CHAPTER 1

The Nature of Cancer

THE EARLIEST KNOWN MEDICAL RECORDS of cancer can be found in ancient Egyptian papyri (thought to date from 2500 BC sources) that were deciphered in the nineteenth century. The texts reference a procedure for cauterization of breast tumors along with pharmacological and magical treatments—and recognize the difference between benign and malignant growths. From fourth-century China, Taoist and doctor Hong Ge’s Urgent Therapeutic Prescription for Axilla Diseases describes breast tumors as carbuncle stones with roots that infiltrate surrounding tissue. Ancient Greek physicians including Hippocrates, Galen, and Paul of Aegina, a seventh-century scholar who wrote about breast cancer in his Medical Compendium in Seven Books, likened the spreading tentacles of a tumor from its central form, and its grip on surrounding flesh, to that of a crab, or karkinoma—the Latin term is cancer, which entered into other European languages. The work and translations of the tenth-century Islamic physician and philosopher Abu Bakr Muhammad ibn Zakariya al-Razi (Rhazes in Latin) introduced Greek, Syrian, Arab, and
Indian medical knowledge to a broader audience, including substantive narratives on the diagnosis and treatment of cancer. Among other contributions, he was one of the earliest scholars and practitioners to introduce the concept of chemotherapy by combining alchemical, chemical, medical, and pharmacological knowledge.³

In spite of its early history of study, cancer seemed to fade into the shadows of medical discussions for long periods of recorded history. Other deadly, typically infectious diseases—tuberculosis, smallpox, typhus, cholera, influenza, typhoid, malaria, measles, yellow fever, and the plague—became the more immediate concerns given their enormous death tolls.⁴ Simply put, not enough people in previous eras lived long enough to develop cancers, let alone suffer and die from them, for the disease to be a primary research focus. In addition, before autopsies were commonly conducted and other modern detection approaches were invented, communities often didn’t know what people died of if it wasn’t outwardly apparent.

Centuries later, lifespans expanded, and inventions such as the microscope, and disciplines including more informed observation, were added to the study of cancer. For example, in 1775, the English surgeon Percivall Pott introduced the first understanding of carcinogenic environmental agents when he discovered a high incidence of scrotum cancer among a population of chimney sweeps.⁵ In 1902, German zoologist
Theodor Boveri recognized the genetic basis of some cancers. The 1926 breast cancer studies of English physician Janet Lane-Claypon laid the groundwork for the field of cancer epidemiology. The list goes on; multitudes of researchers and practitioners have continued to investigate and report their findings in an effort to understand and defeat cancer’s myriad manifestations, with advances in technology aiding their work and its dissemination.

Siddhartha Mukherjee, author of *The Emperor of All Maladies*, writes that doctors in the nineteenth century linked cancer to the rise in civilization, believing that it “was caused by the rush and whirl of modern life, which somehow incited pathological growth in the body. The link was correct, but the causality was not: civilization did not cause cancer, but by extending human life spans—civilization unveiled it.” During the last century, the average life expectancy increased from 47 years to 76 for men and 81 for women. More than half of the adults age 85 in 2011 were expected to live another six years, according to the Federal Interagency Forum on Aging-Related Statistics. In addition, the population of Americans ages 85 years and older was projected to grow from 5.5 million to 19 million by the year 2050. By that same year, more than a quarter of our population will be over the age of 50—part of the common worldwide trend. Melanoma, for instance, is a cancer that is particularly susceptible to the ravages of aging.

Of course, with the advent of modern medical techniques
and procedures, it also became easier to detect cancer. Soon efforts were underway not only to learn more about this disease, but to try to control, even cure it. Yet cancer has proved to be an elusive adversary, a shapeshifter that continues to confound medical experts.

**MANY DISEASES IN ONE**

What makes cancer so difficult to control is that it comprises scores of diseases, not just one. The fundamental, unifying characteristic of cancer is the abnormal growth of cells. This process can begin almost anywhere in the body, and as the cancer cells start to multiply, they crowd out the normal cells, making it too difficult for the body to function properly.

