Röbbe Wünschiers

Genes, Genomes and Society

From Farming to Gene Editing and Beyond

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Preface

The genetic material of a wide variety of organisms has already been used in many different ways. What does this do to us as a society and what can still be expected? With this book, I would like to venture a retrospective, an overview, and an outlook. So, I always try to span temporal arcs. Since I am addressing interested readers—whom I trust to be quite capable—I not only introduce them to relevant basics, but also try my hand at painting pictures: The technically advanced and critical experts may forgive me for some abstract abstraction. If you thumb through the book, you will encounter not only, but also, stuffed, scientific looking illustrations. This should not deter you—I will try to guide your eyes and thoughts. My aim is to provide a diverse readership with the tools to form their own opinions on the subject of genetics and genomics and its application, genetic engineering. You should be able to position yourself as to how you personally want to deal with the **genetic engineering revolution** and what you expect from representatives from politics, science, and society. **Gene editing** methods, with which we can modify the genetic material of all living beings as never before, would be described by

economists as a so-called **disruptive technology.** This means that it displaces existing methods. I therefore believe that it is legitimate to speak of a new generation of researchers, patients, beneficiaries, supporters, and opponents: the **generation of gene editors**. But do not expect a book that is primarily about gene editing. No, it is primarily about the genetic engineering revolution.

Now that you have this book in front of you, I would like to make two wishes. Genetic engineering and its application are the tip of an iceberg called science. It is the result of contributions from many disciplines, what we scientists call interdisciplinary. So, the subject is complex. So, my **first wish** is: please take your time reading, and use encyclopaedias, Wikipedia, uncle Google, or aunt Yahoo when you encounter thought barriers. Since explaining unfamiliar terms has become so easy with the internet, I have not included a glossary. Also talk to friends, ask me, or discuss on *generation-genschere.de*. My **second wish**: Think colourfully and not in black-and-white categories. Sure, sugar makes caries and fat, but it also tastes great and preserves fruits.

One more thing: Do not be scared by **bold print**; it is just to help you find people and key words again. And if you find the **illustrations** too small, check them out in the eBook at screen size.

You read it over and over again and think, sure: now for the **thanks to the** dear partner who put up with the scribbler for so long. But there is nothing to discuss: You cannot do it without time off with little distractions, good food, literature, and joint discussions. Therefore, first and foremost, I thank my wife Catherine from the bottom of my heart. I would also like to thank my colleagues who have supported me as much as possible—first and foremost Sandra Feik, René Kretschmer, Nadine Wappler, Robert Leidenfrost, and Jacqueline Günther. I would like to thank

Josi Hesse for her insight into *fitness, food, and genes* and the staff of the university library in Mittweida for feeding my mind. I thank Sarah Koch at the publishing house for well-dosed, inspiring conversations and creatively constructive e-mail chats. For proofreading and patient editing of comma and point mutations in the German edition, I thank Cornelia Reichert. Finally, it may sound strange, I thank the European Commission for recently rejecting my research proposals and thus giving me the totally unexpected opportunity to deal more intensively with the big picture.

The following **epilogue** from the 1999 book *Biology of the Prokaryotes* should conclude my preface:

> Especially in the beginning, revolutionary new technologies normally lend themselves to controversial discussions. Some people are afraid that these technologies may constitute uncontrollable dangers or may threaten traditional values and techniques. Others argue that because these methods are revolutionary and new, they are extremely promising and hence must be given any opportunity to be developed. Most geneticists and biologists who use recombinant DNA techniques constitute a third, more neutral group for which gene technology is but a logical continuation of the previous developments in genetics as initiated by scientists such as C. Darwin, G. Mendel, and B. McClintock. They are convinced that the biological risks outlined above are not radically new and hence can be handled by using reasonable precautions. In their view, gene technology has shown its outstanding value for basic research in an amazingly short time and will also prove its practical value within reasonable expectations.
>
> Finally, they are aware that gene technology will provoke essential ethical, legal, economic, and social questions due to its potential effects on living organisms, including man.

> At a closer look, however, most if not all of these will be recognised as millennium-old questions, which probably still will be asked in millenniums because perhaps they never can be answered definitively and will have to be asked by each new generation as long as there are human beings [1].

And now, dear friends, I look forward to a cup of tea with you.

