in 1933, when Morgan was celebrating receiving the Nobel Prize for his work, there had been little progress. As he put it starkly in his Nobel Prize lecture: 'There is no consensus of opinion amongst geneticists as to what the genes are – whether they are real or purely fictitious.' The reason for this lack of agreement, he argued, was because 'at the level at which the genetic experiments lie, it does not make the slightest difference whether the gene is a hypothetical unit, or whether the gene is a material particle. In either case the unit is associated with a specific chromosome, and can be localized there by purely genetic analysis.'[17] It may seem strange, but for many geneticists in the 1930s, what genes were made of – if, indeed, they were made of anything at all – did not matter.

In 1926, Hermann Muller made a step towards proving that genes were indeed physical objects when he showed that X-rays could induce mutations. Although not many people believed his discovery – among the doubters was his one-time PhD supervisor Morgan, with whom he had a very prickly relationship – within a year his finding was confirmed. In 1932, Muller moved briefly to Berlin, where he worked with a Russian geneticist, Nikolai Timoféef-Ressovsky, pursuing his study of the effects of X-rays. Shortly afterwards, Timoféef-Ressovsky began a project with the radiation physicist Karl Zimmer and Max Delbrück, a young German quantum physicist who had been working with the Danish physicist Nils Bohr. The trio decided to apply 'target theory' – a central concept in

the study of the effects of radiation – to genes.[18] By bombarding a cell with X-rays and seeing how often different mutations appeared as a function of the frequency and intensity of the radiation, they thought that it should be possible to deduce the physical size of the gene (the 'target'), and that measuring its sensitivity to radiation might reveal something of its composition.

The outcome of this collaboration was a joint German-language publication that appeared in 1935, called 'On the nature of gene mutation and gene structure', more generally known as the Three-Man Paper.[19] The article summarised nearly forty studies of the genetic effects of radiation and included a long theoretical section by Delbrück. The trio concluded that the gene was an indivisible physicochemical unit of molecular size, and proposed that a mutation involved the alteration of a chemical bond in that molecule. Despite their best efforts, however, the nature of the gene, and its exact size, remained unknown. As Delbrück explained in the paper, things were no further on from the alternatives posed by Morgan in 1919:

> We will thus leave unresolved the question of whether the individual gene has a polymeric form that arises through the repetition of identical structures of atoms, or whether it exhibits no such periodicity.[20]

The Russian geneticist Nikolai Koltsov was bolder than Delbrück or Morgan. In a discussion of the nature of 'hereditary molecules' published in 1927, Koltsov, like Delbrück, argued that the fundamental feature of genes (and therefore of chromosomes) was their ability to replicate themselves perfectly during cell division.[21] To explain this phenomenon, Koltsov proposed that each chromosome consisted of a pair of protein molecules that formed two identical strands; during cell division, each strand could be used as a template to produce another, identical, strand. Furthermore, he suggested that because these molecules were so long, the amino acid sequences along the proteins could provide massive variation that might explain the many functions of genes.[22] However perceptive this idea might look in the light of what we now know – the double helix structure of DNA and the fact that genes are composed of

molecular sequences – Koltsov's argument was purely theoretical. Furthermore, it was not unique – in a lecture given in 1921, Hermann Muller picked up on a suggestion by Leonard Troland from 1917 and drew a parallel between the replication of chromosomes and the way in which crystals grow:

> each different portion of the gene structure must – like a crystal – attract to itself from the protoplasm materials of a similar kind, thus moulding next to the original gene another structure with similar parts, identically arranged, which then become bound together to form another gene, a replica of the first.[23]

In 1937, the British geneticist J. B. S. Haldane came up with a similar idea, suggesting that replication of genetic material might involve the copying of a molecule to form a 'negative' copy of the original.[24] Koltsov's views were initially published in Russian and then translated into French, but like Haldane's speculation they had no direct influence on subsequent developments.[25] Koltsov died in 1940, aged 68, having been accused of fascism because of his opposition to Stalin's favoured scientist, Trofim Lysenko, who denied the reality of genetics.[26]

