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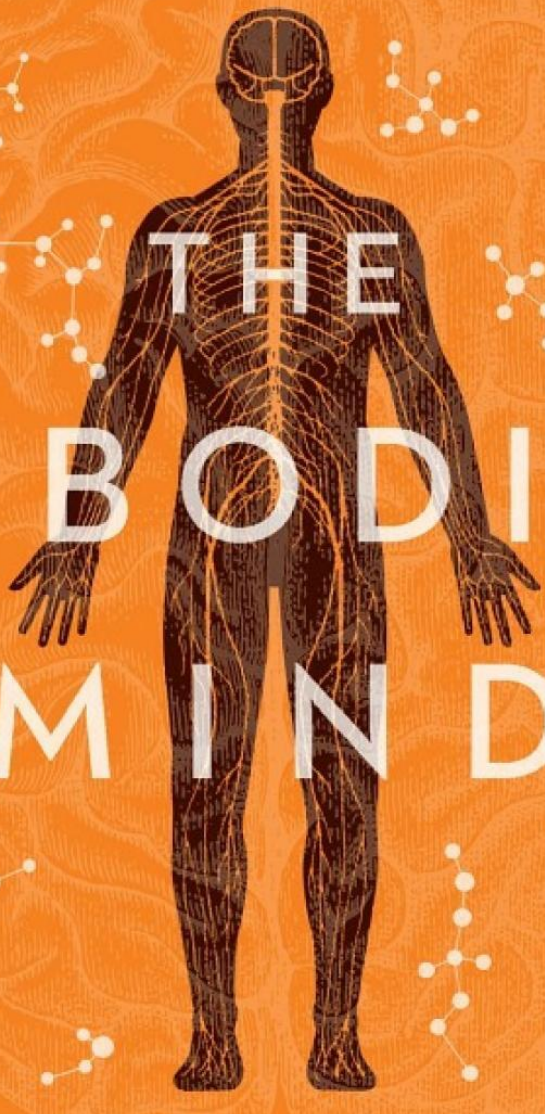
"Fascinating. Dr. Verny takes us on a journey into the fully embodied nature of mental life."
—DANIEL J. SIEGEL, M.D.



THE EMBODIED MIND

UNDERSTANDING THE MYSTERIES OF CELLULAR MEMORY, CONSCIOUSNESS, AND OUR BODIES

INTRODUCTION

As a thirteen-year-old boy I read Sigmund Freud's *The Interpretation of Dreams* in the original German in Vienna. I was totally fascinated by how Freud's slow, methodical questioning eventually led to the discovery of deeply hidden unconscious conflicts in the lives of his patients. Then and there I resolved to become a psychiatrist.

Years later, when I had become a psychiatrist, I continued to be fascinated by dreams and the unconscious. One day, while working with a young man on his dream he suddenly, without any input from me, started to cry like a little baby. He cried for close to ten minutes and then stopped on his own. What just happened? I asked him. He told me that in his mind he found himself in a crib and that he was crying for his mother. Then, he recalled that he had actually seen photos of himself as an infant and some of them pictured him lying in a blue crib whereas the crib that he had just experienced was definitely white. He wondered about the discrepancy.

I suggested that he ask his mother to resolve this question. The next week he returned for his regular appointment and told me that according to his mother, when he was born his parents lacked money for a new crib but were able to borrow one from a neighbor. The borrowed crib was white. A few months later, they were able to buy a new crib for him and that new crib was blue. That is the one of which all the photos were taken.

I felt both intrigued and mystified by this experience, since throughout my studies first at the University of Toronto then Harvard University, I was taught that children remember nothing before the age of two. And yet as I continued to practice, I repeatedly encountered patients who would tell me about events in their lives reaching far back in time to infancy, birth, and even womb life. A few of these memories may have originated from overheard conversations by family members or gleaned from photo albums or videos. However, a considerable number would not have been easily available and were corroborated by evidence supplied by parents, hospital reports, and other documentation. I wondered how to explain these memories scientifically. It was then that after much study, research, and personal contacts with colleagues in obstetrics, psychology, psychiatry, and other sciences, I wrote *The Secret Life of the Unborn Child*, which is now published in twenty-seven countries and continues to enjoy wide popularity.

At the time, almost forty years ago now, I had much solid scientific evidence to back up the central premise of my book; namely, that an unborn child is a sensing, feeling, conscious, and remembering being, at least three months before birth. However, I had little or no scientific evidence to support cognition of any kind extending back further in time. Of course, given the rapidity of development and change in the biomedical sciences these past decades, forty years is practically an eon ago. Much of what is now known in cell biology, genetics, and more important, epigenetics, not only confirms my claims in *The Secret Life*, but enables me to put forward the bold new concepts in *The Embodied Mind*.

What set me on the path toward *The Embodied Mind* was an article I read six years ago reprinted from *Reuters Science News* titled "Tiny Brain No Obstacle to French Civil Servant." It seems that in July 2007, a forty-four-year-old French man went to a hospital complaining of a mild weakness in his left leg. When doctors learned that the man had a spinal shunt removed when he was fourteen, they performed numerous scans of his head. What they discovered was a huge fluid-filled chamber occupying most of the space in his skull, leaving little more than a thin sheet of actual brain tissue. It was a case of hydrocephalus, literally—water on the brain. Dr. Lionel Feuillet of Hôpital de la Timone in Marseille was quoted as saying, "The images were most unusual… the brain was virtually absent." The patient was a married father of two children, and worked as a civil servant apparently leading a normal life, despite having a cranium filled with spinal fluid and very little brain tissue.

To my surprise, I found in the medical literature an astonishing number of documented cases of adults who as children had parts of their brain removed to heal their persistent epilepsy. Following hemispherectomy most children showed not only an improvement in their intellectual capacity and sociability but also apparent retention of memory, personality, and sense of humor. Similarly, adults who have had hemispherectomies enjoyed excellent long-term seizure control and increased postoperative employability.