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Preface to This English Translation

The German edition of this book was published in 2019. At the end of the year 2019, the Chinese biophysicist He Jiankui, the medical father of the first ever germline CRISPR/Cas gene-edited babies, was sentenced to 3 years' imprisonment with a three-million-yuan fine. In 2020, Emmanuelle Charpentier and Jennifer Doudna were honoured with the Nobel Prize in Chemistry *for the development of a method for genome editing*. With this translation, the publisher and I wish to contribute to your understanding of the matter, its background, and ultimately your scientific literacy.

In the original book, I used the term "Gen-Schere", which translates best as genetic scissor but is rarely used in English. I have replaced it with either CRISPR/Cas system or gene editing.

Since 2019, many thousands of human genomes have been analysed, and artificial intelligences are associating their genetic make-up with traits such as disease or cognitive abilities. By the way: This book was translated by an artificial intelligence, a neural network to be precise, too. While proofreading the translation generated by DeepL, I was both amazed and sometimes amused. Once again, it

showed me the importance of context, as with the genetic code. I tried my best to correct all artificial errors.

Finally, wherever possible, I replaced German references by English ones.

Mittweida, Germany Röbbe Wünschiers

Contents

1 Preliminary Thoughts

While the gene editing generation is settling the score with the fossil/plastic-waste/fine-dust generation in terms of climate and environmental protection, methods are emerging in the world's laboratories that could contribute both to climate and environmental protection—or make everything much worse—with genetic engineering knowledge and practices. At the latest since the Swedish schoolgirl Greta Thunberg drew the attention of young, but also older people to the environmental problems of our planet, it has finally become clear: we, young and old alike, have a long-term responsibility that we lived up to more badly than rightly. We have long since given our Earth age its own name: the **Anthropocene,** a term popularised by the German chemist and Nobel Prize winner Paul Crutzen and the US biologist Eugene Stoermer in 2000 [1]. The Anthropocene describes the current era in which humans have become a major influence on biological, geological and atmospheric processes. We are witnessing massive species extinctions, a retreat of permafrost and melting of glaciers and polar ice caps, and the formation of new sediment layers, including plastic particles. At the same time, we know that all living things on our planet are based on a

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simple code consisting of only four building blocks: the genetic code, molecularly written down in DNA (Chap. 2). Can it help us?

Since the 1950s, the beginnings of molecular biology, we have begun to understand this code. Since the 1970s, the beginnings of genetic engineering, we have been able to specifically modify it. Since 1986 we are deliberately releasing genetically modified organisms (initially plants) and since then it can be said that our **ecological footprint** has been joined by a **genetic footprint.** The current genetic engineering revolution was heralded in 2012 when three scientists copied from nature a process for altering (editing) the genetic code with great precision. Imagine editing one of 3.2 billion letters—that is the number of building blocks in the human genome. This book, by the way, has about 480,000 characters. That is the precision of the **new gene editing** (Sect. 5.1), which has also found its way into contemporary German literature like in Martin Sutter's novel "*Elefant*" [2].

And then the "*genetic engineering hammer*", as the German tabloid BILD wrote: On November 26, 2018, the Chinese scientist Jiankui He announced in the course of a scientific conference that for the first time he had sustainably modified the genetic material of at least two babies, the twins Nana and Lulu [3]. Sustainable means that the offsprings of **Nana and Lulu** will also carry the genetic modification in every single cell. A taboo has been broken. In the Anthropocene, the Anthropo-gene, the man-made gene, is created. Where should and can we go from here?

Nana and Lulu are unintentionally sustainable representatives, but also products of the gene editing generation. By the gene editing generation, I primarily mean the currently living age cohort that still has the procreation of offspring ahead of it. This generation has not only an immense global responsibility with regard to the environment and the

earth's climate, but also with regard to the genosphere [4]. This refers to the totality of all genetic systems that ensure the existence, regeneration and reproduction of the biosphere (Sect. 7.4). This generation will be confronted with the question of how much genetic engineering knowledge and genetic engineering practices they want to use, at the latest when they go to the gynaecologist while pregnant or when they go to reproductive physicians with a desire to have children. And those doctors and researchers who make gene editing available and develop them further are what I mean in second place as the gene editing generation. As a society, we are faced with the question of what means are acceptable to us in order to fulfil our responsibility towards the planet and future generations. Can, may or even must genetic engineering contribute to the solution?

