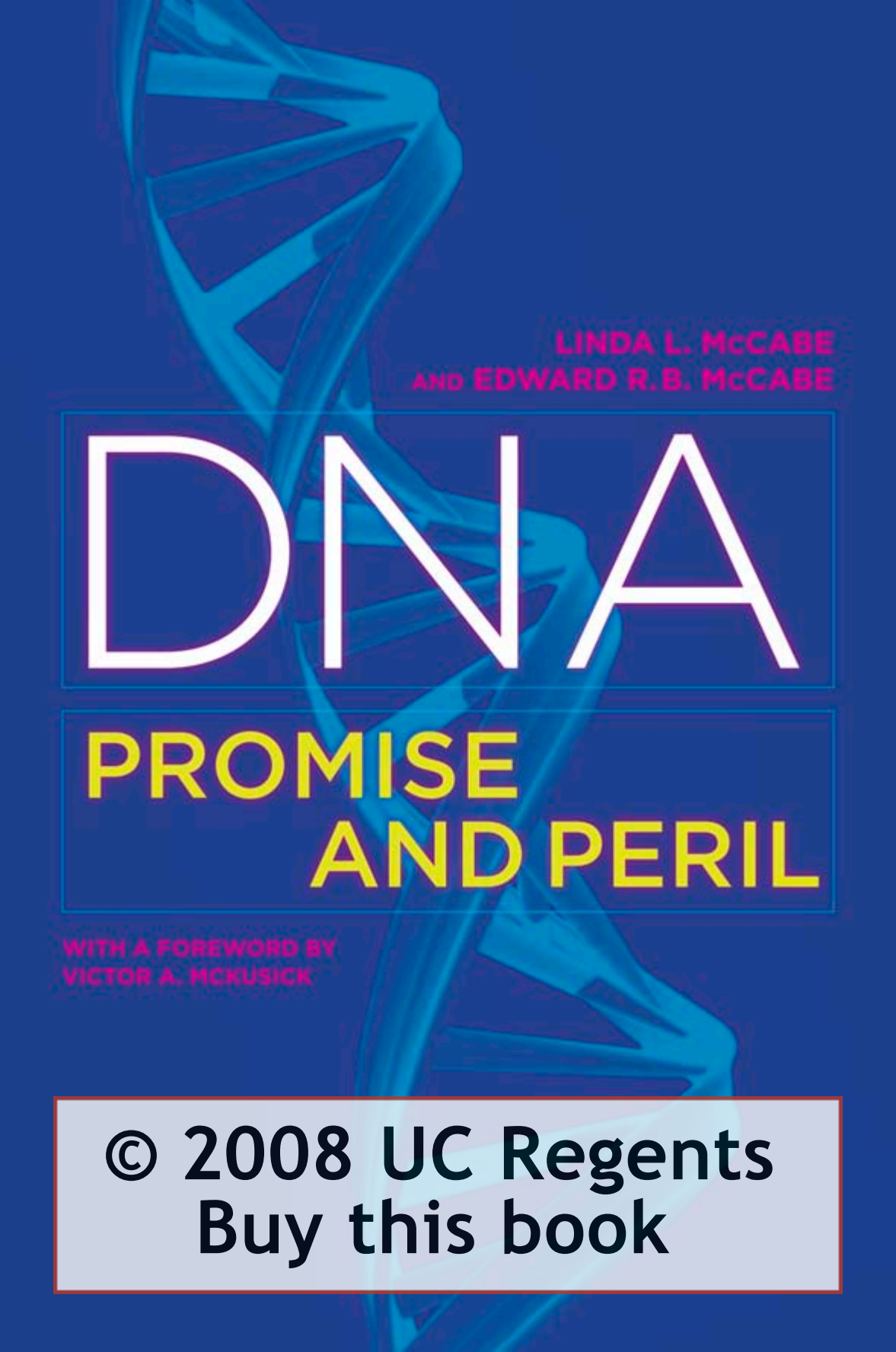

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CHAPTER 1

DNA Sequence Does Not Equal Destiny

Genetic determinism
The Dutch Hunger Winter
The Barker hypothesis

The concept that our DNA sequence — our genome — does not equal or predict our destiny has been extremely difficult for some geneticists to accept. We were attracted to this new field of molecular genetics in the 1980s because of the belief that disease-causing mutations would predict patients' futures. If geneticists could identify the genes responsible for their patients' diseases and the genetic changes or mutations in those genes, then, we believed, geneticists would be able to predict the clinical courses of their patients' diseases. Translating into individual terms, physicians would have the information from the laboratory analysis of a patient's specific mutation to inform the patient and his or her family whether they might expect, for example, a mild or a catastrophic clinical course. Many of us in the genetics community sincerely believed that DNA analysis would provide us with a molecular crystal ball that would allow us to know quite accurately the clinical futures of our individual patients.