If people who lack a large part of their brain can function normally, or even relatively normally, then there must exist, I thought, some kind of a backup system that can kick in when the primary system crashes. I devoted the next six years to studying the medical and scientific literature, searching for evidence to support my hunch.

I found that while many scholars had contributed greatly to advancing science in their own fields, no one had really synthesized this knowledge, "connected the dots," and thought of addressing this puzzle. *The Embodied Mind* attempts to do just that.

Our embodied mind is not the old enskulled one. It is an extended mind that relies on the intelligence of all the cells in our body that contain specific bits of information, micro-memories. All memories, consciousness, and the mind emerge from this linked sentient network.

The Embodied Mind, which I will seek to establish as its own unique psychobiological term, represents a coherent and empirically grounded biological theory that marks a significant departure from the past century's exclusive focus on cortical neurons (brain cells) as the only important cells in information processing, cognition, and memory storage. *The Embodied Mind* is based on studies that demonstrate intelligence and memory in a wide range of systems well beyond the traditional central nervous system, including the immune system, sperm and ova, unicellular organisms, amoebae, and many more. Memory is truly a body-wide web. Whether or not we can consciously access a memory is not as important as the realization that we had the experience, the lived event, which has left some kind of impact, influence, mark, trace, record, or imprint on our cells and tissues.

A large number of these effects may be passed on to our children and grandchildren. Therefore, it is imperative that we become aware of as many of our basic maladaptive urges and behaviors as possible and consciously try to overcome them. At the same time, it is imperative for our sake but especially for the benefit of our future children to live a good and healthy life. We shall vastly improve our lives and the lives of future generations by

actively avoiding stress and anxiety as well as people who are critical or deceitful and instead befriend people who support and value us.

Like musicians in an orchestra playing in different sections, be they strings, woodwinds, brass, or percussion, the cells in the skin contain different information from the cells in the heart and so on. The memory that emerges either consciously or unconsciously as a result of some trigger is "heard" like the music emanating from an orchestra. The higher brain centers take the place of the conductor and coordinate the messages that reach our conscious self and lead to cognition and behavior.

It is time we put to rest the myth of the enskulled brain and mind and adopted the scientifically evidence-based concept of the embodied brain and mind. This is a transformative, novel concept in psychobiology, at once paradigm-shifting and empowering.

We think, feel, and act with our body. We relate to the world with our body. Our mind is body bound. It is my hope that *The Embodied Mind* will help us gain more insights into who we are in relationship to ourselves, our loved ones, society, and the universe. It will motivate us to exercise our free will and encourage us to take responsibility for our own actions.

CHAPTER ONE

DO GENES MATTER?

Introduction

The union of sperm and egg at conception leads to the formation of a fertilized ovum, a one-celled organism, the zygote, that, if successfully implanted into its mother's womb, will eventually become an adult person. This tiny cell will carry the blueprint for the future of an entire human being. Astonishing but true. What is even more amazing is that on the basis of solid scientific evidence I can say that this genetic information is not limited to just architectural plans for building a body but may also include data reflecting experiences and personality characteristics of the parents. Such *acquired* characteristics catapult us into the new science of epigenetics.

I think it is fair to say that epigenetics is the most revolutionary advance in the biological sciences since Charles Darwin's *On the Origin of Species* was published in 1859. Epigenetics is the study of the molecular mechanisms by which the environment regulates gene activity. Epigenetics teaches us that life experiences not only change us but that these changes may be passed on to our children and grandchildren down through many generations. This process is called *trans-generational inheritance*, and has become a hotly debated area of research.

From an evolutionary perspective it makes good sense that exposure of parents to significant environmental conditions such as hunger, warfare, anxiety, and the like should "inform" their offspring in order to better prepare them to meet these conditions when they are born. Obviously, this information can only be conveyed from parents to their children by way of their germ cells (ova and sperm).

In the last decade, genetic research has established that the DNA blueprints passed down through genes are not set in stone at birth. **Genes are not destiny**. Environmental influences, including nutrition, stress, and emotions, can modify the expression (whether they are turned on or off) of those genes without changing the genes themselves.

We shall take a whirlwind tour through genetics: chromosomes, genes, DNA, RNA, etc. Then we shall move on to epigenetics, which I have divided into environmental epigenetics, which deals with physical environmental factors such as pollution, toxins, too much or too little food, and psycho-social epigenetics, which is concerned with relationships, particularly parent-child relationships, and psychological factors such as stress, anxiety, or the presence or absence of affection. We shall pay particular attention to the impact of abusive and neglectful caregiving and parental adversity on a child's epigenome.

Genetics

It is impossible to discuss genetics without the use of scientific jargon. For this, I ask your indulgence and patience. Even if you find some of these terms daunting, please read on. You will get the gist of it. I promise.

The basic unit of inheritance is the chromosome. A chromosome is an organized package of DNA (deoxyribonucleic acid) found in the nucleus of every cell. Different organisms have different numbers of chromosomes. Humans have twenty-three pairs of chromosomes. These consist of twenty-two pairs of numbered chromosomes, called autosomes, and one pair of sex chromosomes, *x* and *y*. If you have *xx*, you become female; *xy*—male. Each child receives half of their chromosomes from their mother and half from their father.

A genome is the complete set of DNA in a cell. The twenty-five thousand to thirty-five thousand genes on the human genome make up only 5 percent of the entire genome. The rest consists of switches and long stretches of noncoding DNA (meaning they do not make proteins). These regions between genes were for a long time dismissed as "junk DNA." Scientists have recently learned that the regions between the genes are the switches that play a vital role in cell functions. Mutations in those DNA regions can severely impact our health.