Beyond growing more quickly than normal cells, cancer can also spread to other parts of the body. This is called metastasis, and the process makes it much more difficult to halt cancer. My laboratory at Johns Hopkins is working to understand what drives the aggressive nature of tumors, and what makes them spread around the body and learn to resist therapy. There are more than one hundred types of cancer, including skin cancer, lung cancer, prostate cancer, and leukemia. Among these are forms that kill millions of people while some subtypes are so rare that only a dozen cases are documented worldwide.

Chemotherapy, surgery, radiation, and immunotherapy
have had varying levels of success in slowing, and sometimes stopping, this growth of abnormal cells. But due to the wide range of cancers, a treatment effective against one form doesn’t necessarily work that well on another. We’ve come to understand that there is no magic bullet. No treatment or vaccine has yet been found that can stop all cancers, and I don’t believe that we’ll find a single cure. I think that our next steps should be determining how to modify this disease, so that’s where my focus is right now.

In recent years, our lab has investigated how important a patient’s age can be when it comes to types of cancer to which they may be susceptible, and how dangerous that cancer will be for them. Treatments or medicines that work well with a younger patient, for example, might have little or no effect for a patient 55 or older. Such insights have led us to become more precise and specific with our approach and methodology.

With cancer, processes rarely happen in isolation. When a person receives an unfortunate diagnosis, it may seem like a bolt out of the blue: stunning and arbitrary. Yet the more secrets we unravel about cancer, regarding how it forms and moves and interacts with other parts of the body, the more we realize that cancer has intricate methods and complex languages of its own.

Of the 1.8 million annual new cancer cases in this country, more than 200,000 will be melanoma diagnoses, one of the few cancers whose incidence is rising significantly—by more
than 44 percent in the last decade. Unlike the very common basal cell and squamous cell carcinomas, melanoma is a highly aggressive form of skin cancer, with a survival rate of only 27 percent for late-stage cancers.

The skin is the largest organ in the body. According to National Geographic magazine, which published a landmark issue about skin in 2017, adults carry an average of 8 pounds (3.6 kilograms) and 22 square feet (2 square meters). This packaging of ours is waterproof and provides insulation and protection from wide ranges in temperature and the damaging rays of the sun. Formally called the cutaneous system, skin is its thinnest on the eyelids and thickest on the heels of our hands and feet.

Some skin types are more likely to suffer from melanoma, including those that are more prone to burning than tanning after exposure to the sun. People who spend a lot of time outdoors, such as athletes and outside laborers, are more likely to develop skin cancer. One’s vulnerability can also depend upon how rigorously such measures as the use of sunscreen and wearing rimmed hats were applied in childhood and adulthood.

The outer layer of our skin is called the epidermis. Home to the protein keratin, which is also found in nails and hair, the epidermis layer also contains Langerhans cells, which alert the body’s immune system to infections and viruses. The epidermis connects with the dermis, our deeper skin layer. Fibers of
collagen and elastin give skin its elasticity and strength. These break down as we age, resulting in wrinkles and making us more vulnerable to cancer. That’s because one of the dermis’s key tasks is to nourish the outer layer, the epidermis, with its network of blood and lymph vessels.

Melanocytes—cells with long protrusions that look rather like weird sea creatures—are found in the epidermis’s lower region, near the boundary with the dermis. These cells produce melanin, the darker pigments that are a primary factor in skin coloring. When they’re working well, in concert with other body components, the melanocytes direct pigment to cells in the upper layers of skin, providing a natural sunblock. People native to regions closer to the equator have adapted over time by producing more melanin particles. In comparison, those who originate from lands farther to the north or south are prone to be fairer in skin color—seemingly an effective adaptation until people shift more radically and quickly in location. For example, sunny Australia, where much of the population is of northern European descent, has among the world’s highest rates of skin cancer.