We were committed to this belief in ways that would be life-changing. In 1986, we packed up our family, left the University of Colorado and our ranch outside Denver, and moved to Houston to be part of Tom Caskey's recently established Institute for Molecular Genetics at Baylor College of

Medicine. We made this move to learn how to identify the genes and mutations responsible for disease.

This was an exciting time in genetics, particularly at Baylor. Caskey's institute was growing rapidly from six to more than twenty investigators. Caskey was traveling the world, bringing back news about the new disease-causing genes that were being identified. We refer to this period at Baylor as the "Camelot of genetics," because if you had a reasonably good new idea, you could implement it. For example, we received funding from the National Institutes of Health (NIH) to create the Mental Retardation Research Center, which was developed around the idea of identifying the genes and mutations responsible for mental retardation and developmental delay. This center brought together faculty from many different departments at Baylor. They all joined enthusiastically because of the wonderful possibilities the research evoked. The faculty in this center would have the opportunity to be at the forefront of understanding diseases responsible for mental retardation at the most fundamental level — the DNA changes. Identification of these new genes and their mutations would give physicians novel insights into diseases previously understood only at a descriptive level. It was an exhilarating era in our professional careers and in those of colleagues at Baylor and around the world.

Caskey was involved in the Human Genome Initiative of the U.S. Department of Energy even before the NIH became the primary source of support and the effort was renamed the Human Genome Project. The discussions of the thrilling possibilities and phenomenal challenges in sequencing the human genome were incredible. The laboratory methods and informatics, or information-processing technologies, that were needed to complete the project did not yet exist. In addition, there were tensions between those who wanted to identify the entire genomic sequence and those who thought the early focus should be on genes associated with diseases.

Many geneticists believed that biomedical science would be revolutionized when the human genome sequence — the complete 3 billion base pairs of an individual's DNA — would become available. We will show you that there have been dramatic and truly revolutionary changes that have occurred as a result of the Human Genome Project. But we also intend to show that the rhetoric accompanying the sequencing of the human genome has been and continues to be excessive in its promises. Each of us has seen headlines and media reports attributing extremely ambitious results to this project — for example, "Human Genome: The Book of Life," and articles referring to the human genomic sequence as "the master blueprint of a human."

Such characterizations may have been intended as analogies to describe a complex subject in simpler terms. Too often, the result has been a perception that individual human futures are fully described in the sequences within each individual's genome, a concept referred to as genetic determinism. The Human Genome Project is a major triumph, but to suggest that investigators understand human life or have a blueprint for the construction of a human based on this sequence would be a wild overstatement. James Watson, the initial head of the NIH's Human Genome Project, stated, "The goal of the Human Genome Project is to understand the genetic instructions for human beings. . . . Getting the instructions is a big job; understanding those instructions can consume many hundreds of years."

It is essential to understand that the genetic instructions are not immutable, but quite plastic. An individual's unique experiences can permanently alter the expression of genes in that individual's genome. If this is the case, then it is easy to see how identical twins, with distinct experiences, may have very different patterns of gene expression and therefore different states of health and disease. Since identical twins are shaped by individual experiences, then the concept of a clone — be it human or another animal — as a "Xerox copy" of the original is also invalid.

Each individual is composed of complex and dynamic biological networks encoded by his or her genome. Environmental experience can influence those networks. If you think of those influences as pressures on the system, then you might anticipate that a push from the environment would be met with a push back from the genes that would be transient and would cease when the environmental pressure dissipated, or shortly thereafter. It is now recognized, however, that some environmental experiences may have specific and measurable effects that permanently and chemically modify specific genes within an individual's genomic DNA, resulting in lifelong alterations in the expression of these genes. These permanent alterations in gene expression are referred to as imprinting and can have serious health consequences that may not become obvious until some future time in one's life or the lives of one's offspring. This influence of the environment on expression of the genes in the genome is referred to as an epigenetic effect.