Robert Sapolsky, professor of biology, neuroscience, and neurosurgery at Stanford University, when discussing the human genome says in his wonderful book, *Why Zebras Don't Get Ulcers*, "It is like you have a 100-page book, and 95 pages are instructions on how to read the other 5 pages."

In his seminal *On the Origin of Species*, Darwin wrote that evolutionary changes take place over many generations and through millions of years of natural selection. Following in Darwin's footsteps, geneticists have had remarkable success in identifying individual genes with variations that lead to simple Mendelian traits and diseases (see endnotes) such as phenylketonuria (PKU), sickle-cell anemia, Tay-Sachs disease, and cystic fibrosis. However, diseases with simple Mendelian patterns of inheritance are rare, while most human diseases such as cancer, diabetes, schizophrenia, and alcohol dependence, or personality traits and behavior, are the result of a multitude of genetic and psycho-socio-economic-cultural elements and therefore, considered complex and multifactorial.

Time magazine's covers often reflect a dominant cultural, political, or scientific phenomenon. The October 25, 2004, cover portrayed a woman praying with the inscription THE GOD GENE. It refers to an article in that issue that hypothesizes on the presence of a "God Gene" in our genome. Of course, nothing could be further from the truth.

There is no God Gene, or Anger Gene, or Selfishness Gene, or Schizophrenia Gene. It takes many genes to develop a disease or bring about a personality trait. By the same token, a different combination of the same genes can create high intelligence, musical abilities, foresight, etc. Researchers from the University of Geneva report that genetic variation at a single genomic position impacts multiple, separate genes. **If one element changes, the whole system changes. Genes teach us a crucial life lesson:** *Everything is connected.*

A case in point is the finding that personality changes can affect body shape and body movements, at least in zebrafish (figure 1), as a powerful new study from North Carolina

State University demonstrated recently. The researchers bred one group of fish to be bolder and another group to be shy. Zebrafish that were bred to be bold displayed a sleeker body shape and an ability to dart around the water more quickly when startled than those bred to be shy. This study supports the assumption that traits like personality or temperament may be genetically correlated with other traits, like body shape. The body is one complex ecosystem where if even the smallest part changes, everything changes, like the proverbial "domino effect."

The genome's functioning is dependent on its intracellular environment (the environment in the cell surrounding the nucleus) and its relationship to the extracellular environment, including hormones and neurotransmitters. The extracellular environment, in other words, the tissues and organs of the body outside the cell, are in turn affected by the environment of the individual—for example, by the availability of food or social interactions. Consequently, we unconsciously adjust our lives to everything that transpires inside and outside of us. It's wonderful that our body can do this on its own. We don't even have to think about it most of the time.

With a few exceptions, every cell type in a multicellular organism carries the same endowment of genetic instructions encoded in its DNA genome. Nevertheless, each cell type expresses (activates) only those genes required for its specific performance of function. The proteins that package the genes in the cell nucleus are called histones. Histones act as spools around which DNA winds (figure 1.2). Histones play an important role in gene regulation. More on this in the next section.

The dominant view of heredity is that all information passed down from one generation to the next is stored in an organism's DNA. Very recently, cellular biologist Antony Jose has advanced a new, we might say revolutionary, theoretical framework for heredity. Jose challenges the common view of heredity that all information passed down from one generation to the next is stored in an organism's DNA and argues that DNA is just the ingredient list, not the set of instructions used to build and maintain a living organism. The instructions, he says, are much more complicated, and they are **stored in the molecules** that regulate a cell's DNA. Jose's new framework recasts heredity as **a complex, networked information system** in which all the regulatory molecules that help the cell to function can constitute a store of hereditary information.

Jose's framework helps us to understand how the storage of information has evolved with complexity over the millennia that must include now the cytoplasm and the cellular membrane in addition to the nucleus. It reemphasizes the need to abandon outmoded concepts of central control mechanism and instead introduce concepts of networks and feedback loops.

The early twentieth century geneticists' view of heredity saw the development of an organism as a one-way flow of information from nuclear DNA to messenger RNA to protein production. This model, also known as *the central dogma of genetics,* is now being superseded by the recent rise of epigenetics. As we shall see, epigenetics is based on the ways that extranuclear factors interact with genes to bring about the changes in an individual.

Epigenetics

Another cover of *Time* magazine, in early January 2010, also depicted a double helix of DNA, this time as a giant zipper hanging down across the cover, its shiny gold slider opening part way, as if unzipping an actual strand of DNA. This time the cover story was: "Why Your DNA Isn't Your Destiny: The new science of epigenetics reveals how the choices you make can change your genes—and those of your kids." This time, *Time* was on the right track.

While Darwin's work defined evolution as a process of incidental, random mutation between generations and survival of the fittest, the new science of epigenetics is much closer to the greatly maligned theory of French biologist Jean-Baptiste Lamarck, who suggested that an organism can pass to its offspring characteristics acquired during its lifetime.

Epigenetics is the study of changes in gene activity that do not alter the genes themselves but still get passed down to at least one successive generation. These patterns of gene expression are governed by the cellular material—the epigenome—that sits on top of the genome, just outside it (hence the prefix *epi*, which means "above"). A key component of epigenetics is methylation, in which a chemical group (*methyl*) attaches to parts of the DNA—a process that acts like a dimmer on gene function in response to physical and psychosocial factors. Epigenetic "switches" turn genes on or off, and all points in between (figures 1.3 and 1.4).

Methylation is a dynamic process, and levels of methylation can change from moment to moment and over the course of a person's lifetime depending on the person's experiences, whether these be external or internal. The opposite process to methylation is acetylation. Methylation turns down or totally silences the function of a gene while acetylation turns on the gene, partially or totally.