Koltsov's assumption that genes were made of proteins was widely shared by scientists around the world. Proteins come in all sorts of varieties that could thereby account for the myriad ways in which genes act. Chromosomes are composed partly of proteins but mainly of a molecule that was then called nuclein – what we now call deoxyribonucleic acid, or DNA. The composition of this substance showed little variability – the leading expert on nucleic acids was the biochemist Phoebus Levene, who for over two decades explained that nucleic acids were composed of long chains of repeated blocks of four kinds of base (in DNA these were adenine, cytosine, guanine and thymine – subsequently known by their initials – A, C, G and T) which were present in equal proportions.[27] This idea, which was called the tetranucleotide hypothesis ('tetra' is from the Greek for four) dominated thinking about DNA; it suggested that these long and highly repetitive molecules probably had some structural

function, unlike the minority component of chromosomes, proteins, which were good candidates for the material basis of genes simply because they were so variable. As Swedish scientist Torbjörn Caspersson put it in 1935:

> If one assumes that the genes consist of known substances, there are only the proteins to be considered, because they are the only known substances which are specific for the individual.[28]

This protein-centred view of genes was reinforced that same year when 31-year-old Wendell Stanley reported that he had crystallised a virus, and that it was a protein.[29] Stanley studied tobacco mosaic disease – a viral disease that infects the tobacco plant. Stanley took an infected plant, extracted its juice and was able to crystallise what looked like a pure protein that had the power to infect healthy plants. Although viruses were mysterious objects, in 1921 Muller had suggested that they might be genes, and that studying them could provide a route to understanding the nature of the gene.[30] Viruses, it appeared, were proteins, so presumably genes were, too. During the 1930s, many researchers, including Max Delbrück, began studying viruses, which were considered to be the simplest forms of life. Whether viruses are alive continues to divide scientists; whatever the case, this approach of studying the simplest form of biological organisation was extremely powerful. Delbrück, along with his colleague Salvador Luria, focused on bacteriophages (or 'phage') – viruses that infected bacteria, and in the 1940s an informal network of researchers called the phage group grew up around the pair as they tried to make fundamental discoveries that would also apply to complex organisms.[31]

Stanley's discovery caused great excitement in the press – for the *New York Times* it meant that 'the old distinction between life and death loses some of its validity'. Although within a few years valid doubts were expressed about Stanley's claim that he had isolated a pure protein – water and other contaminants were present and, as he admitted, it was nearly impossible to prove that a protein was pure – the overwhelming view among scientists was that genes, and viruses, were proteins.[32]

The most sophisticated attempt to link this assumption with speculation about the structure of genes was made in 1935 by the Oxford crystallographer Dorothy Wrinch. In a talk given at the University of Manchester, she suggested that the specificity of genes – their ability to carry out such a wide variety of functions – was determined by the sequence of protein molecules that were bound perpendicularly to a scaffold of nucleic acids, a bit like a piece of weaving. As she emphasised, however, 'there is an almost complete dearth of experimental and observational facts upon which the testing and further development of the hypothesis now put forward must necessarily depend.' Nevertheless, her conclusion was optimistic, as she encouraged her colleagues to explore the nature of the chromosome and of the gene:

> The chromosome is not a phenomenon belonging to a closed field. Rather it should take its place among the objects worthy of being treated with all possible subtleties and refinement of concept and technique belonging to all the sciences. A concerted attack in which the full resources of the world state of science are exploited can hardly fail.[33]

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In the 1930s, most geneticists were not particularly concerned with finding out what genes are made of; they were more interested in discovering what genes actually do. There was a potential link between these two approaches. As the *Drosophila* geneticist Jack Schultz put it in 1935, by studying the effects of genes it should be possible 'to find out something about the nature of the gene'.[34] One of the scientists who took Schultz's suggestion very seriously was George Beadle, who had studied the genetics of eye colour in *Drosophila* in Morgan's laboratory, alongside the Franco-Russian geneticist Boris Ephrussi. When Ephrussi returned to Paris, Beadle followed him to continue their work. Their objective was to establish the biochemical basis of the mutations that changed the eye-colour of *Drosophila* flies. Beadle and Ephrussi's experiments failed: the biochemistry of their system was too complicated, and they were unable to extract the relevant

chemicals from the fly's tiny eyes. They knew the genes that were involved, and they knew the effect they had on eye colour, but they did not know why.