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Observations of those who suffered through the Dutch "Hunger Winter" of 1944–45 demonstrated that, through imprinting, environmental

influences might program biological systems to behave in specific ways many decades into the future. Near the end of World War II, as Allied troops advanced across northern Europe in the summer and fall of 1944, quick liberation of the Netherlands was anticipated. However, when the Allied offensive stalled at the Rhine River, and the Dutch government in exile called for a strike of railway workers to support the Allies, a German reprisal banned all food transport to the Netherlands. This food embargo was in effect from October until early November 1944. By that time, however, the winter of 1944–45 had begun, the waterways were frozen, fuel was in short supply, and food could not be transported from the rural eastern to the urban western portions of the Netherlands.

From November 1944 until liberation from Nazi occupation by the Allies in May 1945, there was an incredible shortage of food in the western part of the Netherlands. Because of substantial rationing of food throughout the war, people did not have reserve stores of foodstuffs, and the famine was worse as a result. To survive, the Dutch even ate tulip bulbs, being careful to remove the bulbs' poisonous centers. Caloric restriction was extreme, compared with the typical adult requirements of 1,600 to 2,800 calories per day, depending on age, gender, and level of activity. Official daily rations for most adults fell from 1,800 calories in December 1943, to 1,400 calories in October 1944, to less than 1,000 calories per day by late November 1944. At the peak of the famine, the official daily rations for adults were 400 to 800 calories per day, well within starvation range. Although infants under one year of age were supposedly protected by an officially sanctioned ration that never decreased below 1,000 calories per day, there was an extremely high death rate from malnutrition and infection in the first year of life during the famine. From this tragedy, the Dutch Famine Birth Cohort was developed to study the effects of the famine on fetuses.

Individuals who had been exposed as fetuses to extreme undernutrition during the Dutch famine experienced increased risks to their health when they became adults. A glucose tolerance test measures the regulation of glucose uptake and metabolism, and adults who were still in the womb in the second or third trimester during the famine had abnormal glucose tolerance tests consistent with insulin resistance. Insulin resistance is seen in those with or at risk for adult-onset, or type 2, diabetes mellitus. The uterine environment had changed the expression of genes in their genomes, which led to the development of insulin resistance and a much higher incidence of type 2 diabetes in adulthood.

Additional adult health problems or predispositions have been noted in the Dutch Famine Birth Cohort. Fifty-year-old individuals who were exposed to the Hunger Winter when they were early in their gestation

had a blood lipid profile with increased LDL ("bad cholesterol") and decreased HDL ("good cholesterol"). This profile predisposed them to developing blockage in their arteries, including those of the heart (coronary arteries), referred to as coronary artery disease. Therefore, they were at increased risk for high blood pressure and heart attacks. Exposure to the famine in early gestation was also associated with an increased body mass index (BMI) indicative of obesity. The association of obesity, diabetes, abnormal blood lipid profile, and high blood pressure is referred to as the metabolic syndrome. It is intriguing that all of these features were observed in the Dutch Famine Birth Cohort.

The Dutch Hunger Winter came to a relatively abrupt halt when the Allied forces liberated the Netherlands. Some of the most striking findings were in those adults who had been small for gestational age at birth, consistent with starvation in the womb, and who then put on weight rapidly in early childhood following liberation. This phenomenon may have relevance for populations around the world who are emerging from disadvantaged economies and suddenly experience more abundant food resources. Individuals conceived in more calorie-restricted situations and then reared where food is more available may be at risk for a variety of common complex diseases in adulthood. They may develop individual disorders like obesity, diabetes, hyperlipidemia (high levels of fat in the blood), or cardiovascular disease; or they may develop all of them together, the metabolic syndrome.

Evidence from the Dutch Famine Birth Cohort also suggests that there may be intergenerational effects from the Hunger Winter. Investigators looked at a group of females whose mothers became pregnant with them during the famine and gave birth after the Allied liberation. When these individuals reached adulthood, they achieved normal height, but when they gave birth, their babies were small. This would suggest that the environment experienced by their grandmothers during the Hunger Winter could be influencing a second generation. Judith Hall, a prominent geneticist from the University of British Columbia, has pointed out that the egg that became you was developing in your mother when she was a fetus in your grandmother's womb. So there could be second-generation effects that are the direct result of influences on the developing egg, or ovum. Alternatively, there may be as yet unknown epigenetic influences that are maintained for many generations. Studying multigenerational effects will require accurate medical records, and it will require more than family lore. While we know some things about our mothers' environments during their pregnancies with us, we know almost nothing about the environmental experiences of our grandmothers during their pregnancies with our mothers.