The epidermis and dermis layers sit atop the extracellular matrix. It all fits together like a cake, as my graduate student Gloria Marino loves to describe it, perhaps because she is a superlative baker herself. You have the frosting (epidermis), the cake (dermis), and the cake stand (the extracellular matrix, or ECM).
In recent years, we’ve also learned that genetic or microenvironmental changes can trigger cancer movement, signaling it to move elsewhere in the body and start invading. At first, the melanocytes may begin to grow out of control in a particular spot. Left untreated, a single melanoma growth can work its way down from the epidermis layer and into the dermis layer, where it can grow larger. Once it does so, reaching this lower level in the skin, the cells have access to blood and lymph vessels—gateways to the rest of the body. Think of it as a car that was once restricted to traffic-clogged, two-lane streets. This melanoma car has hit the on-ramp to a high-speed freeway. It can now travel throughout the body and become a life-threatening illness.

The microenvironment is defined as the immediate, small-scale world of a cell or group of cells. Instead of looking at everything from on high, a satellite view so to speak, we’ve zoomed way in, looking at this particular world—the surfaces and tissue surrounding the cell. We can think of the microenvironment as the neighborhood where the tumor lives. And the other components, or “people,” will make up this neighborhood.

In the microenvironment, it benefits the tumor to know the guy who lives in the house next door and who’s down the street. As in any neighborhood, there are a lot of different types of houses and a lot of different types of residents. In this case, they are the other cells. In this context, the world of
the microenvironment, the way the streets run, which direction they go, which ones are one-way, is critically important. Also, how the houses are constructed. How stable are they? How permeable? How big? All of this makes up the biophysical matrix of the cancer.

Just as important, we need to know how the “people” in this neighborhood, in this microenvironment, interact with the tumor—how they communicate with it. The initial conversations may be the equivalent of, “What’s the best way to get to the grocery story?” In the case of cancer cells, that translates to finding the best places or host areas where they can grow.

At a higher level, these relationships can be about who’s going to be a friend. Who’s going to be their ally and help them grow and even move? Those are the kind of neighbors in the microenvironment the cancer will seek out. Ultimately, it has a profound influence on the cancer cells and what level of destruction they can achieve.

Once the cancer goes deeper, through that first layer in the epidermis and into the dermis, it reaches the fibroblasts, which act like the skin’s construction workers, providing the collagen and elastin. They’re the most common cells of connective tissue in animals. At this level, the signals going to that tumor cell can be many and of great consequence.

We know that like many other cancers, melanoma is a disease of aging. The incidence of melanoma increases dra-
matically after the age of 60, and the prognosis is worse for the elderly, who present with more metastatic disease and respond more poorly to most therapies. Part of why we see less metastasis in younger people is because of these conversations—you may have more signals to the cell telling it to stay where it is in younger people. In older people, you can have more signals telling the cell, “Hey, get out of there. Go find a better site and really colonize.”

In the lab, we can use fibroblasts of different ages and by doing so change the overall age of the artificial skin we grow for our research, offering us great insights about the impact of tumor cell behavior, as well as the role of aging. (For more about how this skin is made, see pages 70-74.) Our studies show that the melanoma cells are more likely to invade other parts of the body in the elderly than in the young. That’s because in younger skin, the epidermis and dermis layers are more defined. The skin in younger people is firmer, less wrinkled, which you would expect. Yet when you look closer, through the microscope, you see that the melanoma also stays in tight nests, right near the surface of the skin, in the younger skin. The makeup of the collagen is that much thicker in such cases.

In comparison, when we study the skin of those ages 55 to 65 everything can be much different. Here, the melanoma cells are able to move more easily. The skin isn’t holding them in place as much. The skin has been worn down over time; that means the cancer could move to the subcutaneous tissue—the
blood, the lymphatics. This makes it easier for the cancer to travel throughout the body.