Beadle returned to the US, determined to crack the problem of how genes could affect biochemistry, but equally certain that he had to use an organism that could be studied biochemically. He found the answer in the red bread mould *Neurospora*. This hardy fungus can survive in the near absence of an external supply of vitamins because it synthesises those it needs. To gain an insight into the genetic control of biochemical reactions, Beadle decided to create *Neurospora* mutants that could not synthesise these vitamins.

Together with microbiologist Edward Tatum, Beadle followed Muller's approach and irradiated *Neurospora* spores with X-rays in the hope of producing mutant fungi that required added vitamins to survive, thereby opening up the possibility of studying the genetics of vitamin biosynthesis. Beadle and Tatum soon found mutants that were unable to synthesise particular vitamins, and published their findings in 1941.[35] Each mutation affected a different enzymatic step in the vitamin's biosynthetic pathway – this was experimental proof of the widely held view, going back to the beginning of the century, that genes either produced enzymes or indeed simply were enzymes.[36] When Beadle presented their findings at a seminar at the California Institute of Technology (Caltech) in Pasadena, the audience was stunned. He spoke for only thirty minutes and then stopped. There was a nonplussed silence – one member of the audience recalled:

> We had never heard such experimental results before. It was the fulfilment of a dream, the demonstration that genes had an ascertainable role in biochemistry. We were all waiting – or perhaps hoping – for him to continue. When it became clear that he actually was finished, the applause was deafening.[37]

In the following year, Beadle and Tatum suggested that 'As a working hypothesis, a single gene may be considered to be concerned with the primary control of a single specific chemical reaction.'[38] A few years later, a colleague refined this to the snappier 'one gene, one

enzyme hypothesis'. There was support for this view from work on human genetic diseases such alkaptonuria – in 1908 Archibald Garrod had suggested that this disease might involve defective enzyme production. But Beadle and Tatum's hypothesis met with opposition at the time, partly because it was known that genes have multiple effects, while their hypothesis – or rather, the 'one gene, one enzyme' catch-phrase by which it came to be known – seemed to suggest that each gene did only one thing: control an enzyme.[39]

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Trinity College sits in the heart of Dublin, its grey three-storey neoclassical buildings positioned around lawns and playing fields. At the eastern end of the campus there is another grey building, built in 1905 in a rather different style. This is the Fitzgerald Building, or the Physical Laboratory as it is called in deeply engraved letters on the stone lintel. On the top floor there is a lecture theatre, and in the late afternoon of the first Friday of February 1943, around 400 people crowded onto the varnished wooden benches. According to *Time* magazine, among those lucky enough to get a seat were 'Cabinet ministers, diplomats, scholars and socialites', as well as the Irish Prime Minister, Éamon de Valera.[40] They were there to hear the Nobel Prize-winning physicist Erwin Schrödinger give a lecture with the intriguing title 'What is life?' The interest was so great that scores of people were turned away, and the lecture had to be repeated the following Monday.[41]

Schrödinger had arrived in Dublin after fleeing the Nazis – he had been working at Graz University in Austria when the Germans took over in 1938. Although he had a reputation as an opponent of Hitler, Schrödinger published an accommodating letter about the Nazi takeover, in the hope of being left alone. This tactic failed, and he had to flee the country in a hurry, leaving his gold Nobel medal behind. De Valera, who was interested in physics, offered Schrödinger a post in Dublin's new Institute for Advanced Studies, and the master of quantum mechanics found himself in Ireland.[42]

On three consecutive Fridays, 56-year-old Schrödinger walked into the Fitzgerald Building lecture theatre to give his talks, in which

he explored the relation between quantum physics and recent discoveries in biology.[43] His first topic was the way in which life seems to contradict the second law of thermodynamics. Since the nineteenth century it has been known that, in a closed system, energy will dissipate until it reaches a constant and even level: physicists explain this in terms of the increasing amount of disorder, or entropy, that inevitably appears in such systems. Organisms seem to contradict this fundamental law because we are highly ordered forms of matter that concentrate energy in a very restricted space. Schrödinger's explanation was that life survives 'by continually sucking orderliness from its environment' – he described order as 'negative entropy'. This apparent breach of one of the fundamental laws of the Universe does not cause any problems for physics, because on a cosmological scale our existence is so brief, our physical dimensions so minute, that the iron reality of the second law does not flutter for an instant. Whether life exists or not, entropy increases inexorably. According to our current models, this will continue until the ultimate heat death of the Universe, when all matter will be evenly spaced and nothing happens, and it carries on not happening forever.