The Dutch famine was a severe form of food restriction. While perhaps

not as striking, we would anticipate more subtle effects from less severe environmental influences. For how many generations the effects of such subtle influences on our genomes will persist has yet to be investigated.

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These observations from the Dutch Hunger Winter are consistent with what has come to be known as the Barker hypothesis — that there are fetal origins of adult disease. David Barker, from the University of Southampton in England, hypothesized that many adult diseases arise from fetal environmental experiences. Barker was searching for archives that would provide detailed, accurate birth weights and living conditions from sixty years previously so that he could examine associations with cardiovascular health. With some luck and fortunate coincidence, he happened upon and gained access to records generated by an "army" of midwives organized and trained by Ethel Margaret Burnside in the county of Hertfordshire.

In his initial study in 1995, Barker was able to use the National Health Service Central Registry to find 15,000 men and women born in Hertfordshire prior to 1930. One-fifth had died. Nearly one-half of those died from coronary artery disease or related problems. Those with a low birth weight had a disproportionately large share of deaths.

The midwives returned when the babies were one year old to check on household conditions and weigh the infants again. Males who weighed 18 pounds or less at one year of age had a threefold increased risk of death from a heart attack compared with those who weighed 27 pounds or more. Those who were smaller at birth and had a slower weight gain in infancy might be at higher risk for cardiovascular disease.

Subsequent studies by Barker's team and others have confirmed the fetal origins of adult disease. The most concerning pattern of growth is low weight for gestational age at birth, slow weight gain in early childhood, and then a rapid increase in body weight. The increased risk for obesity, diabetes, hyperlipidemia, hypertension, and coronary artery disease has been confirmed in many different populations. In addition, other disorders have been proposed to have fetal origins, including kidney disease, lung disease, liver metabolic abnormalities, unipolar (depression or mania) and bipolar (depression and mania) major affective disorders, and schizophrenia. There is also growing evidence that experiences after birth may also have significant influences on the risks for adult disease.

The knowledge that adult diseases may have their origins in fetal exposures indicates that nurture can influence nature. These effects can be profound and long-lasting. It is important to recognize, however, that not all

individuals who were exposed to undernutrition in the womb developed adverse outcomes. These were epidemiologic investigations of groups of individuals and showed relative increases or decreases in risks associated with fetal environment.

The Barker hypothesis shows that two individuals conceived with identical genomes may have different fates after they are born and achieve adulthood. The concept of fetal origins of adult disease, or durably programming the reading of the genome in the womb, indicates that these eventual fates will be based on environmental exposures. Identical twins with identical genomes occupying the same womb could still experience different uterine environments, if, for example, the vascular delivery of nutrients differed between the twins. Clones developing in different wombs would be even more likely to have different environmental experiences and therefore would be less likely to have identical patterns of gene expression.

The plasticity of the genome would have been impossible to consider until very recently. However, evidence is accumulating that there are dynamic interrelationships between our genomes and our environments. The nature-nurture debates often seem to lose sight of the powerful and continuous interplay between these forces. Such plasticity and dynamism is exciting to watch unfold and argues ever more strongly against genetic determinism. Genetic imprinting provides scientific evidence for the biological uniqueness of individuals with identical genomic DNA, including identical twins and clones. It is not the sequence of the individual's genome that is important, but how it is read, and the reading of the genome is influenced by imprinting, or epigenetic environmental events.

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In the chapters that follow we will explore the recent history of genetics and genomics and how the advances of the past and present may play out in the future. We will share with you examples of the thrilling and provocative insights that enable us to better understand population dynamics and the diseases of individuals and groups. Just as science and society are coevolving, the science is taking place in a social context and is influenced by the voices expressed in that context; we will introduce you to thought-leaders in these fields and examine their influence. We propose to be your guides through this journey and hope that you will find the trip as enjoyable, stimulating, and surprising as we have found the last thirty years in genetics and genomics.