The *framing of the* public discussion by the critics seemingly excludes this possibility (Fig. 1.1). Scientists find it harder than ever to be heard in today's world. Complex

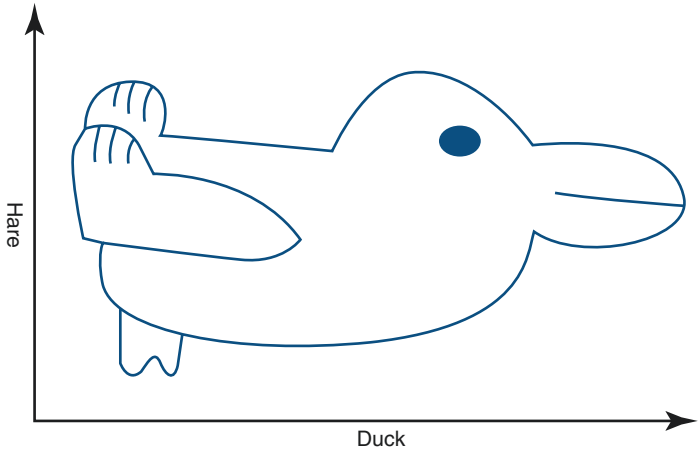

Fig. 1.1 It is all a question of perspective. Skilful framing can quickly turn a rabbit into a (newspaper) duck

discourses do not fit into our fast-moving times. And industry, with its monopolization and capitalization of genetic engineering, especially in the seed business, has contributed quite significantly to the current, albeit very vague, public opinion against genetic engineering. In addition, there is the European trauma of eugenics, which was first formulated in England, developed further in the USA and fatally abused in Nazi Germany. This mixture has given rise to today's fear that genetic engineering could escape democratic control through the power of capitalism. And thus, the discussion of risks (Sect. 3.7) of genetic engineering is usually less about the technology itself than about its social embeddedness. My argument is not that genetic engineering is the best of all solutions. But I do argue clearly against it being the primary culprit for problems such as the decline in biodiversity or the pollution of arable land with pesticides [5]. Sewage treatment plants have problems not because there are toilets, but because people dispose of their antibiotics in the toilet; washing machines are not to blame for environmentally unsound detergents; genetic engineering does not exempt us from good agricultural practices. I do, however, speak out against the prevailing sweeping actionism. All activities to combat climate change must be measured against their effect on the Earth system as a whole, as the English chemist James Lovelock and the US microbiologist Lynn Margulis formulated in the 1970s with their **Gaia hypothesis** [6].

When I told a child psychologist a few years ago about my intention to write a book about genetic engineering, she said: *Yes, that's an important topic.* And then, *I hope you're against genetic engineering.* This reflexive reaction against genetic engineering relaxed in further conversation after we had illuminated various aspects and discussed scenarios. But I often experience this: rejection as a reflex, illumination of the topic, differentiation of opinion. Cases of the

use of genetic engineering are then assessed differently and differences between genetic engineering and genetic technology also become clear. The colourful picture does not necessarily make a decision for or against the use of genetic engineering, even in individual cases, any easier. But we have to take the time. This reflex also reinforced my need to deliver this book as a contribution to this debate.

In 2018, a study was published describing that **extreme opponents** of genetically modified food have a below-average level of education in genetic engineering [7]. In contrast, however, these same people consider themselves to be particularly well informed. This observation was made in Germany as well as in France and the USA. The study came to the same conclusion with regard to the attitude of the interviewees towards genetic engineering and their knowledge of the medical application of genetic engineering such as gene therapy (Sect. 5.3). The situation is different when it comes to the topic of climate change: representatives of extreme positions demonstrate greater factual competence here. The study thus once again underlines the **emotionality** of the topic of genetic engineering. And it shows the well-known phenomenon that extreme attitudes are often accompanied by a closing off to other and new information. I argue that this also applies to **extreme proponents.** This does not even have to be intentional, but can also run subconsciously. This phenomenon, known as an **anchoring effect**, is used by our brains to attach new information to existing information. For example, the idea that climate change is a real threat to humanity can lead us to associate any information about natural disasters with climate change. Applied to genetic engineering, this can lead to the **black-or-white fallacy** that we can only do with or without it. And I experience this again and again: In February 2016, I participated in a panel discussion on *Green genetic engineering: devil's work or ethical imperative?* .

