11 Mistakes Happen: The Mutations of Cancer

The Gross sisters, Pauline and Tilly, were well known in Ann Arbor, Michigan, for their skill as seamstresses. The sisters served an upscale clientele in Gay Nineties Ann Arbor, including Dr. Aldred Scott Warthin. A renaissance man—accomplished musician, certified music teacher, scholar and scientist, author of three books—Warthin was a pathologist on the faculty at the University of Michigan, a position he held for thirty-six years.

Warthin admired Pauline Gross's work and employed her to supplement his wardrobe. He also recognized her intelligence and enjoyed his conversations with her. It was during one of those conversations, in 1895, that Warthin learned of Pauline Gross's awful premonition: she would die young. "I'm healthy now, but I fully expect to die an early death from cancer. Most of my relatives are sick, and many in my family have already passed on." Her great-grandfather, who had emigrated to Michigan from Plattenhardt, Germany, in 1831, died of intestinal cancer at the age of sixty. Six of his ten children died of cancer, as did thirty-three of his seventy grandchildren. And Pauline, just as she had feared, succumbed to the disease before her thirtieth birthday.

Why was cancer so prevalent in this family? His interest piqued, Warthin investigated the family medical history. He confirmed Pauline's contention that cancer was passed down through the generations, and concluded that "in certain families [there is] an inherited susceptibility to cancer." For thirty years he studied the disease that had struck down Pauline and so many of her relatives. His work earned Dr. Warthin the title "father of cancer genetics"—he was the first person to document the genetic basis of cancer.

Warthin understood that Pauline's family harbored a genetic defect—a mutation, though he did not know what that is and did not use that

word—that caused those who inherited it to develop cancer. That he reached this conclusion is all the more remarkable because he did so before anyone knew anything about genes and Mendel's rules of inheritance: when Warthin began his studies, Mendel's work was yet to be uncovered, and the discovery that genes are made of DNA lay fifty years in the future.

Mutations are bad: they can lead to cancer. But they also provide the spice of life. Stroll down a major thoroughfare of any metropolis in America and you'll see a remarkable diversity of people. People with skin of the darkest ebony, the lightest ivory, and every shade in between. People with eyes of blue, of brown, and of all colors in between. People with full lips, thin lips, and all thicknesses in between.

There are approximately six and a half billion people on this planet, and if we examined them all in one big police lineup we could tell every one of them apart (except for the identical twins, and even there a sharp eye could distinguish many of them). And the child that is being born at the very moment you are reading this will grow up to look like no other person on earth. That is why the gold standard at the airport security gate is still the photo ID. Each person's appearance is truly unique.

Despite this individuality, if we determined the personal DNA codes of several of the people in that global police lineup (not quite feasible yet, but it will be soon), we would find that they are remarkably similar: The DNA codes of any two people are about 99.9 percent identical (ignoring for the moment the little Y chromosome present only in males). For every 1000 base-pairs of DNA, only a single one (on average) will be different between two individuals. That's true for *any* two individuals on Earth, regardless of what continent they hail from and what racial or ethnic group they belong to. (There will, in addition, be many small and large insertions and deletions of base-pairs.)

How can such little difference in our personal DNA codes lead to such an enormous diversity of physical characteristics? This is one of the major unanswered questions in biology, and the fact that some of those DNA sequence differences influence your susceptibility to disorders such as cancer, diabetes, and heart disease only raises the stakes.

Perhaps our high degree of DNA sequence identity should be unsurprising. After all, each of us has the same body plan, with internal organs forming in the same place, arteries and veins and nerves traversing the

same territory, and sets of bones, muscles, cartilage, and tendons arranged the same way to provide structural support. We all have roughly equivalent dimensions: none of us grows to be the size of an elephant or stops growing after reaching the size of a mouse. At a behavioral level, we all learn a language, recognize our family members, and experience a range of emotions that are undeniably human.