Schrödinger encountered far greater difficulties when he came to discuss his second topic: the nature of heredity. Like Koltsov and Delbrück before him, Schrödinger was struck by the fact that the chromosomes are accurately duplicated during ordinary cell division ('mitosis' – this is the way in which an organism grows) and during the creation of the sex cells ('meiosis'). For your body to have reached its current size there have been trillions of mitotic cell divisions and through all that copying and duplicating the code has apparently been reliably duplicated – in general, development proceeds without any sign of a mutation or a genetic aberration. Furthermore, genes are reliably passed from one generation to another: Schrödinger explained to his audience that a well-known characteristic such as the Hapsburg, or Habsburg, lip – the protruding lower jaw shown by members of the House of Hapsburg – can be tracked over hundreds of years, without apparently changing.

For biologists, this apparently unchanging character of genes was simply a fact. However, as Schrödinger explained to his Dublin audience, it posed a problem for physicists. Schrödinger calculated

that each gene might be composed of only a thousand atoms, in which case genes should be continuously shimmering and altering because the fundamental laws of physics and chemistry are statistical; although overall atoms tend to behave consistently, an individual atom can behave in a way that contradicts these laws.[44] For most objects that we encounter, this does not matter: things such as tables or rocks or cows are made of so many gazillions of atoms that they do not behave in unpredictable ways. A table remains a table; it does not start spontaneously turning into a rock or a cow. But if genes are made of only a few hundred atoms, they should display exactly that kind of uncertain behaviour and they should not remain constant over the generations, argued Schrödinger. And yet experiments showed that mutations occurred quite rarely, and that when they did happen they were accurately inherited. Schrödinger outlined the problem in the following terms:

> incredibly small groups of atoms much too small to display exact statistical laws … play a dominating role in the very orderly and lawful events within a living organism. They have control of the observable large-scale features which the organism acquires in the course of its development, they determine important characteristics of its functioning; and in all this very sharp and very strict biological laws are displayed.[45]

The challenge was to explain how genes act lawfully, and cause organisms to behave lawfully, while being composed of a very small number of atoms, a significant proportion of which may be behaving unlawfully. To resolve this apparent contradiction between the principles of physics and the reality of biology, Schrödinger turned to the most sophisticated theory of the nature of the gene that existed at the time, the Three-Man Paper by Timoféef-Ressovsky, Zimmer and Delbrück.

As Schrödinger explored the nature of heredity for his audience, he was forced to come up with an explanation of what exactly a gene contained. With nothing more than logic to support his hypothesis, Schrödinger argued that chromosomes 'contain in some kind of code-script the entire pattern of the individual's future development

and of its functioning in the mature state.' This was the first time that anyone had clearly suggested that genes might contain, or even could simply be, a code.

Taking his idea to its logical conclusion, Schrödinger argued that it should be possible to read the 'code-script' of an egg and know 'whether the egg would develop, under suitable conditions, into a black cock or into a speckled hen, into a fly or a maize plant, a rhododendron, a beetle, a mouse or a woman.'[46] Although this was partly an echo of the earliest ideas about how organisms develop and the old suggestion that the future organism was preformed in the egg, Schrödinger's idea was very different. He was addressing the question of *how* the future organism was represented in the egg and the means by which that representation became biological reality, and suggesting these were one and the same:

> The chromosome structures are at the same time instrumental in bringing about the development they foreshadow. They are law-code and executive power – or, to use another simile, they are architect's plan and builder's craft – in one.[47]

To explain how his hypothetical code-script might work – it had to be extremely complicated because it involved 'all the future development of the organism' – Schrödinger resorted to some simple mathematics to show how the variety of different molecules found in an organism could be encoded. If each biological molecule were determined by a single 25-letter word composed of five different letters, there would be 372,529,029,846,191,405 different possible combinations – far greater than the number of known types of molecule found in any organism. Having shown the potential power of even a simple code, Schrödinger concluded that 'it is no longer inconceivable that the miniature code should precisely correspond with a highly complicated and specified plan of development and should somehow contain the means to put it into operation.'[48]

Although this was the first public suggestion that a gene contained something like a code, in 1892 the scientist Fritz Miescher had come up with something vaguely similar. In a private letter, Miescher had argued that the various forms of organic molecules

were sufficient for 'all the wealth and variety of hereditary transmission [to] find expression just as all the words and concepts of all languages can find expression in twenty-four to thirty alphabetic letters.'[49] Miescher's view can appear far-seeing, especially given that he was also the discoverer of DNA, or, as he called it, nuclein. But Miescher never argued that nuclein was the material making up these letters and his suggestion was not made public for nearly eighty years. Above all, the vague letter and word metaphor was nowhere near as precise as Schrödinger's code-script concept.