During the discussion with experts and the audience, I urged caution in the use of the then still fairly new methods of gene editing with the CRISPR/Cas system—more of which later (Sect. 5.1). As is all too often the case, I once again experienced black-and-white painting. Neither supporters nor opponents were able to approach each other, the fronts were fixed. As if to confirm this, a former colleague from my time at *BASF Plant Science* approached me after the lecture and accused me of stirring up fears. She said that the new technology offered unimagined opportunities and that we had to be careful this time to inform the public well about the advantages instead of talking too much about the potential disadvantages and thus spreading unnecessary worries. Knowing the lady well, I knew what she meant. Contrast *this time* with the past: the introduction of genetic engineering into agriculture in the 1980s. At that time, not much was enlightened, but simply genetically feasible things were implemented. The broken trust, as mentioned, is interpreted today by many market experts as a source of resistance to genetic engineering. With the new genetic engineering, gene editing based on the CRISPR/Cas system, a new attempt could be made to publicly and controversially discuss the opportunities and risks of genetic engineering. By controversial, however, I do not mean a clash of fronts, as we have seen so far. I expect controversial discussions to take place within each front. We need to move away from black or white and (learn to) think more colourfully.

Finally, take a little test: Can you explain the meaning of *genome*? Numerous recent international studies show that most people are genetically illiterate [8, 9]. The word genome has no clear meaning for everybody and is most likely to be associated with gene manipulation. Genes are as abstract as atoms. And manipulating genes cannot bode well. After all, we do not like to be manipulated by the media. Genetic modification? That is more like it. Genetic

optimization? An American social researcher laughed at me when I used that term: *You want to optimize nature?* She meant that nature is already optimal after all. Design? With gene editing we can design living beings. Hmm. Designing living beings on the drawing board and then constructing them in the lab?—I show you where we are with that in Sect. 6.2. So, let us not be manipulated and taken in by distorted images through contrived names! Let us take them for what they are: Meaningful images.

After these preliminary thoughts, now accompany me into the simply fascinating world of molecular biology and genetics and paint your own personal picture.

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2
What is Genetic Information?

We live in the age of DNA, the deoxyribonucleic acid. This is the complicated chemical name for the carrier molecule of genetic information, which contains the blueprint of every cell from bacteria to humans. In German one writes actually **DNS**, whereby the S stands for Säure. In France DNA is called ADN (*acide désoxyribonucléique*). In 2018, **DNA** has been officially added as emoji, which can graphically enrich tweets, posts and other messages (Fig. 2.1).

Before a cell divides into two daughter cells, it duplicates its genome. We humans pass on our genetic information to the next generation via egg and sperm cells, the so-called germ cells. This can lead to changes (mutations) in the information. These arise either when the information is copied or as a result of exposure to chemicals or radiation (Sect. 3.1). Mutations contribute to the fact that no living being is like another. Even identical twins have been shown to differ in their genetic information, although only minimally [1]. Mutations can be harmful, beneficial or have no effect, i.e., they can be neutral. It is the variability of the genome that drives evolution through variation and

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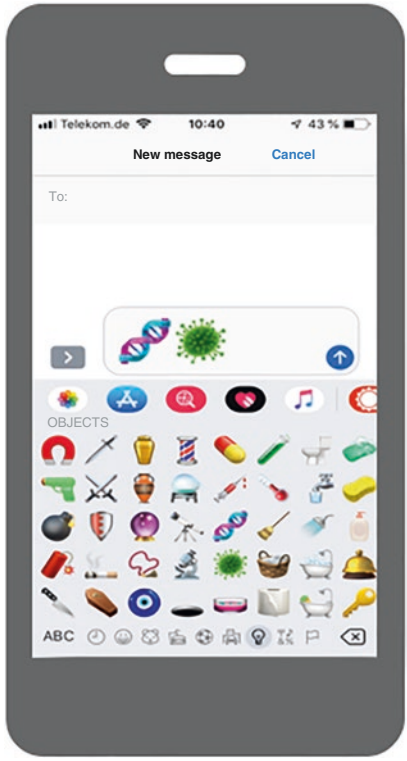

Fig. 2.1 In 2018, 65 years after its structure was elucidated, DNA and also viruses became available as emoji

selection, as described by Charles Darwin and Alfred Russel Wallace in the mid-nineteenth century. For some time now, however, we have also known that experiences in the widest sense, gained during one's lifetime can be passed on to subsequent generations, as Jean-Baptiste Lamarck also assumed at the beginning of the nineteenth century. The mechanism behind this is known as epigenetics and is currently revolutionising thinking about medicine, genetic engineering and evolution. It is described in more detail in Sect. 8.1.