On the other hand, maybe our DNA sequences are not so similar. With a genome of three billion base-pairs in each set of chromosomes, that 0.1 percent difference means that every human has about six million differences in his or her personal DNA code from anyone else in the global police lineup. Six million is more than the number of DNA base-pairs in the blueprints for entire (albeit one-celled) organisms, so maybe we should be wondering why we aren't even more different from one another than we are. Why don't some of these changes in our DNA sequence cause some of us to have nine kidneys, or to develop in only nine weeks of gestation, or to grow to be nine feet tall?

The reason we all look roughly similar is that our twenty thousand or so genes must coordinate precisely with each other to enable a fertilized egg to become first an embryo, then a fetus, and finally a baby (as discussed in chapter 4). Any changes in the DNA sequence that resulted in a set of instructions that lead to anomalous formation of organs—too few, too many, too different—would be fatally incompatible with the requirements of the developing embryo. In fact, developmental problems like these happen surprisingly frequently: up to 50 percent of all conceptions produce a defective embryo that is spontaneously aborted early in a pregnancy (often without the mother's knowledge), and at least half of those cases are likely due to changes (mutations) that occurred in the DNA of the fetus.

The constraints on the human form make it even more remarkable that we can distinguish *everyone* in the global lineup. The range of subtle variation that exists is astonishing: ears that stick out a bit more than average, eyes painted from an enormous palette of colors, lips that turn up, turn down or turn crooked. Where does all that variation come from? It comes from mutations, which are mistakes made in copying DNA. Every sperm and egg contains one copy of a person's complete set of genes. Although it's a quite good copy, it's not perfect: perhaps 200 new mistakes—differences in the DNA base-pairs from the parent's template DNA—arise in each

set of chromosomes when they are copied and passed on to the next generation. That's remarkable accuracy for a biological machine composed of at least twenty parts that has to copy six billion base-pairs of DNA, but these mistakes accumulate as they get passed down through the generations.

A few million mutations, give or take some, accumulated in the generations from early humans leading up to us. Most have no effect on our appearance or health or anything else, but some of them, perhaps fewer than one hundred thousand in each person, are responsible, in their almost limitless combinations, for the astounding diversity of the global police lineup. Some are in genes that encode enzymes that work to synthesize the pigment of our skin. A mutation that enhances the function of one of those enzymes might cause more pigment to be synthesized, resulting in skin of deeper ebony; a mutation that cripples the function of one of the enzymes might cause less pigment to be synthesized, resulting in skin of lighter ivory.

Some DNA sequence variations are in genes that encode proteins that determine the pigmentation of the eye. Some cause one of those proteins to be more active and make more blue pigment; others diminish the function of the protein and lead to darker-colored eyes. Some of the one hundred thousand or so DNA sequence changes are in genes that encode proteins involved in the development of facial features during gestation of the fetus. They might result in full lips by causing more of a critical growth factor to be produced, resulting in more cells being recruited for development of the lips. Or they might cause less of the growth factor to be made, resulting in thinner lips. If the copying of DNA were more accurate than it is, the global lineup would be much more monotonous.

Now let's line up all one hundred billion of our colon cells and examine them. Unlike individuals in the global police lineup, all these cells look the same. Well, of course they do: They're clones, all descended from one cell that, early during life in the womb, committed itself to give rise to the colon. And that one cell was derived from a single cell produced at conception by the union of one of Dad's sperm and one of Mom's eggs.

That first colon cell and its descendants divided thousands of times in the course of forming and continually replacing the cells of your colon—almost as many generations as modern humans underwent in their entire

history on earth. But in the copying of DNA that occurred for each of these divisions, mistakes were made. It was unavoidable. Not very many mistakes, and most were of no consequence, but every once in a while a mistake was made in an important gene.

If a mistake inactivated a gene that is required for the cell to stay alive, no harm was done: one colon cell will not be missed with billions of others just like it. But if a mistake inactivated a gene that regulates growth—one that applies the brakes to a mature colon cell, whose days of cell division should be over—the cell starts growing again, and can eventually become a mass of cells called a tumor.