When tumor cells are in a firm setting or matrix, they cannot move around that well. But put those tumor cells in the skin matrix of an older person and then they can start to swim. The cancer cells love those possibilities. It can be so liberating for them. What was once holding them in place has lost its firm grip upon them. The door has swung open, and they can now break off and travel to locales elsewhere in the body.

THE RISK FACTORS

The risk of melanoma is slightly higher if one of your first-degree relations (parents, brother, sister) has or had melanoma. About 10 percent of those with melanoma have a family history of the disease. Those who are fair-skinned and even freckled run a higher risk of the disease. Our biological parents provide the genetic blueprints for our bodies. Genes are long sequences of DNA that help make the necessary proteins for bodily functions. For example, such proteins determine our eye color, height, hair color, and muscle mass, among many other characteristics; they can be switched “on” or “off,” determining whether specific characteristics are expressed or not.

To understand gene modification, we need to delve briefly into the structure of chromosomes. Strands of DNA are wound around proteins called histones, which can look like beads on
a string, with the histones serving as the beads and the DNA as the string wrapped around them. When DNA is loosely packed, or the string is not tightly wound around the histone “beads,” a DNA sequence can be read and used to produce proteins. In essence, the gene is switched on. But when the DNA is tightly packed, the physical trait associated with this gene will not be expressed, and the gene is switched off.

External stimuli, such as long-term exposure to the sun or other factors in our environment, can determine whether genes, including those connected to cancer, are activated or remain dormant. Genes are basically the codes of the body. They are what says to the cell, “you need to do X, Y, or Z.” Whether it’s time to grow; whether it’s time to move. And to do that we need to make these proteins that are going to help us do these different things.

Once those genes are activated and the proteins made, pathways are downstream. Think of it as the genes being the instruction manual, while the pathways are the gears and the mechanics of how the cell is working. Normal cell growth or uncontrolled cell division depends upon what has been switched on or off.

While men and women suffer from melanoma at almost the same rate in the United States (that 60:40 ratio), women often survive longer. We aren’t sure why, but hormones may be a key consideration. We’re now trying to understand how cells in men and women age differently and how that contrib-
utes to tumor progression. It could also be that women take better care of themselves, in terms of prevention and visits to the dermatologist if something is seen as out of the ordinary.

The cell of origin in melanoma is the melanocyte. It’s dotted with dark black pigment, known as melanin, which it can pass to other cells, specifically keratinocytes, to protect them from the sun. Weirdly, when these cells start to become cancerous, they start to look more like the normal epithelial cells you find in the precursors for other cancers. Once melanocytes become melanoma, they may take several different forms and appearances. Most common is cutaneous melanoma, on the skin. Acral lentiginous melanoma is found on the hands and soles of the feet. Reggae singer Bob Marley, for example, developed this form of melanoma in his big toe, which spread to his brain. Mucosal melanoma is found in the body’s mucous membranes, while ocular melanoma usually begins as a small freckle in the eye.

The most common forms of melanoma are found on the leg, back, or face. They often develop from an existing mole, which can be triggered by excessive exposure to the sun. Early on, the melanoma doesn’t form lumps or tumors. It isn’t malignant, meaning it cannot yet spread to the internal organs and elsewhere. Yet, as we’ve seen, the melanoma lesion can spread down into the dermis layer; that’s where it can begin to grow and metastasize throughout the body, lungs, brain, spleen, liver, heart, and, rarely, to the bone. The growth of the
abnormal melanocytes can accelerate and spread, especially in older individuals.

Most moles are round, flat, and no larger than a pencil eraser. Few of these moles develop into melanoma. Still, about 20 percent of the white population can develop dysplastic nevi or atypical moles. (Fair-skinned individuals are often more prone to skin cancer because of the lack of melanin, which is a superb natural sunscreen.) Atypical moles differ markedly from common moles; they may be larger and can also be several shades of brown and even pink in color. They’re also known for their irregular borders and inconsistent shape. These moles are the ones to keep an eye on, as changes in their appearance, in shape or color, make them candidates for removal and further examination by biopsy.