Schrödinger then explored what the gene-molecule might be made of and suggested that it was what he called a one-dimensional aperiodic crystal – a non-repetitive solid, with the lack of repetition being related to the existence of the code-script. The non-repetition provided the variety necessary to specify so many different molecules in an organism. Although Troland, Muller and Koltsov had all suggested two decades earlier that genes might grow like crystals, Schrödinger's idea was far more precise. His vision of gene structure was focused on the non-repetitive nature of the code-script, rather than on the relatively simple parallel between the copying of chromosomes and the ability of crystals to replicate their structure.[50]

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Schrödinger's words would have had little influence had they simply hovered in the Dublin air and briefly resonated in the minds of the more attentive listeners. The sole international report to describe the lectures, which appeared in *Time* magazine in April, did not refer in detail to anything that Schrödinger said, and there are no indications that any of his ideas escaped to the outside world. The only detailed account appeared in *The Irish Press*, which managed to condense his main arguments, and included both the code-script and aperiodic crystal ideas.[51] Other newspapers found it difficult to give the story the attention it deserved; when Schrödinger gave a version of his lectures in Cork in January 1944, the local newspaper, *The Kerryman*, gave his talk equal coverage to the Listowel Pig Fair (there was good demand for the 126 pigs on sale, they reported).[52]

Schrödinger felt that the public would be interested in his views,

and as soon as he had finished the lectures he began to turn them into a book, with the addition of a brief and deliberately controversial conclusion. Schrödinger had closed his lectures with a pious nod in the direction of his overwhelmingly Catholic audience, proclaiming that the 'aperiodic crystal forming the chromosome fibre' was 'the finest masterpiece ever achieved along the lines of the Lord's quantum mechanics'. But in a new Epilogue, written specially for publication and entitled 'Determinism and free will', Schrödinger explored his lifelong belief in the mystical Hindu philosophy of Vedanta. He argued that individual human identity was an illusion, and he criticised official Western creeds for their superstitious belief in the existence of individual souls. His point was not that there was no evidence that souls exist but rather that individual consciousness is the illusory expression of a single universal soul. He expressed this in what he admitted were 'blasphemous and lunatic' terms for the Christian tradition, but which he apparently considered to be true: 'I am God Almighty'.

The book was about to be printed by a respected Dublin publishing house when someone in the company got cold feet. In 1940s Ireland the Catholic Church retained a stranglehold over culture, and it was not possible to criticise Christian beliefs in the terms that Schrödinger had used in the final chapter. The publisher pulled out. Undeterred, Schrödinger sent the manuscript to a friend in London, and it was eventually published by Cambridge University Press in December 1944. The combination of Schrödinger's name, the intriguing title and a prestigious publisher with a global reach, coupled with the imminent end of the war, meant that the book was widely read and has remained in print ever since. Despite the commercial success of *What is Life?*, that was the end of Schrödinger's excursion into biology. He never wrote publicly on the topic again, even after the discovery of the existence of the genetic code in 1953.[53]

The immediate impact of *What is Life?* can be seen from the enthusiastic reviews it received in both the popular press and in scientific journals. There were over sixty reviews in the four years after publication, although few writers noticed what now seem to be far-seeing ideas – the aperiodic crystal and the code-script – and it was translated into German, French, Russian, Spanish and Japanese.[54]

There were two extended reviews in the leading scientific weekly *Nature*, one by the geneticist J. B. S. Haldane, the other by the plant cytologist Irene Manton. Haldane got straight to the heart of the matter, picking up on the aperiodic crystal and the code-script innovations and making a link with the work of Koltsov. Manton also noted Schrödinger's use of the term code-script, but she took it to mean 'the sum of hereditary material' rather than a particular hypothesis about gene structure and function. The *New York Times* reviewer put his finger on the central point:

> The genes and chromosomes contain what Schrödinger calls a 'code script,' that gives orders which are carried out. And because we can't read the script as yet we know virtually nothing of growth, nothing of life.