If we line up the cells of that colon tumor and examine them we see something quite startling: freaks of nature! They might remind us of the poor denizens of the circus tent: the two-headed lady, the hairy man, the seven-foot giant, and the three-foot dwarf. Even if these are the first cells you have ever seen, you will likely have little trouble telling them from their normal siblings. They are ugly. But worse than just being ugly, these cells don't do their colonic jobs. They do just one thing, and they do it all too well: they divide and divide and divide some more. And when they split off from the colon and migrate to distant sites in the body, they continue to divide. Eventually they overwhelm the body. Sadly, they overwhelmed Jay Monahan, the husband of the CBS News anchor, Katie Couric. Monahan was forty-one years old when his cancer was discovered, and he succumbed to the disease nine months later, leaving behind a shocked and grieving wife and two young daughters.

A few months after his death, Katie Couric told an interviewer, "Frankly, I still can't believe it. When I think about it, it just permeates every cell in my body. You can forget about it temporarily. But then the grief comes like a huge wave and like a horrible invasion of your heart and soul."

Monahan's death was especially difficult for Couric because she never saw it coming. "He had no symptoms. Jay was tired, but we thought it was because he was flying back and forth to California for his job. And we had two small children bringing every bug in America into the house. We had no idea what was going on in his body. This cancer is so insidious."

Had Monahan had a colonoscopy exam a few years earlier, the cancer might have been detected when it was treatable, when it was not yet growing vigorously and hadn't spread past the colon. "My husband's mom, who is now in her sixties, has ovarian cancer—it was diagnosed

about three years ago," said Couric. "His grandmother died of breast cancer. There is a growing body of thought that these glandular cancers—breast, ovarian, uterine, prostate, and colon—may be related, that there is, perhaps, a genetic link. If we had known this, Jay might have been screened for colon cancer."

Two years after her husband's death, in March 2000, Couric underwent a colonoscopy live on national television to raise awareness of the disease and proclaim the benefits of the exam. "I want everyone to understand that women as well as men get colon cancer," she said. "Young people as well as old people get it. And frankly, very few people take advantage of the preventive tools that exist. Too many Americans don't get tested because they don't want to talk about that part of their body. . . . I think we have to use the words, say them. Colon. Rectum. Bowels. The more matter-of-fact you are with the language, the more it helps. You can't be squeamish about it. It might cost you your life."

In 2000, Couric testified before the Senate Select Committee on Aging: "I . . . have a dream that sometime in the near future everyone could have their colonoscopies . . . and that they do it before they become symptomatic—because when symptoms start to present themselves, oftentimes the disease has already progressed." In 2004, Couric established the Jay Monahan Center for Gastrointestinal Health at the New York–Presbyterian/Weill Cornell Medical Center, which offers screening and treatment for the disease. Katie Couric is doing all she can to prevent others from suffering the kind of grief she experienced when she lost her husband to colon cancer. And it's having an effect: after her public colonoscopy there was a 20 percent increase in colonoscopies nationwide.

What drove Jay Monahan's and Pauline Gross's cancers were mutations—mistakes in copying the DNA. Some mutations make the cells divide when they should not, causing them to grow out of control; some let rogue cells escape detection by the immune system when it tries to hunt them down and eliminate them; and some enable cells to find clever new ways to commandeer nutrients and oxygen when the body tries to protect itself by starving them or choking off their air supply. These cells accumulate mutations relentlessly, becoming increasingly aggressive, taking over more and more of the body. They are like zombies that keep coming back no matter how often they are whacked over the head with a shovel.

In the late stages of cancer there can be up to 150,000 mutations in the cells of the tumor—150,000 DNA sequence differences from the innocent colon cell that gave rise to the tumor. So although a few copying mistakes in the chromosomes of the sperm and egg are generally viewed as good (variety is the spice of life), they are decidedly not so good when they drive inappropriate division of other cells of your body.

