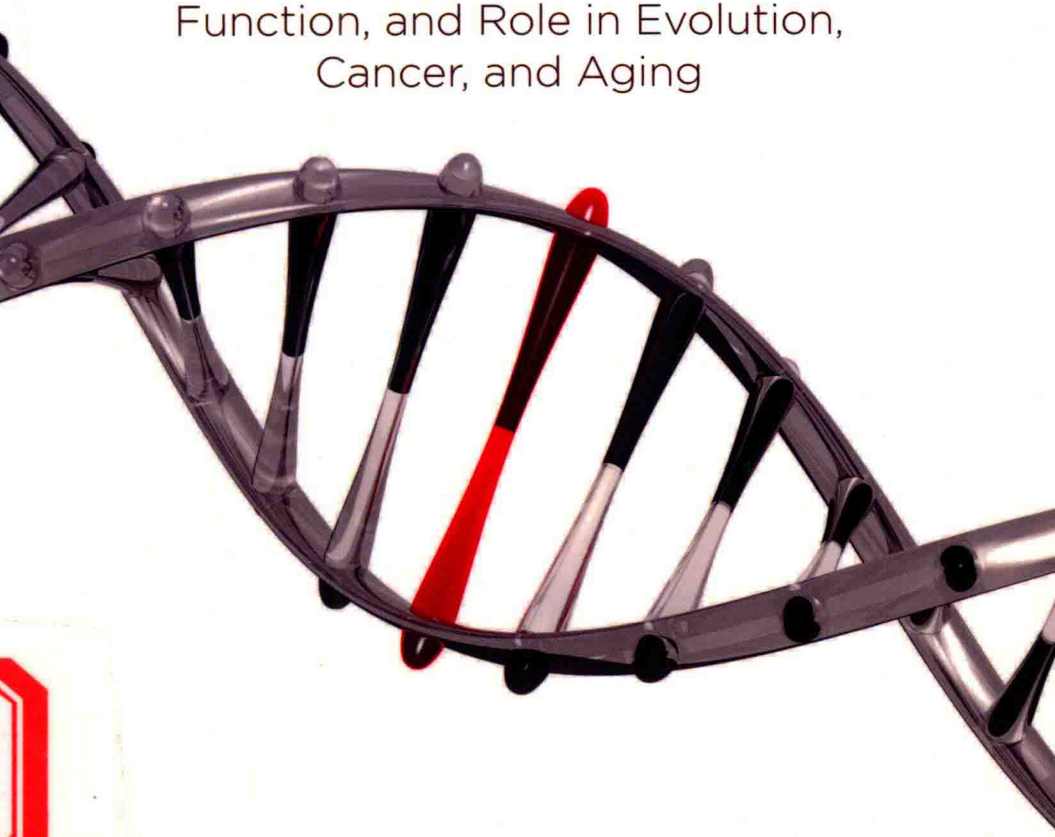
It's in Your DNA

From Discovery to Structure, Function, and Role in Evolution, Cancer, and Aging



Eugene Rosenberg

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With drawings by
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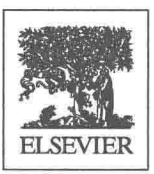

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For Ilana, my partner in science and life.

Preface

The mission of this book is to share with the interested reader the pleasure of understanding one of the greatest achievements of science—uncovering the mystery of DNA. To fully appreciate this achievement, I have strived to explain in a simple but scientifically correct manner the key experiments and concepts that led to our current knowledge of what DNA is, how it works and the increasing impact it has on our lives. Although the book was written for a layperson to understand, I also kept in mind students, teachers, and young scientists.

In addition to emphasizing the observations and reasoning behind each novel idea and the critical experiments that were performed to test them, I have provided a brief sketch of the lives and personalities of key scientists, many of whom I knew personally. The importance of DNA research to science and medicine is reflected by the fact that 27 Nobel Prizes have been awarded for research on DNA. The prizes were awarded to scientists from 12 countries (Appendix). Among the pioneers of DNA research that will be discussed in this book are four extraordinary women, who have become feminine icons: Rosalind Franklin, whose X-ray pictures of DNA made possible the discovery of the double-strand helix structure of DNA; Barbara McClintock, whose discovery of "jumping genes" gave rise to genetic engineering; Lynn Margulis, who put forth original ideas on evolution that were initially controversial but are now accepted; and Elizabeth Blackburn, who discovered that shortening the ends of the DNA molecule contributes to aging. Telling a science story from the point of view of the scientist enables the reader to imagine themselves in that position.