It is through epigenetic switches that environmental factors like prenatal nutrition, stress, and postnatal maternal behavior can affect gene expression that is passed from parents to their children. Epigenetic changes represent a biological response to one or more environmental factors. These factors may be positive and life affirming or negative and life threatening. Epigenetic changes serve a very important function during pregnancy by biologically preparing offspring for the environment into which they will be born. **Think of genetics as the hardware and epigenetics as the software in your computer**.

One of the primary objectives of epigenetics is to study data transfer from one generation to the next by biological rather than psychological means. Biological inheritance speaks to the idea that the germ cells (sperm and eggs) are affected by significant environmental events, and that these changes in the genome are then passed on to descendants. Epigenetics offers us the knowledge and the means by which we can enhance physical and mental health, both in our offspring and ourselves.

The union of sperm and egg at conception leads to the formation of a zygote (a fertilized ovum). This tiny cell will carry a set of complete instructions for building an entire human being. I wondered: Is the information limited to just architectural plans for constructing a body, or does it also include data that will affect the mind? Before we move on to address this question, we should mention three other biological ways by which information may be exchanged between people that do not involve germ cells.

It has recently been discovered that some of the cells carried in the blood that pass between mother and child during pregnancy remain in their bodies. Also, a few cells from prior pregnancies persist in mothers for many years. This process is called *microchimerism*. Human and animal studies have found fetal origin cells in the mother's skin, bloodstream, and all major organs, including the heart. What these studies show is that each of us carries two different cell populations, our own plus one from our mother. Women who have carried a child harbor at least three unique cell populations in their bodies—their own, their mother's, and their child's.

Similarly, *blood donations* and *organ transplants* can pass information on a cellular level to a recipient. If my hypothesis of cellular memory is correct, then these "donor" cells may, as in the case of microchimerism, affect their recipients' minds and bodies in ways we are just beginning to explore.

Environmental Epigenetics

In this section we shall discuss how physical factors such as food, nicotine, or odors affect the genome.

A 1988 paper published by John Cairns in *Nature*, one of the most distinguished science journals, started a tectonic shift in genetics. The paper described an experiment in which a particular strain of bacteria, E. coli, that could not metabolize lactose (a sugar found in dairy products), was placed on a lactose medium (scientific jargon for food on which bacteria grow, usually in a petri dish). Instead of starving—which according to classical Darwinian theory they should have—the bacteria very quickly underwent genetic changes, allowing them to digest lactose and thus survive. Cairns reported that at least in some cases, *selective pressures* could specifically direct mutations. Good-bye Darwinist orthodoxy.

Cairns "brazenly," as some critics said, raised the specter of possible Lamarckian hereditary mechanisms—one could not have been more heretical than that in 1988. In the same issue of *Nature*, Franklin Stahl, emeritus professor of biology at the University of Oregon, endorsed Cairns's conclusions and presented his own model of how "*directed mutations*" may take place.

Cairns today is professor of microbiology at the Radcliffe Infirmary, Oxford University, and remains a recognized leading authority in mutation genetics. His 1988 article is one of the most frequently cited papers in the field, and has launched an entire new area of study.

At about the same time as Cairns was performing his experiments, Dr. Lars Olov Bygren, at the University of Umeå, Sweden, wondered, "Could parents' experiences early in their lives somehow change the traits they passed to their offspring?" Bygren and many other scientists have now amassed abundant historical evidence suggesting that powerful environmental conditions (near death from starvation, for instance) can leave an imprint on the genetic material in eggs and sperm. **These genetic imprints can short-circuit evolution and pass along new traits in a single generation.**

A decade after the publication of Cairns's paper, professor of biology at Indiana University P. L. Foster wrote, "Much subsequent research has shown that mutation rates can vary, and that they increase during certain stresses such as nutritional deprivation. The

phenomenon has come to be called "*adaptive mutation.*" Today, adaptive mutation has been transformed into epigenetics. And suddenly, every university lab is pursuing it.

A favorite animal that geneticists love to study is C. elegans. Between October 1994 and January 1995, seventy-three scientific articles about C. elegans appeared in international journals. C. elegans is a very primitive worm about 1 mm in length that lives in the soil (figure 1.5). C. elegans is an appealing and effective model organism for research because it is easy to work with in the lab, requires little food, and produces a large number of offspring by self-fertilization within a few days.

The worm is conceived as a single cell that undergoes a complex process of *morphogenesis*.[1] It has a nervous system with a "brain" (the circumpharyngeal nerve ring). It exhibits behavior and is even capable of rudimentary learning. C. elegans produces sperm and eggs, mates, and reproduces. All 959 somatic cells of its transparent body are visible with a microscope, and its average life span is a mere two to three weeks. Importantly, worms and humans share up to 80 percent of their genes. Not surprisingly, approximately half of all the known genes that are involved in human diseases can also be found in C. elegans. Scientists delight experimenting on this creature.

For example, researchers at Duke University have conducted a new study on the effects of starvation. What they did was to starve one group of C. elegans roundworms for one day and another group for eight days at the first stage of larval development after hatching. When feeding was resumed, the worms that were starved longer grew more slowly, and ended up smaller and less fertile. They also proved more susceptible to a second bout of starvation. Their offspring were smaller, fewer, and less fertile. However, these children and grandchildren of famine turned out to be more resistant to starvation, as if they had a memory of famine.

The field of epigenetics gained momentum when several decades ago scientists studied the children born to women who were pregnant during a period of famine toward the end of World War II in the Netherlands. They found that these children carried a particular chemical mark, or epigenetic signature, on one of their genes. The researchers linked that finding to differences in the children's health later in life. The children grew smaller than the Dutch average and had higher than average body mass. Their children were also smaller and more susceptible to diabetes, obesity, and cardiovascular disease. These changes were detectable over three subsequent generations.