Many kinds of copying mistakes get made in the DNA copying process. The simplest type is a substitution of one base for another. Most of the time the copying machinery puts the correct base in the copy—an A opposite a T and a G opposite a C in the template—but every once in a while it messes up and inserts the wrong base: say, a G instead of an A opposite a T, or an A instead of a G opposite a C.

Recall that triplets of the bases specify amino acids according to the genetic code. Here are five triplets in the middle of a gene, with the amino acid each triplet specifies shown below:

... CTG CAG **TTG** GAG AGC ...
leucine glutamine leucine glutamate serine

A mutation in a person that changes the first base of the TTG, leucine, triplet to a G would change the base sequence to become:

... CTG CAG GTG GAG AGC ...

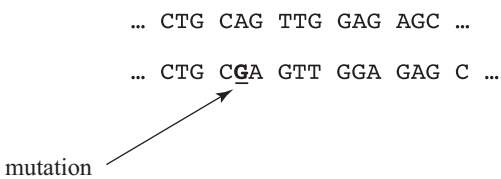
Because GTG specifies the amino acid valine, this gene would now specify a protein with these amino acids:

... CTG CAG **GTG** GAG AGC ...
leucine glutamine valine glutamate serine

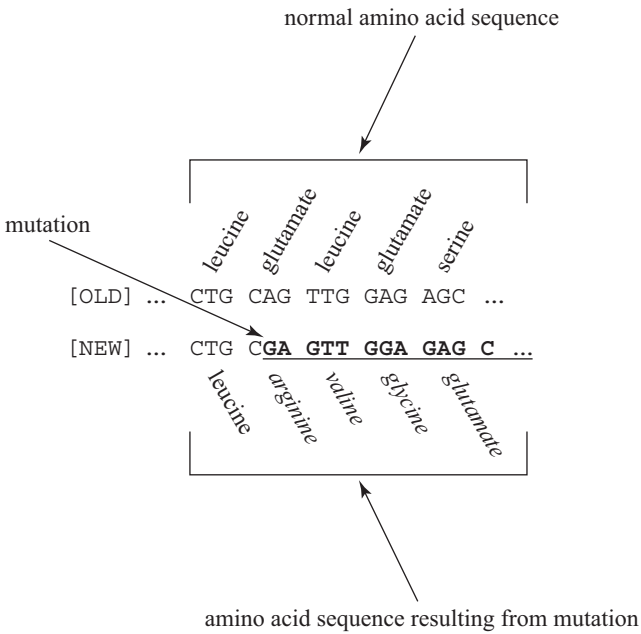
In most proteins, which contain hundreds of amino acids, the change of this one amino acid may have little or no effect. Or it may disrupt the structure of the protein enough to cause a complete loss of function of the protein. Mostly, though, single amino acid changes have little effect on the chemical properties of the protein. And some single base substitutions in DNA don't change the amino acid sequence of the protein at all, because

the genetic code has multiple different base triplets that specify the same amino acid.

Insertions and deletions of base-pairs, by contrast, almost always have a large effect on the encoded protein. These mutations typically cause all of the amino acids in the protein to change from the point of the insertion or deletion onward to the end of the protein, because they shift the "register" of the triplets, so that all the bases form new groups of three. Consider the insertion of a G base after the fourth base of the DNA sequence:



This mutation creates a new triplet CGA, and changes as well all subsequent triplets. Compare the old sequence without the mutation with the new sequence, containing the mutation that adds a base, to see what happens to the protein:



Because insertions and deletions change many amino acids, not just one, they nearly always result in a defective protein that cannot do its job.

Insertion and deletion mutations can span many base-pairs. Indeed, millions of base-pairs can be inserted into or deleted from a chromosome. Whole genes, even stretches of DNA that encode many genes, can be deleted, or duplicated to result in extra copies of a gene, which leads to increased, sometime toxic, levels of its encoded protein.