2.1 The DNA Molecule

Sometimes I wonder whether the term DNA needs to be explained at all, since it seems to have arrived in society. BMW boss Harald Krüger, for example, speaks of *corporate DNA* [2] in the field of vehicle construction. In an article about the Catholic Church I read about *Catholic DNA*, [3] and in a report about the English Kingdom and the Brexit I read about *cultural DNA* [4]. The German philosopher and journalist Thorsten Jantschek, in a video message on the occasion of the awarding of the Prize of the Leipzig Book Fair, even talks about the fact that the book *corresponds to the spiritual DNA of the Republic* [5]. DNA is a symbol for something common and meaningful. Well, DNA is indeed common to all forms of life, and as genetic information it also provides meaning.

For most genetic engineers, DNA is reduced to the sequence of the four letters A, T, G and C. So: ...CGATTAGCTGCT... A, T, G and C are the abbreviations for the **nucleobases** adenine, thymine, guanine and cytosine. Together with the sugars ribose and phosphate they form the building blocks of DNA, the **nucleotides** (Fig. 2.2).

They form, like a string of pearls linked together, the hereditary molecule DNA. This molecule forms a **double helix,** i.e., consists of two molecular strands. The detailed structure was elucidated in 1952 by the English biophysicist Francis Crick and the American geneticist James Watson on the basis of X-rays taken by the English chemist Rosalind Franklin. They found that the two strands were complementary: If the sequence of nucleotides (DNA sequence) of one strand is known, then the sequence of the opposite strand can be elucidated, since A always pairs with T and G with C (**base pairing** of complementary nucleotides. The

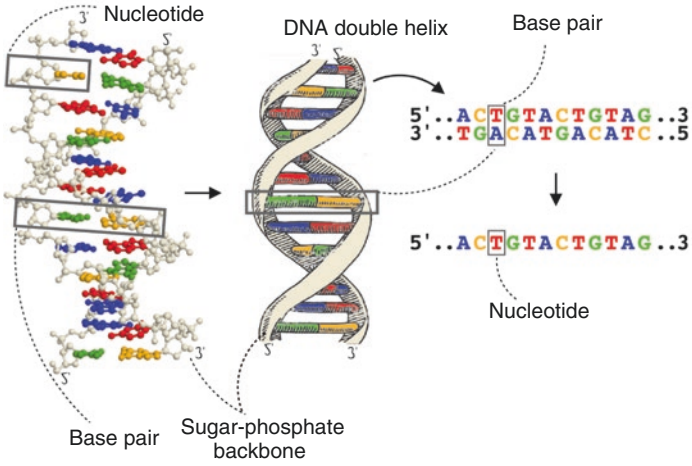

Fig. 2.2 Different representations of DNA with twelve base pairs as a molecular model (left), schematic structure (middle), text with both single strands (top right) and one single strand (bottom right). According to the chemical nature of DNA, it is assigned a direction with the designations 5′ and 3′

human genome consists of 3.2 billion nucleotides distributed over 23 **chromosomes** of different lengths (Fig. 2.3). One can also speak of 3.2 billion base pairs **(bp)** instead of 3.2 billion nucleotides (**nt**). In addition, there are 16,569 nucleotides each on the chromosome of the **mitochondria,** the cells' energy power stations.