In narrating the DNA story, I have used the historical or case-study approach, in which I describe the seminal ideas in DNA research from their conception to their latest development, emphasizing the observations and reasoning behind each concept and the critical experiments that were performed to test them. In this way, I intend to stimulate the reader's innate sense of scientific inquiry. Learning how someone made an important discovery can be as interesting as the discovery itself. In the DNA story, the journey matters. For it is precisely in the substitution of evidence for dogma, as a basis for belief, that science has made its greatest offering.

The historical approach also leads the reader to appreciate how science progresses. An important discovery leads to a new question. Often the question is put in the form of a hypothesis that can be tested experimentally. The results of the experiment can lead to a new concept, which again provokes another question. Revolutions occur when disparities or anomalies arise between theoretical expectation and research findings that can be resolved only by changing

fundamental rules of practice. These changes can occur suddenly: in a relative instant, the perceived relationships among the parts of a picture shift, and the whole takes on a new meaning. Examples that are included in this book include Darwin's evolutionary theory, Mendel's gene concept, Avery's demonstration that DNA is the genetic material, the helical model of DNA, the one gene–one enzyme concept, and more recently, the key role of symbiotic microorganisms in adaptation, behavior, development, metabolism, and evolution of plants and animals, including humans.

Throughout the book, I have attempted to strike a balance between theoretical and applied aspects of DNA research. Scientific progress is motivated by both a desire to know and a desire to use this knowledge. Nowhere is this more evident than in DNA biology. The ability to manipulate DNA has led to genetically engineering microbes to produce valuable drugs, such as the human hormone insulin, human growth hormones to prevent dwarfism, blood-clotting factors for treating hemophilia (the "bleeding disease"), and vaccines. Genetic engineering is used in agriculture to produce plants with beneficial characteristics, such as herbicide resistance, improved shelf life, disease resistance, stress resistance, and resistance to insects. The DNA engineered crop that probably has the greatest potential to improve human health worldwide is Golden rice, created to fight vitamin A deficiency, which affects 250 million people around the world and can cause blindness and even death.

Genetic engineering has also been performed on animals. Although most of the genetically modified animals were produced for research purposes, some were engineered to enhance production or food quality traits. Two of the most interesting are genetically modified salmon for use in the aquaculture industry to increase the speed of development and potentially reduce fishing pressure on wild stocks and dairy cows genetically engineered with human genes to produce milk that would be the same as human breast milk. This could potentially benefit mothers who cannot produce breast milk but want their children to have breast milk rather than formula.

Genetic engineering of humans is in its infancy. Recently, the British House of Commons approved a technique of creating babies from three people, the mother, the father, and a female mitochondrial donor. The technique was developed to help women with mitochondrial disease have healthy babies. Eggs are collected from a potential mother with damaged mitochondrial DNA and a female donor with healthy mitochondria. The nucleus which contains the vast majority of the genetic material is then removed from both eggs. The mother's nucleus is inserted into the donor egg, which can then be fertilized by sperm from the father. It results in babies with 0.1% of their DNA from the second woman and is a permanent change that would be passed down through the generations.

I hope this book stimulates interest in DNA and provides the necessary background for a greater appreciation of the increasing number of discoveries that are making an impact on our way of life.

Acknowledgments

I have several people to thank. My colleagues, Ed Kosower, David Gutnick, Gerry Cohen, Irun Cohen, Moshe Meverich, Isaak Witz, and John Ringo read parts of the book and provided valuable suggestions and up-to-date references in their specialties. I developed the hologenome concept of evolution in collaboration with my wife and scientific partner, Ilana Zilber-Rosenberg. My daughter, Stephanie Rotem, read large parts of the book and offered many suggestions for clarification from the advantage point of an interested layperson.

Avshalom Falk drew the amusing and informative cartoons that are spread throughout the book. Avshalom is a professional microbiologist who has the ability to see humor in science and the talent to express it in the form of artwork.