It is not just food that can starve offspring. In humans, so can poverty—as demonstrated by a British study at the University of Bristol. The researchers selected forty men from a group of three thousand born in 1958—half born into rich households and half born into poor ones. In the study, subjects were chosen from the top and bottom 20 percent according to socioeconomic status, so ensuring they had examples of both extremes.

Focusing on stretches of DNA called *promoter regions*, which translates to *switches*, the team examined more than 20,000 sites throughout the genome. The patterns were different between the two groups on almost one third of the sites. Most tellingly, methylation levels were drastically different at 1,252 sites of the men who came from poor households, but only at 545 sites in men from rich families. Because the samples were taken in middle age, the researchers couldn't tell exactly when the epigenetic methyl

groups were added or subtracted. While it is possible that the genes were altered in infancy, childhood, or even adulthood, the scientists conducting the experiments were of the opinion that the epigenetic changes they observed in adult DNA were largely the result of early life experience.

Today the most common surgical procedure in fertile women is delivery by elective cesarean section. Therefore, pregnant women or those planning on starting families should be aware of the research that has shed light on the fact that children born by cesarean section are at increased risk of developing asthma, type 1 diabetes, obesity, celiac disease, cancer, and suppression of their immune response.

Investigating this phenomenon, molecular cell biologists at the renowned Karolinska Institute in Sweden studied epigenetic alterations in the cord blood taken from elective C-section and vaginal delivery babies born at term. Blood stem cells from infants delivered by C-section were more DNA-methylated than DNA from infants delivered vaginally. The researchers found specific epigenetic differences between the groups in 343 DNA regions, including genes known to be involved in processes controlling metabolism and immune deficiencies. These studies clearly indicate that the epigenome of an infant is sensitive to the prenatal environment and the experience of birth.

During the recent COVID-19 pandemic it was observed that some people became severely ill, while others tested positive with the virus but remained symptom free. The multigenerational weakening of the immune system described here may be a hitherto unrecognized factor, along with socioeconomic ones, which of course cause stress, physical and mental, accounting for these wide variations.

Complex diseases such as cancer, diabetes, obesity, autism, and birth defects are increasing in prevalence at rates that cannot be explained by classical genetics alone. Studies in humans and animals strongly suggest that epigenetic mechanisms may be responsible.

Social Epigenetics

Using mice as a model to investigate human breast cancer, researchers have demonstrated that a negative social environment (in this case, isolation) causes increased tumor growth. The findings also support previous epidemiologic studies suggesting that social isolation increases the mortality of patients suffering of chronic diseases, as well as clinical studies revealing that social support improves the outcomes of cancer patients. The presence of compassionate and caring people can alter the level of gene expression in a wide variety of tissues including the brain. Of course, our recent experiences with the COVID-19 pandemic taught us firsthand the veracity of the human need for interaction.

One of the most beautiful and imaginative experiments that I have encountered in my professional life is the "Kidnapping-and-Cross-Fostering Study" devised by Gene Robinson, director of the Institute for Genomic Biology at the University of Illinois. What Robinson did was to pluck about 250 of the young bees from two African hives ("killer bees") and two European hives (a gentle bee strain), and paint marks on the bees' backs to identify their origins. (I don't think Robinson painted many bees. That's what postgrads are for.) Then he and his team switched each set of newborns and placed them into the hive of

the other subspecies.[2] European honeybees raised among more aggressive African bees not only became as belligerent as their new hivemates—they came to genetically resemble them. And vice versa. What this experiment convincingly proves is that in a very short time the social environment can radically change gene expression and behavior.

David Clayton, a neurobiologist and a colleague of Gene Robinson at the University of Illinois, found that if a male zebra finch heard another male zebra finch sing nearby, a particular gene in the bird's forebrain would be stimulated and it would do so differently depending on whether the other finch was strange and threatening or familiar and safe. Songbirds demonstrated massive, widespread changes in gene expression in just fifteen minutes.

We are learning that brain responses to social stimuli can be massive, involving hundreds, sometimes thousands of genes. Even as recently as twenty years ago no self-respecting geneticist or neuroscientist would have thought in their wildest dreams that social experiences lead to changes in brain gene expression and behavior. Yet they do.

Trans-one-generation (F1)

The term *trans-one-generation epigenetics* refers to the effect maternal or paternal genetic factors exert on a child. Scientists designate these as F1 factors.

At one time or another, I am sure all of us have wondered why some people are always calm, no matter what, while others get anxious at the drop of a hat. Recent research on rats provides a clue. Mother rats seem to fall into two groups. Those that spend a lot of time licking, grooming, and nursing their pups, and others that simply ignore their pups. Highly nurtured rat pups tend to grow into calm adults, while rat pups deprived of nurturing care grow up anxious. The nurturing behavior of a mother rat during the first week of life shapes her pups' epigenome. And the epigenetic pattern that the mother establishes tends to endure, even after the pups become adults. **The difference between a calm and an anxious rat is not genetic; it is epigenetic.**

These data indicate that a higher level of maternal caretaking behavior during the first week of life promotes adult behavior that is characterized by stress resilience and increased maternal care in the offspring. In this instance, what is true for rats also applies to humans. Future parents, please take note.

In 2011 a University of Delaware group decided to study whether early life adversity alters gene expression. They exposed male and female infant rats to stressed "abusive" caretakers for thirty minutes daily during the first seven days of life. They induced abuse in mother rats by placing them in an unfamiliar environment with limited space. As a result, caretakers began to step on, drop, drag, actively reject, and roughly handle their infants. This treatment, naturally, elicited distress responses in the infants.

Brain-derived neurotrophic factor (*Bdnf*) regulates the survival and growth of neurons and influences synaptic efficiency and plasticity. The maltreated infant rats were found to have significant decrease in Bdnf gene expression that was in line with previous findings where early life experiences are known to have a lasting impact on this gene, leading to detrimental changes in personality and behavior. This underperforming Bdnf gene persisted through development and into adulthood.