In most animals, plants and humans, the chromosomes are present as double copy (**diploid**), sometimes even multiple copied (**polyploid**)—in bacteria, on the other hand, they are usually single copied (**haploid**). Thus, every human cell has inherited 23 **chromosomes** each from the father and mother. If the DNA of the 46 chromosomes of a single human cell were combined to form a thread, it would be about two metres long. The DNA of all human cells would reach from the earth to the sun and back about four

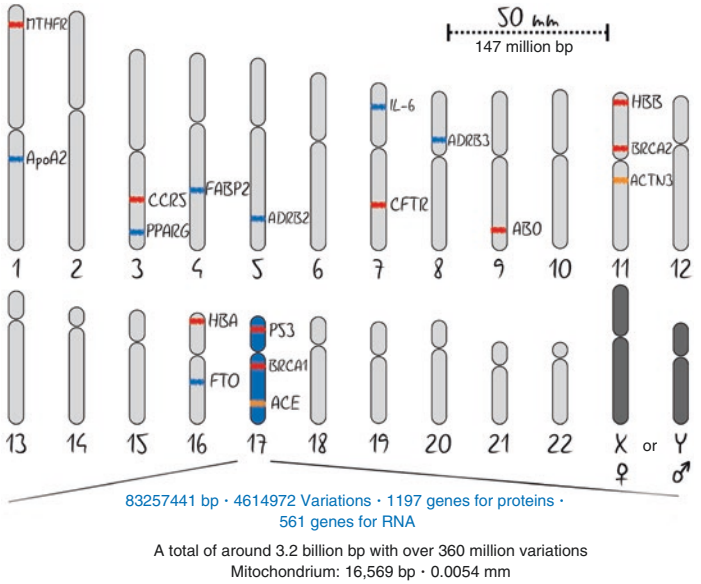

Fig. 2.3 The simple (haploid) human chromosome set. The chromosomes are between 16 and 85 centimetres long. CFTR refers to the location of the gene that causes cystic fibrosis (mucoviscidosis) in a defective form. AB0 is the location of the gene that determines blood groups. The CCR5 gene is associated with resistance to the HI virus. The genes HBA and HBB are mutated in α and β thalassemia, respectively. At blue marked positions are genes that the company *for me do* uses for the classification of nutrition types; at orange positions, however, are genes that allow predictions about the type of athlete (Sect. 7.3)

times (nine billion kilometres). That is just about the same as the orbit of the planet **Saturn** around the sun. The Japanese berry *(Paris japonica)* has a genome size of around 149 billion nucleotides distributed over ten chromosomes, making it almost 47 times larger than the human genome and would form a continuous DNA thread 91 m long [6]. Directly after this comes the marbled lungfish (*Protopterus*

aethiopicus) with a genome size of 130 billion nucleotides distributed over 14 chromosomes. The smallest known genome with only 159,662 nucleotides is that of the bacterium *Carsonella ruddii,* which lives symbiotically in leaf fleas.

On the chromosomes, the genetic information is distributed among **genes** (Sect. 2.3). The totality of all genes of a living being is called **genome** or **genotype.** A gene can be understood as a package of genetic information that codes for a specific trait, for example the blood group. The totality of all characteristics of a living being makes up its **phenotype**, its appearance. For example, since there are several blood groups (0, A, B, AB), there must be several variants of the gene, which we call **alleles** (Fig. 4.6). From each gene we carry one maternal and one paternal allele. Some traits, such as eye colour, involve at least eight genes [7].

The basis of all diagnostic analysis and genetic engineering work is a thorough understanding of the function of a particular section of the genome. In the early days, this was only possible in a very rough way. So-called genetic **markers** were associated with phenotypic manifestations such as diseases or other characteristics. These markers were initially not nucleotide sequences (DNA sequences), but rather physical observations, such as the fact that DNA breaks down into fragments of varying size after treatment with a DNA-cutting enzyme (restriction enzyme). The size and distribution of the fragments could be measured and correlated with characteristics. Today we can read the entire genetic material (the **DNA sequence**) of a living being, from bacteria to humans (Chap. 4). Approximately 99.5% of a person's genome is similar nucleotide by nucleotide (base pair by base pair) to the genome of any unrelated other person (Sect. 4.1) [8, 9].

2.2 The Genetic Code

How can the genetic information in the form of the sequence of 3.2 billion nucleotides contain the blueprint of cells, even of entire living beings? To understand this, we must consider the flow of information (Fig. 2.4).