All of these kinds of changes, and more, that occur during the production of sperm and eggs are responsible for the diversity of the global human lineup. But when they occur in other cells of our bodies, they can lead to the kinds of cancers that afflicted Jay Monahan and so many members of Pauline Gross's family.

It took almost a century after Pauline Gross confided her fear of cancer to Dr. Aldred Warthin for a defect in the gene responsible for the disease in her family to be identified. The gene, called *MSH2*, encodes a protein that is part of the quality-control machinery that fixes copying mistakes in DNA.

One of the reasons copying of the genome is so accurate, with only a few mistakes in every billion base-pairs copied, is that the cell has several ways to repair copying errors in DNA. One of them, called mismatch repair, finds and fixes misincorporated bases that occur when the copying machinery inserts the wrong base—for example, an A in the new copy opposite a C in the template instead of the G that should go there. Those two bases, the A and the C, are mismatched—they are improperly paired, like a two-prong 110-volt plug trying to fit into a three-prong 220-volt socket—and the mismatch repair machinery recognizes that and fixes it.

A misincorporated base happens perhaps once in every five million to ten million base-pairs copied. Nearly all—99.9 percent–of the mismatches get fixed by the highly efficient mismatch repair machinery. A few of them—about one in a thousand—slip by and become the mutations we have been talking about.

But if you are unfortunate enough to inherit in your personal DNA code a defect in one of the genes specifying a protein of the mismatch repair machinery itself—as Pauline Gross was—then all of your cells carry that defective gene. This mutation has no immediate effect, because there's another, good copy of the gene on the other chromosome (recall that there

are two copies of each gene, one on the chromosome from Mom, and one on the chromosome from Dad), and this good copy provides a functional version of the protein necessary for mismatch repair. But if one of the random mutations that occurs in our cells as they divide throughout our lifetime happens to affect the other, good, copy of the mismatch repair gene, then that cell loses its ability to fix mismatched bases.

The consequence will be a greatly increased rate of mutation in that cell—one thousand times the normal rate. As that cell divides it will accumulate mutations at a furious pace. Some of these are bound to eventually affect genes involved in controlling growth of the cell, so cancer is almost inevitable: About 90 percent of people who inherit a defective *MSH2* gene get cancer.

People who inherit this defective gene begin to develop cancer in their twenties, because that's how long it takes for the other, good copy of the gene to acquire a mutation in one of the cells, and then for the cells with that mutation to grow and accumulate the further mutations in other genes that lead inexorably to the tumor that sends the unfortunate person to a clinic. Most of them get cancer by the time they are in their forties; Pauline Gross died before she saw thirty. The cancer usually occurs in tissues with rapidly dividing cells, such as the colon and the endometrium, the lining of the uterus, because each cell division provides another chance to pick up more mutations. Pauline Gross died of endometrial cancer.

Now that the causative gene has been identified, Pauline's relatives can find out whether or not they're at high risk of developing cancer. Her great-grand-niece, Ami McKay, a thirty-eight-year-old Canadian author, learned that she had the defective gene. "Peering into my DNA did indeed change me," she said. "As you might imagine, it caused me to take an immediate inventory of my health . . . I became vigilant about making doctor's appointments and setting up annual screenings. But the results also infused my life with a curious sort of fearlessness. . . . Whenever I think of hesitation, of saving my imagination for another day, I think of Pauline."

Her sister Lori learned she did not have the defective gene. Forty members of the family were tested for the defective gene after giving blood at a family reunion in Ann Arbor, Michigan, the Gross sisters' hometown; five of them received unwanted news. More happily, a total of ninety-seven

family members were told they do not carry the defective gene, either because of the results of the test, or because their parents or grandparents were known not to carry it. But they should not let down their guard: remember, a history of cancer was not so obvious in the family of Jay Monahan, Katie Couric's husband.

Mutations are egalitarian: they are happening in all of us all the time. If we live long enough, it's likely they'll eventually get us. But in the meantime, enjoy the diversity they provide in the global police lineup.

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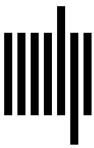

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