I was blessed by having excellent teachers during my formative years, Dan Atkinson, Syd Rittenberg, and Ralph Martinez at UCLA, Steve Zamenhof and David Rittenberg at Columbia University, and C.B. van Niel at Stanford University. When I was a graduate student, Zamenhof told me that if I really understood a subject I should be able to write it in a manner that my mother-in-law could understand it. I tried to follow his advice in this book.

I also thank the editors of Elsevier, especially Kristi Gomez, Patricia Gonzalez, Karen East and Kirsty Halterman, who recognized the value of the book and helped bring it to fruition.

Prologue

In 1974, 18-year-old James Bain was convicted of breaking and entering, kidnapping, and rape of a 9-year-old boy in Polk County, Florida, and sentenced to life in prison. The story is a long and tragic one with many mistakes and misjudgments. The 9-year-old boy was kidnapped from his home on the night of March 4th, dragged to a nearby field, and raped. When the victim returned home, he was wearing only a white t-shirt and jockey underwear. The police collected his underwear and sent it to the FBI for serological testing. Bain became a suspect after the victim described his assailant as a 17- or 18-year-old African–American man named "Jimmy" having bushy sideburns and a mustache. The boy also told the police that he remembered seeing a red motorcycle; a similar one of this description was owned by Bain. In addition, the victim's uncle stated that the man he was describing sounded like James Bain, who he knew as a student at the high school where he was assistant principal. After his uncle mentioned the name, the victim adopted Bain as the rapist. When the police arrived at Bain's house just after midnight on the night of the crime, Bain was at home with his sister where he had been all evening. Although James Bain had an alibi, did not confess to the crime, and maintained his innocence continuously; the police arrested him.

During the trial, the defense argued that Bain had no criminal record and could not have been the rapist because he was home at the time, 2 miles from the scene of the rape. Four family members testified that Bain was home watching television with his sister during the specified time. However, family members are known to be poor alibi witnesses because juries believe they could be biased, saying only what is good for the family member. Later Bain said: "But (the jury) didn't pay that no attention. I think they mainly convicted me when the victim stood up in the courtroom and pointed at me as the perpetrator. He was crying and everything in the process."

The State's case was also based on blood tests on the jockey underwear of the victim performed pretrial by the FBI. At the time, serology was considered the most technologically advanced procedure for identifying criminals. The tests verified that the rapist did deposit semen on the victim's underwear and sperm heads were seen on the underwear. FBI analyst, William A. Gavin, testified that the semen on the underwear was blood group B, that Bain's blood group was AB (with a weak A), and that Bain could not be excluded as the depositor of the semen. The underwear itself was admitted at trial as State's Exhibit #1. Contrary to the

FBI testimony, a defense expert, Dr. Richard Jones, testified at the trial that Bain's blood group was AB (with a strong A) leading to his conclusion, contrary to the FBI's, that Bain could not have deposited the semen on the victim's underwear. Despite the conflicting testimony on the serology report, the jury convicted Bain of all three charges and sentenced him to life in prison.

During the 35 years that Bain was incarcerated in six different prisons, he became a master welder, learned to play chess, and studied various subjects in school for 27 of his 35 years behind bars. Bain grew close with many other prisoners but often waited years to tell them he was innocent. "I had to know someone before I told them. Anything could go wrong. If they don't believe you, they could get mad. Y'all have a fight, and someone winds up dead," he said. In spite of this mistrust, from his first day behind bars, he befriended older inmates with some level of legal knowledge to help him write requests to the court for transcripts of his trial—a right granted by the Supreme Court. But he neither received them nor heard back from the court. Eventually, Bain learned about DNA evidence.