Analogous to words in a text, there are strings of letters that are translated into **proteins**. A certain class of proteins are **enzymes**. They form the toolbox of a cell, because they are responsible for the metabolism. Another class of proteins are building materials, such as the keratin from which

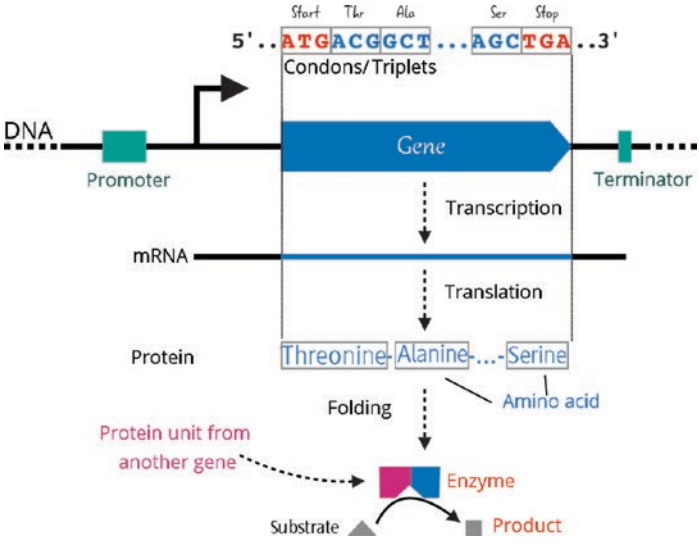

Fig. 2.4 Processes in gene expression. Codons on the hereditary DNA molecule code for amino acids, the building blocks of proteins. As a rule, proteins consist of several hundred amino acids. The promoter region of the DNA serves to regulate transcription. A protein can have an enzymatic activity, either alone or, as shown, in concert with other proteins and thus convert chemical substances (substrates)

our hair is made. Proteins, like DNA, are also made up of a chain of molecular building blocks, the **amino acids**. The sequence of three nucleotides on the DNA (a so-called **codon** or **triplet**) codes for one amino acid. A total of twenty amino acids are coded in this way (Sect. 6.2). In addition, there are codons that mark the start and end of the protein. If the DNA contains the sequence ...ACGGCT...AGC... in the protein, this translates into the amino acid sequence ...-threonine-alanine-...-serine-... Thus, this process is called **translation**. It is preceded by a **transcription** of the DNA information into an RNA molecule, the so-called *messenger* RNA (mRNA). **RNA** (ribonucleic acid) is single-stranded, differs slightly in its chemical structure from DNA, is therefore more mobile in the cell and can be broken down more quickly. The process that expresses the genetic information stored on the DNA via the RNA to the protein is called **gene expression**. A small change in the DNA sequence, such as a nucleotide exchange in the codon ACG to CCG, can thus lead to a change in the protein (threonine in proline). And since a protein fulfils a function, functional changes or failures may be the consequence. In this way, around 20,000 proteins are encoded in the human genome.

The fact that the genetic code applies equally to all known living beings led to the famous saying of the French biochemist and Nobel Prize winner Jacques Monod that everything that applies to bacteria must also apply to elephants [10] (Fig. 2.5).

Interestingly, only about 3% of our DNA codes for proteins. What is the rest for? In order to answer this question, we need to take a detailed look at the structure of genetic information.

Fig. 2.5 (Almost) everything that applies to the bacterium *Escherichia coli* will also apply to an elephant

2.3 The Gene

The term gene (Sect. 2.1) obviously plays a central role in genetics, genomics and genetic engineering. It also seems that, just like DNA, genes have taken their place in our vocabulary. Examples of this may be a newspaper article entitled *Transporter with car genes* [11] in the section on cars and traffic, or the placing of the term *Sarrazin gene* in third place among the words of the year 2010 in Germany, after *Wutbürger* and *Stuttgart 21* [12]. In fact, however, hardly any other term in genetics is as much in discussion as the gene [13]. Over the years, the view on the nature of genes has changed. In his 1976 book *The Selfish Gene*, Richard Dawkins attributed to the gene a selfish end in itself, loosely based on the motto: The chicken is only the transition from one egg to another [14]. The background is the fact that at least individuals with sexual reproduction pass on only half of their genes to the next generation. According to this, there is competition between the genes for passing them on. Genes that are not alleles and therefore do not compete with each other can therefore also cooperate. Itai Yahnai and Martin Lercher outline cooperation as a