In contrast, some scientists later recalled that they had been unimpressed by the book. In the 1980s the Nobel Prize-winning chemist Linus Pauling claimed that he was 'disappointed' on reading *What Is Life?* and stated: 'It was, and still is, my opinion that Schrödinger made no contribution to our understanding of life.'[55] Also in the 1980s, another Nobel laureate, biochemist Max Perutz, wrote of Schrödinger: 'what was true in his book was not original, and most of what was original was known not to be true even when the book was written', while in 1969 the geneticist C. H. Waddington criticised Schrödinger's aperiodic crystal concept as an 'exceedingly paradoxical phrase'.[56] As well as these restrospective criticisms, some dissenting views were voiced at the time. In a review, Max Delbrück was critical, even though he had received a publicity boost from Schrödinger's espousal of his work in the Three-Man Paper. He claimed Schrödinger's term aperiodic crystal hid more than it revealed:

> genes are given this startling name rather than the current name 'complicated molecule' … There is nothing new in this exposition, to which the larger part of the book is devoted, and biological readers will be inclined to skip it.

This was distinctly ungenerous, as Schrödinger's hypothesis was in fact quite precise and did not simply involve coining a new name. Delbrück concluded by grudgingly accepting that the book 'will have an inspiring influence by acting as a focus of attention for both physicists and biologists.' In another review, Muller said that he, too, expected that the book would act as a catalyst for 'an increasingly useful rapprochement between physics, chemistry and the genetic basis of biology'. Muller clearly felt aggrieved that Schrödinger had not cited his work, and pointed out that he had suggested the parallel between gene duplication and crystal growth in 1921 (Muller did not mention that he had taken this concept from Leonard Troland). He also dismissed the idea that there was anything novel in Schrödinger's discussion of order and negative entropy, as these were both 'quite familiar to general biologists'. Neither Delbrück nor Muller made any comment about the code-script idea.

Despite their overall scepticism, Delbrück and Muller were absolutely right: Schrödinger's book did indeed inspire a generation of young scientists. The three men who won the Nobel Prize for their work on the structure of DNA – James Watson, Francis Crick and Maurice Wilkins – all claimed that *What is Life?* played an important part in their personal journeys towards the double helix. In 1945 Wilkins was handed a copy of *What is Life?* by a friend when he was working on the atomic bomb in California. Shaken by the horror of Hiroshima and Nagasaki, Wilkins was seduced by Schrödinger's writing and decided to abandon physics and become a 'biophysicist'. Crick recalled that his 1946 reading of Schrödinger 'made it seem as if great things were just around the corner'; Watson was an undergraduate when he read *What is Life?* and as a result he shifted his attention from bird biology to genetics.[57]

Even though some of the ideas developed in *What is Life?* were visionary and the book undoubtedly inspired some individuals who played a central role in twentieth-century science, there are no direct links between Schrödinger's lectures and the experiments and theories that were part of the decades-long attempt to crack the genetic code, and historians and participants differ about the significance of Schrödinger's contribution.[58] The view of mutation put forward in the Three-Man Paper, which Schrödinger espoused so vigorously,

had no effect on subsequent events, and his suggestion that new laws of physics would be discovered through the study of the material basis of heredity was completely mistaken. Even the code-script idea, which looks so prescient today, had no direct effect on how biologists looked at what was in a gene. None of the articles that later formed part of the discovery of the genetic code cited *What is Life?*, even though the scientists involved had read the book.

In fact, the meaning of Schrödinger's 'code-script' did not have the same richness as our 'genetic code'. Schrödinger did not think that there was a correspondence between each part of the gene and precise biochemical processes, which is what a code implies, nor did he address the issue of what exactly the code-script contained, beyond the vague suggestion of a plan. Ask any biologist today what the genetic code contains, and they will give you a one-word answer: information. Schrödinger did not use that powerful metaphor. It was completely absent from his vocabulary and his thinking, for the simple reason that it had not yet acquired the abstract wide-ranging meaning we now give it. 'Information' was about to enter science, but had not done so when Schrödinger gave his lectures. Without that conception of the content of the code, Schrödinger's insight was merely part of the zeitgeist, a hint of what was to come rather than a breakthrough that shaped all subsequent thinking.