DNA evidence was used for the first time in 1988 to convict a murderer and in 1989 to pardon a convicted person who was serving time in a US prison. Since then, DNA evidence has been used to exonerate more than 300 persons either on death row or serving lengthy prison sentences. When Bain was informed of the novel DNA technology, he submitted handwritten motions 5 times seeking DNA testing, but he was denied each time. On the fifth time that James was denied his request for testing, the appeals court wrote that he had waited too long. It wasn't until Florida passed a new law that allowed cases to be reopened for DNA testing that his fifth and final rejection was overturned and early in 2009 the Innocence Project of Florida stepped in to assist Bain. The Innocence Project is a nonprofit legal organization that is committed to exonerating wrongly convicted people through the use of DNA testing. The State Attorney agreed to the DNA testing and the victim's underwear worn during the rape in 1974 was sent to DNA Diagnostics Center, a private laboratory in Fairfield, Ohio. Fortunately, the underwear had been stored in plastic bags in A/C rooms, so the DNA was accidentally preserved. Testing the DNA of sperm found on the underwear excluded James Bain as the donor of the sperm, confirming that someone other than Bain raped the victim. According to the Innocence Project Legal Organization, misidentification from an eyewitness accounts for 75% of all convictions later overturned by DNA evidence.

It has been known for many years that DNA testing is valuable to the justice system because it is extremely sensitive and unbiased. Only a few molecules are required to identify the individual that deposited the DNA. Furthermore, unlike witness identification of a suspect, the test is not prejudice to race, gender, or economic status.

On December 17, 2009, James Bain was declared innocent and released from prison. He walked out of the courthouse with members of his family and his legal team. Bain had spent 35 years in prison—the longest time served by innocent man eventually freed using DNA evidence.

James Bain. *(From https://www.innocenceproject.org/cases/james-bain/. Used with permission from Florida Innocence Project.)*

Under Florida's wrongful incarceration statute, Bain received compensation from the state of Florida for his time in prison—about $1.7 million, $50,000 for every year he spent in prison. A few months after he was released, he said: "Part of me went into hibernation in prison, but every day, I'm waking up a little more." When taken to a 3-D screening of Avatar, he commented, "Most definitely amazing," but what amazed him more than the movie, he says, was all the iPhones and BlackBerrys flashing in the audience during the previews, "Like being on an airport runway, with rows of small lights everywhere."

He thinks about traveling a lot, he says. But for now, he's home with family, reveling in the company of his mother, siblings, nieces, and nephews. He sleeps with a fan on to feel the movement of air. He sits with his hands apart to remind himself there are no handcuffs. He eats with a fork, knife, and spoon. "I'm rusty, but I'm coming back," he says.

Speaking to students on his wrongful conviction experience at the University of South Florida on February 24, 2016, Bain told listeners: "I tried and tried, ladies and gentlemen, to get my case heard. But each time, it was a failure. Each time."

The exoneration of James Bain is just one example of how knowledge about DNA has affected the lives of people in the recent past and will do so to an even greater extent in the future. DNA fingerprinting is used not only in criminal investigations but also has revolutionized maternity/paternity testing, forensics, and identification of disaster victims.

Basic and applied research on DNA has led to enormous progress in biology and medicine. Deoxyribonucleic acid, or DNA for short, has been playing a central role in all organisms, from simple microbes to man, for more than 3 billion years. However, it is only in the last century that we have begun to understand what DNA is and how it operates to determine what we are, and how this information is transmitted to our children. Biology only makes sense in terms of evolution, and changes in DNA are at the core of evolution. DNA

provides the instructions for producing all life forms. We now have the tools to read these instructions and begin to understand the sequence of changes in DNA that led to the evolution of *Homo sapiens* as well as other animals and plants.

An interesting example of how DNA technology can teach us about the ancient history and evolution of modern humans is the analysis of DNA from a 45,000-year-old bone of a Neanderthal man found in Siberia. The analysis indicates that 1%–4% of the DNA of anyone living outside Africa today is Neanderthal in origin. These findings reveal that Neanderthals interbred with ancestors of modern humans when modern humans began spreading out of Africa. Another surprising discovery based on a detailed analysis of the DNA of the Neanderthal man is that he had red hair and pale skin.

Recent results have shown that many important evolutionary innovations involved acquiring genes from microbes, rather than building them from scratch. In fact, all animals and plants live in symbiotic association with abundant and diverse microbes. Humans, for example, contain as many microbial cells as human cells and more than 400 times more microbial genes than human genes. The title of this book, "*It's in Your DNA*" refers to both your human and microbial DNA. Your symbiotic microbes play an important role in your development, behavior, general health, and ability to adapt to changes in your diet.