Abusive and neglectful caregivers are known to leave children particularly susceptible to cognitive and emotional dysfunction. Indeed, childhood maltreatment is significantly associated with the later diagnosis of adolescent and adult major depression, schizophrenia, borderline personality disorder, and post-traumatic stress disorder.

Sensitive caregiving, on the other hand, is of immense value to a child. For example, neurobiologist Regina Sullivan at the NYU School of Medicine found that rat infants experiencing pain had several hundred genes more active than rat infants free of pain. With their mothers present, however, fewer than one hundred genes were similarly expressed (activated). Sullivan has successfully demonstrated that a mother comforting her infant in pain alters gene activity in a part of the brain involved in emotions (amygdala) and thus elicits a positive short-term behavioral response in her child.

This has important implications for understanding the biology of attachment and bonding in the postnatal period. Every expression of a mother's affection changes gene activity in her infant's brain, which leads the infant to gradually develop attachment to the mother. The smiling child's response elicits epigenetic changes in the mother. The repetition of this interaction over time eventually contributes to the development of mutual love: the love of the mother for her child (bonding) and the child's love for their mother (attachment).

Trans-two-generation (F2 and F3)

F2, F3 epigenetics is used here to refer to measuring the effects of parental behavior, stress, or trauma on their children, grandchildren, and great-grandchildren; i.e., first-, second-, and third-generation effects, F1, F2, and F3. These effects are often sex-specific.

I admire the following study from Emory University. It is beautifully simple and straightforward. The researchers tested a certain distinct smell experience of parents on the behavior and brains across generations of their progeny. The scientists gave male lab mice electric shocks every time they were exposed to the smell of acetophenone, a chemical used in perfumes. As a result of this classical conditioning technique the mice became anxious at the mere scent of acetophenone. **Their children came to fear the smell too, even though they had never been exposed to it.**

The mice showed no reaction to other smells and had no fear responses to sounds or different types of warnings. To confirm this, the scientists even took sperm from the first set of mice, then used in vitro fertilization (IVF) techniques to implant the sperm in females from another lab. The pregnant mice were raised in isolation, away from any contact with other mice, and yet their children still demonstrated an increased sensitivity to the original scent.

Similar results were achieved by Australian researchers studying mice infected with the toxoplasma parasite. They discovered that sperm of infected fathers carried an altered "epigenetic" signature that impacted the brains of resulting offspring. Molecules in the sperm called microRNAs (miRNAs) appeared to influence the offsprings' brain development and behavior (see section "How Epigenetic Changes Are Passed On" for more on miRNA). Transgenerational inheritance of similar epigenetic modifications has

been associated with neuropsychiatric dysfunction in these mice's children and grandchildren.

Other researchers studied the effect of stress in four generations of rats. They found that a single exposure to prenatal stress in mothers increased the risk of preterm birth and adversely affected their offspring in many areas. The scientists involved in the study emphasized that **the causes of many complex diseases are likely rooted in the experiences of our ancestors.**

Exposure of mothers to nicotine and other components of cigarette smoke is recognized as a significant risk factor for behavioral disorders, including attention deficit hyperactivity disorder (or ADHD) in many generations of descendants. To study whether the same applies to fathers, researchers at Florida State University in Tallahassee exposed male mice to low-dose nicotine in their drinking water during the stage of life in which the mice produce sperm.

They then bred these mice with females that had never been exposed to nicotine. While the fathers were behaviorally normal, both sexes of offspring displayed hyperactivity, attention deficit, and cognitive inflexibility. When female (but not male) mice from this generation were bred with males never exposed to nicotine, male offspring displayed fewer, but still significant, deficits in cognitive flexibility.[3] Analysis of spermatozoa from the original nicotine-exposed males indicated that multiple genes had been epigenetically modified, including the dopamine D2 gene, critical for brain development and learning, suggesting that these modifications likely contributed to the cognitive deficits in the descendants. These findings underscore the need for more research on the effects of smoking by the father, rather than just the mother, on the health of their children.

How about grandparents who smoke? Well, we have a study on that, too. After analyzing data from more than 14,500 children born in the United Kingdom during the 1990s, epidemiologists from the University of Bristol found that people with a maternal grandmother who smoked during her pregnancy had a 53 percent increased risk of developing autism. The study also revealed that girls whose maternal grandmother smoked during pregnancy were 67 percent more likely to have autism-linked traits. For two of the traits (social communication and repetitive behavior) the investigators demonstrated that granddaughters were much more affected than grandsons.

Today, in most parts of the world marijuana is perceived as benign and less harmful than alcohol. Duke University researchers have proven this belief unfounded. They analyzed differences between the sperm of males who smoked or ingested marijuana compared to a control group with no such experiences. They identified significant hypomethylation in the sperm of men who used marijuana compared to controls, at a gene that has been strongly implicated in autism, schizophrenia, and post-traumatic stress disorder. This hypomethylated state was also detected in the forebrain region of rats born to fathers exposed to THC, giving rise to cognitive deficits.

Researchers from the Mount Sinai School of Medicine in New York decided to study more psychological issues with far-reaching results. They subjected adult male mice to chronic social defeat stress. Then they bred the stressed mice and a control group of male mice with normal female mice. Once their offspring were born, they were assessed by a variety of standard tests for depressive and anxiety-like symptoms. Plasma levels of

DNA. There is much discussion among geneticists as to how epigenetic changes are passed on through sperm and ova. Now scientists are discovering that the classical genetic code is not the only code involved in the regulation of cell differentiation and behavior in multicellular organisms. There is a second level of control that contributes to the regulation of gene activity. One of these is based on chemical modifications of the histone proteins. I briefly mentioned histones at the beginning of this chapter. Histones have attracted relatively little attention until now. Histones are distinct from DNA, although they combine with it during cell formation, acting a bit like a spool around which the DNA winds (figure 1.2).