Babies are not usually born with moles, unless they have what are known as congenital nevi, a syndrome where large melanocytic lesions are present, sometimes covering the whole trunk. More “regular” moles will begin to appear in young children and teenagers. While most moles will never cause health problems, according to the American Cancer Society, someone with a great many moles is more likely to develop melanoma later in life.

So, if a dermatologist finds a spot or mole and suspects it could be cancerous—what comes next? The doctor may opt for a skin biopsy, which is done with a local anesthetic. Of course, this can be done for various forms of cancer. A bit of
numbing medicine is injected into the area, and the doctor will either shave away the top layers of skin or use a cookie cutter–like tool to go slightly deeper into the skin. If the latter procedure is used, a few stitches may be necessary. In either case, only a small scar is the result.

If the tumor has grown deeper into the skin, the doctor will do an incisional biopsy, which removes a portion of the tumor, or perform an excisional biopsy, which removes the entire tumor, as well as a small outline of skin surrounding it.

When the melanoma is suspected to have spread further, nearby lymph nodes may be biopsied as well, to see whether any cancer has spread to them. Melanoma can spread quickly, perhaps reaching the lymph nodes, lungs, or brain while still being very small on the skin and at its original site. That’s when CT scans and other imaging tests can better locate these more serious cancers.

A cancer’s stage or staging helps doctors determine how serious the cancer is and decide how best to treat it. This is done by first determining the thickness of the tumor and how serious the ulceration, or breakdown of the skin, is over and around the melanoma.

In Stage 0, the cancer is confined to the epidermis, the outermost layer of skin. In this case, it has not spread to any nearby lymph nodes or more distant parts of the body and can simply be removed without further treatments.

In Stage I, the tumor is no bigger than two millimeters, or
2/25ths of an inch. While it could be ulcerated, it’s been determined that the cancer has not spread to the lymph nodes or elsewhere in the body.

In Stage II, the tumor is more than one millimeter in thickness, but it has not yet spread to distant parts of the body.

By Stage III, however, a number of classifications are added to each level. In this staging, the tumor is anywhere from one millimeter to four millimeters in thickness, but it may have spread to two or more nearby lymph nodes. In addition, it may have spread to small areas of nearby skin.

Stage IV is the highest and most dangerous level in melanoma and all cancers. Here, the major concern isn’t necessarily the thickness of the tumor or whether it’s ulcerated or even whether it’s spread to nearby lymph nodes. The major characteristics of this high level is that the tumor has spread to distant lymph nodes and even on to such organs as the lungs, brain, and liver. The American Cancer Society reports that the five-year survival rate for many cancers has improved in recent years. Still, the survival rate for Stage IV melanoma is 25 percent.

**SURVIVAL IS AT STAKE**

As a tumor gets larger, it often outgrows its nutrient supply. When that happens, the tumor will send signals to blood vessels that are swimming by and say, “Hey, divert a branch over here,”
and then they’ll grow new blood vessels into the tumor. That’s a process we call angiogenesis.

Tumors can range from a few to thousands of cells. They can be cancerous (malignant) or noncancerous (benign). What’s interesting is that the tumor, regardless of size, is clever enough to send them similar signals, ones that they would have during regular development. The endothelial cells, which cover the inner surface of the blood vessel, don’t know any better and do what they’re told, even if they’re receiving signals from a tumor cell.

Cancer cells can move quickly when their survival is at stake. As we’ve seen, this is not a random process—this is what allows tumor cells to metastasize to distant sites. It can be a very aggressive situation. It’s not as though they fall into the bloodstream and then settle somewhere else. Even when cancer cells move to a new location, their activity is much greater than what we knew about or realized a few years ago. When they do arrest in a new location, they move into the new tissue, including vital organs. And once they’re there, they’re intent on growing and surviving.