DNA technology has revolutionized modern medicine. Many therapeutic drugs, such as insulin, human growth hormone, and human blood clotting factors, are now produced using DNA technology, making them much less expensive and safer. For example, prior to the development of DNA technology, human blood clotting factors were produced from donated blood that was inadequately screened for HIV. Insulin was extracted from the pancreas glands of cattle, pigs, and other farm animals. Animal-derived insulin is different from human insulin, and therefore produced allergic reactions in some patients. Human growth hormone was manufactured by extraction from the pituitary glands of cadavers, as animal growth hormones have no therapeutic value in humans. Production of a single year's supply of human growth hormone for one patient required up to 50 pituitary glands, creating significant shortages of the hormone.

DNA-based methods are used for rapid diagnosis and monitoring of hundreds of maladies, from determining the specific microbial strain that causes an infectious disease to detection of cancer. Seventy percent of clinical decision-making is now based on diagnostic test results. The pharmaceutical industry estimates that annual revenue from the sale of diagnostic kits exceeds US $200 billion. More importantly, rapid and accurate diagnostic tests save millions of lives.

Two of the major medical problems today are cancer and the aging process. As I will explain in this book, deleterious changes in DNA are at the core of both problems. The challenge is to discover ways to prevent accumulating DNA damage and possible methods to reverse the process in order to provide for longer and healthier lives.

The impact of DNA in our life can be illustrated from a few of the many recent *New York Times* headlines:

MPs Say Yes to Three-Person Babies
Rise in Overturned Sexual Abuse Convictions From DNA Testing
A Genetic Entrepreneur Sets His Sights on Aging and Death
Genetic Manipulations to Avoid Devastating Diseases in Babies
Bringing Extinct Animals Back to Life is Really Happening
Genetically Modified Foods: Questions Remain
I Like Your Genes: People More Likely to Choose a Spouse With Similar DNA
Genes That Might Determine Whether You Have Straight, Curly or Wavy Hair
How Far Would You Go to Modify Yourself Using the Latest DNA Technology?
How DNA Forensics Could Identify Lost Nigerian Girls

All of these subjects are part of the exciting story of DNA that I wish to share with you. The story involves creative scientists, who are often interesting people, brilliant experiments, which I will endeavor to describe in a clear and accurate manner, and an outcome that gives us some understanding of the most basic questions in biology: Where do we come from? What are the causes of cancer and aging? What does the future hold for humans? Let me assure you at the outset that the DNA story is so interesting that even without adding spice, it will taste good.

Contents

Chapter 1

The Beginning

The Past—the dark unfathomed retrospect!
The teeming gulf—the sleepers and the shadows! The past!
The infinite greatness of the past!
For what is the present after all but a growth out of the past?

—Walt Whitman, Passage to India in *Leaves of Grass*

The past is never dead. In fact, it's not even past.

—William Faulkner in *Requiem for a Nun*

Theoretical physicists hypothesize that the universe began with a colossal explosion often referred to as the *Big Bang* theory, approximately 13.8 billion years ago. The key idea is that the universe is expanding. Consequently, the universe must have been denser and hotter in the past. In particular, the *big bang* theory suggests that at some moment all matter in the universe was contained in a single point, which is considered the beginning of the universe. After the initial expansion, the universe cooled sufficiently to allow the formation of subatomic particles, including protons, neutrons, and electrons. The gases and dust from that explosion produced the earliest generation of stars, and over a period of billions of years, the stars exploded, and their debris formed other stars and planets. Our solar system was formed in this way 4–5 billion years ago. During the next billion years, the molten Earth cooled, forming a hardened outer crust.

About 3.8 billion years ago, earth's atmosphere consisted of gases, such as hydrogen (H_2), nitrogen (N_2), hydrogen sulfide (H_2S), methane (CH_4), and water (H_2O). As the temperature decreased, water vapor condensed causing millions of years of torrential rains, during which time the oceans formed. Gases and water from the earth's core came to the surface through volcanoes. Ultraviolet radiation bathed the earth, and the simple compounds interacted with one another to form more complex organic molecules, including the building blocks for life. Organic molecules are those containing carbon and that are typically found in living systems.

How organic molecules formed the first living cells, that is, the origin of life, remains one of the most challenging unsolved problems in biology. The best fossil evidence indicates that microorganisms first appeared on Earth about 3.8 billion years ago and the first multicellular creatures about 1 billion years ago. Thus,

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