A new collaborative study by McGill University and Swiss researchers have discovered that histones are part of the content of sperm transmitted at fertilization. The researchers created mice in which they slightly altered the biochemical information on the histones during sperm cell formation. The offspring for two successive generations were adversely affected both in terms of their development and in terms of their survival.

These findings are remarkable because they indicate that information in addition to DNA is involved in heritability. **The study highlights the critical role that fathers play in the health of their children and even grandchildren.**

Another proposed mechanism for gene regulation involves small noncoding RNAs called *micro RNAs (miRNAs)* found in many mammalian cell types including sperm. About 60 percent of the genes of humans and other mammals appear to be targeted by miRNAs. miRNAs constitute a newly discovered type of gene regulator, where each miRNA controls a distinct set of genes. miRNAs are proving to be master regulators of virtually all cell processes with broad controls stretching into cell cycle, signal transduction, and energy metabolism pathways, among others.

In a Tufts University School of Medicine study, male mice exposed to chronic social instability stress during adolescence transmitted stress-associated behaviors to their female offspring across at least three generations even if they never experienced significant stress themselves or interacted with their fathers by way of the male lineage. One mechanism for this effect was found to be sperm miRNA.

Sperm miRNA expression in humans has been known to be affected by environmental factors, such as smoking and obesity. However, a University of Delaware group was first to demonstrate sperm miRNA changes in response to stress in humans, and raised the possibility that sperm miRNA could be a biomarker for early abuse as well as elevated susceptibility of offspring to psychiatric disorders.

miRNAs play an important role in defending the body from invasions by viruses, as we were so tragically reminded when the COVID-19 crisis erupted. They do so by latching onto and cutting the RNA material of the virus. One of the reasons that the COVID-19 virus has had such a devastating effect on older people and those with underlying conditions is because as we age and develop chronic medical diseases, our miRNA numbers dwindle, reducing our ability to destroy invading viruses.

Further new details about miRNAs have been successfully unraveled by neurobiologists at the University of Maryland studying extracellular vesicles. The male reproductive tract, the *caput epididymis*, the structure where sperm matures, is where these tiny vesicles packed with miRNAs originate. Vesicles fuse with sperm to change its payload delivered to

the egg. The caput epididymis responds to the father's stress by altering the content of these vesicles.

Extracellular vesicles have emerged as important mediators of intercellular communication, involved in the transmission of biological signals between cells. They have been identified as regulating a diverse range of biological processes, effects of stress as well as contributing to the development of infectious diseases, cancer, and neurodegenerative disorders. Extracellular vesicles help pass information between cells and onto offspring. In an important departure from past assumptions, the scientists leading the Maryland study **have now accepted the idea that sperm can be vulnerable to environmental factors.**

Similarly, evidence is accumulating that preconceptional exposure to certain lifestyle factors, such as diet, physical activity, and smoking affects the development of the next generation through alterations of the epigenome of sperm cells.

A related study at the University of Massachusetts Medical School showed that embryos fertilized using sperm from the distant portion of the epididymis—where sperm have not yet gained a full payload of regulatory RNAs—exhibit gene dysregulation early in development and then fail to implant in the uterus efficiently. Clearly, small RNAs in sperm are essential for a healthy pregnancy.

In the last decade, scientists have established that small RNA molecules can be found outside cells in blood, urine, tears, cerebrospinal fluid, breast milk, amniotic fluid, seminal fluid, and others. Moreover, scientists have discovered that small bits of circulating RNA can reflect particular conditions, such as the presence of a cancerous tumor or pregnancy-related disorders.

While some scientists remain skeptical that extracellular RNA and DNA are anything more than debris, a combined team of neurogeneticists from the University of Oxford and Massachusetts General Hospital regard them as a **newly discovered form of communication among cells** that plays a significant role in human health. For example, mutiple studies suggest that small RNAs act as instructions that help coordinate an immune response.

I am in total agreement with Marcus Pembrey, emeritus professor of pediatric genetics at University College London, who has been championing the idea of epigenetic inheritance for over a decade. Pembrey has said, "It is high time public health researchers took human transgenerational responses seriously. I suspect we will not understand the rise in neuropsychiatric disorders or obesity, diabetes, and metabolic disruptions generally without taking a multigenerational approach."

Personal Epigenetics

For a long time, we have known that the mind affects the body and conversely, that the body affects the mind. For example, people under stress are more likely to become ill and people who suffer from the flu or other health issues often feel blue or even depressed. On the other hand, pursuing activities that engage you fully, searching for meaning outside yourself, having friends, being married, and being intimate are all strongly associated with happiness, which in turn is associated with good health. In medical parlance this reciprocal process has been referred to as psychosomatic medicine or body-mind medicine.

Another way in which the mind can affect the body is through the widespread practice of meditation. According to a study undertaken in Wisconsin, meditating for eight hours on mindfulness, altruistic love, and compassion induces major epigenetic modifications. Compared to a control group whose members did not meditate but engaged in leisure activities in the same environment, the researchers found that the meditators were more resilient to infections and diseases in general than the control group. The meditators achieved positive, highly beneficial **epigenetic transformation by way of self-regulation.** We would all benefit, I think, if we adopted the results of this study to our own lives.

Let us look at another study on self-regulation. Researchers divided eighty-four hotel maids in New York into two groups. One group was told that the work they do on their job is good exercise and satisfies the Surgeon General's recommendations for an active lifestyle. This information was the equivalent of a placebo. The other group (control) was not given this information. Although actual behavior did not change, four weeks after the start of the experiment, the informed group perceived themselves as getting significantly more exercise than before. Compared to the control group, they showed a decrease in weight, blood pressure, body fat, waist-to-hip ratio, and body mass index. The women in the experimental group did not work harder than the controls but **their belief system actually changed the way their bodies functioned**.