What we’ve learned in recent years is that not every organ is conducive to the outgrowth of every single type of cancer. There are different sites where cancer cells tend to go. For example, prostate cancer cells prefer to go to the bone; melanoma prefers to travel to the lung. Some of this movement is purely for physical reasons. A lot of cancer goes to the lungs or
the liver because a lot of blood flows to those organs, carrying the tumor cells with it.

In other cases, it can depend upon what growth factors are being secreted. It’s all about what the most conducive environments are for the tumor cells to grow. This has been coined the “seed and soil” hypothesis of cancer, where tumor cells (seeds) grow only in microenvironments conducive to them (soil). (Interestingly, this theory was proposed more than 130 years ago by Stephen Paget.) To do this, they need to establish communication with the surrounding cells (“signaling”) in their new environment, and it’s those conversations that are so fascinating.

**IMPORTANT CONVERSATIONS**

How do cells talk to each other? This is a fascinating area of study that researchers are just beginning to understand. When people ask me, “Why haven’t you cured cancer yet?” I reply, “Well, come spend a few days in the lab with me.” That’s where we’re studying the ongoing conversations between cells. What we’re overhearing and exploring can lead in many different directions. Through these “discussions,” we’re finding out more and more about cancer. In some ways, the work reminds me of the Sherlock Holmes and Famous Five mysteries I read as a kid. We’re lab detectives.

Within the body, there are a great many conversations
going on daily, all at the same time. Cells in our fingertips signal to neurons in the brain that we just touched something hot or sharp, for example; cells exposed to the sun ask neighboring cells to protect them by making melanin. A tumor exists in a very complex neighborhood made up of a milieu of different cells, from immune cells, to fibroblasts (“the construction workers”), to blood cells. Fibroblasts may communicate directly through contact with each other, or indirectly, by releasing factors such as growth factors or fats, for example, or through little “bubbles” known as exosomes (more on that in a minute). Immune cells contribute to the conversation, not only by talking to the tumor cell, but by their complex interactions with each other as well. Often these immune cells are at odds with each other, the “bad” immune cells regulating and suppressing the “good” ones in a bid to allow the tumor to grow and colonize distant sites. One such example of the bad guys is the myeloid-derived suppressor cell. These cells can act not only to suppress immune activity in the tumor microenvironment, but also to forge new paths by going to distant sites where cells metastasize, to get the lay of the land, so to speak. The conversation may be something like, “All right, we’re going to a lung to suppress the immune microenvironment there.” That way the tumor cells can come in and not only survive but thrive. Other regulatory populations like T regulatory cells also have similar suppressive effects.

Fibroblasts are another critical part of the discussion.
These cells lay down the framework on which tumors grow, the cake stand if you will. They also act as teachers, instructing the behavior of the cancer cells, whether directly through secreted factors, or indirectly through microvesicles such as...
Exosomes. Exosomes are like tiny bubbles full of lipids, proteins, and nucleic acids. They are released by all cell types and carry the hallmark of their cells of origin in their cargo, which can then travel throughout the body and be taken up by other cells. When fibroblasts and other cells release exosomes, that can dictate the behavior of the cancer cells that take them up. Whether the message is delivered directly, or packaged in an exosome, cells have ways of talking to each other, and these conversations dictate tumor cell behavior.

For example, we’ve recently shown in our research that older fibroblasts give fats to tumor cells, and the tumor cells receive that fat by expressing a transporter known as FATP2 on the surface of their cells. Once they absorb that fat, they can use it to migrate and to resist therapy. Since our goal is to interrupt the conversations that drive tumors to be more aggressive, we interrupted this particular conversation by inhibiting the activity of FATP2 on tumor cells. When we did this, the cells, previously resistant to therapy, now became uniquely sensitive. Understanding how to harness, interrupt, or facilitate the conversations between the tumor and its environment, which changes as we age, is critical for effective cancer therapy. It takes us one step closer to learning how to make cancer deaths less inevitable after a diagnosis, or at least, we hope, to extending remission times.