Examining these studies in aggregate, they clearly illustrate that our thoughts and feelings are much more powerful than we realize. A thought is a set of neurons firing that, through complex brain wiring, will activate multiple intersecting pathways, emotional and pain centers, memories, the autonomic nervous system, the genome, and other parts of the embodied mind. The genome responds equally to both: external; that is, environmental stimuli and internal stimuli (thoughts, feelings, moods) with epigenetic modifications.

The Good News

According to a new study from the University of Helsinki, classical music fans, when listening to Mozart's Violin Concerto No. 3 in G major, were found to upregulate the activity of their genes involved in dopamine secretion and transport, synaptic neurotransmission, learning and memory, and downregulate the genes mediating the destruction of neurons, which is all for the good. What this means is that if you find something pleasurable, it can change your gene expression. Not Mozart, per se.

How we live our lives can have significant effects on how we age and develop diseases, including cancer. On the physical side of the equation, if we look at colon cancer, researchers from the University of Basel found that aspirin and hormonal replacement therapy reduced the methylation rate of colon cancer–related genes, whereas smoking and high body mass index (BMI) increased it.

Steve Cole, professor of medicine, psychiatry, and biobehavioral sciences at the UCLA School of Medicine, has written much on the subject of self-regulation. He holds, and I totally agree with him, that we are architects of our own lives more than we realize. Our subjective experience carries more power than our objective situation. If we feel good about ourselves, not only will our health improve but so will our relationships. Others will like

and respect us, which in turn will make us feel even better about ourselves. Thus, we create a self-reinforcing reward system grounded in epigenetics.

Being optimistic also helps. A thorough review of the medical literature to determine the strength of the association between optimism and physical health revealed that optimism was a significant predictor of health outcomes in cardiovascular disease, including immune function, cancer, complications related to pregnancy, and physical symptoms such as pain. People who feel enthusiastic, hopeful, and cheerful—what psychologists call "positive affect"—are less likely to experience memory decline as they age. It does not necessarily mean they will never get ill (mentally or physically), but optimists diagnosed with bipolar illness are able to manage the disease better than pessimists. The same applies to people suffering from depression. All these and many more studies add to a growing body of research on the contribution an optimistic outlook makes to health.

Of course, I am not suggesting a "fake it till you make it" attitude. Cultivating creativity, imagination, self-reflection, and living a meaningful and engaged life takes work but is an investment in our overall well-being—and potentially the well-being of our children.

Summary

In the 1850s, when Darwin first advanced his theory of natural selection and survival of the fittest, the underlying molecular mechanisms of genetics were unknown. However, over the past fifty years, advances in genetics and molecular biology have led to a neo-Darwinian theory of evolution based on epigenetics. Our survey of recent discoveries in epigenetics has made it abundantly clear how nature (genes) and nurture (the environment) work in concert. It is not one or the other that is responsible for a disease or personality trait. The only thing we know for sure is that we are the product of a dynamic interaction between these forces and that nothing about us is written in stone. Therefore, as long as we breathe we are a work in progress, constantly changing. Epigenetic modifications are dynamic and potentially reversible processes that take place over our entire lifetime.

In view of the above cited research—which does not claim to be exhaustive but rather representative of the field—there is robust biological evidence of transgenerational transmission of trauma to offspring by both, fathers and mothers. Probable familial factors are miRNAs and lncRNAs (long noncoding RNAs), as well as epigenetic changes in maternal and paternal germ cells. In the case of fathers, extracellular vesicles play an important role. In mothers there is the insulin-like protein and programming of the HPA axis of her baby during pregnancy.[4]

An epigenetic hypothesis for environmental contributions to physical and emotional health continues to gain traction. Even more significantly, clear and convincing evidence from basic and clinical research at leading universities indicates that an organism adapts to changes in its environment through alterations in their gene expression. Consequently, before their offspring is even conceived, parental life experiences and environmental exposures modify their germ cells and in turn affect the development and health not only of their children, but that of their grandchildren and great-grandchildren. Similarly,

children's fears, and their children's fears, anxieties, and personality attributes, may be affected by their parents' mindsets.

In addition, compelling scientific data show that our social lives, interactions of others and ourselves, can change our gene expression with a rapidity, breadth, and depth previously unknown. Genes don't make us who we are. Gene expression does. And gene expression varies depending on the life we live. In other words, the food we eat, the water we drink, the air we breathe, our interpersonal relationships, and our relationship to ourselves—they all affect us on a deep biological level, which in turn affects our minds.

Do genes matter? Absolutely. But so does the physical, psychological, and social environment, not only from birth on but extending back to the nine months of womb life, conception and, in many ways, several generations further back. The advance of epigenetics has shattered the old Darwinian paradigm of genetics.

KEY TAKEAWAYS

- **An individual's adult physical and mental health is heavily influenced by their early prenatal environment.**
- **The unborn child will adjust as best they can to the external environment they are going to encounter upon birth by way of prenatal epigenetic changes.**
- **Generally speaking, the life experiences of parents may impact the development and health of their descendants.**
- **In particular, parental nicotine, cannabis, and alcohol use has been shown to be associated with adverse neurodevelopmental outcomes in offspring.**
- **Traumatic experiences of parents lead to extra-sensitivity to traumatic events in offspring, and this may persist for several generations.**
- **Gene activity increases or decreases in response to changes in our environment.**
- **Our interactions with others and ourselves rapidly lead to changes in brain gene expression and behavior.**
- **Genes don't make us who we are. Gene expression does. And gene expression varies, depending on the life we live.**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