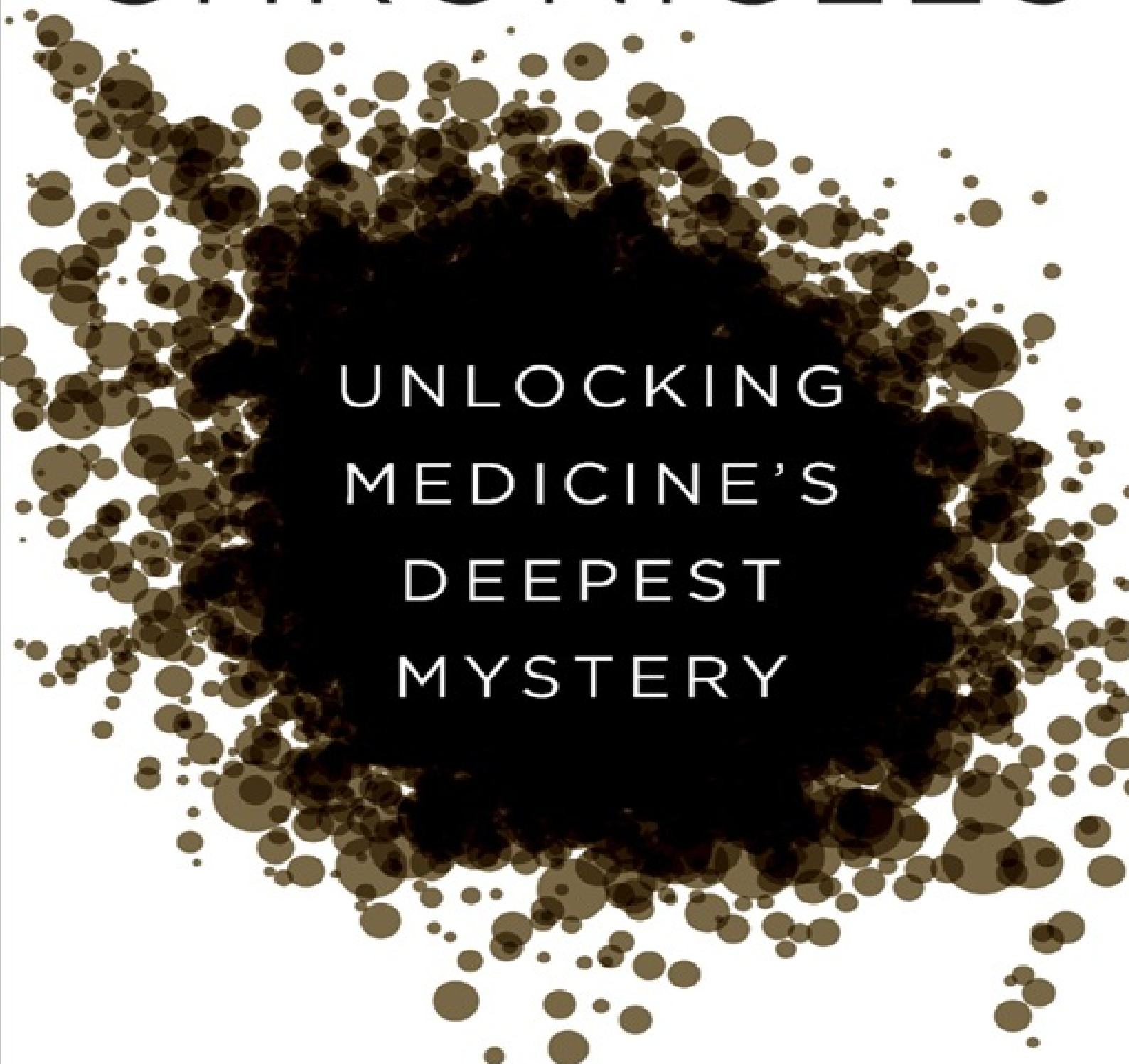
THE CANCER CHRONICLES



UNLOCKING MEDICINE'S DEEPEST MYSTERY

GEORGE JOHNSON

The Cancer Chronicles

Unlocking Medicine's Deepest Mystery

George Johnson

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For Joe's girls,

Jennifer, Joanna, Jessica, and Emmy

and for his wife, Mary Ann

We must never feel disarmed: nature is immense and complex, but it is not impermeable to intelligence; we must circle around it, pierce and probe it, looking for the opening or making it.

—Primo Levi, *The Periodic Table*

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Author's Note

Several years ago, for reasons that will become clear in these pages, I was driven to lea everything I could about the science of cancer. How much could I as an outsider, a longtim science writer more com- fortable with the sharp edges of cosmology and physics, grasp this wet, amorphous, and ever-changing terrain? I imagined the expanse before me as boundless rain forest whose breadth and diversity could never be captured within a sing book or even a single mind. I would find an opening at one of the borders and enter, cuttin my own path, exploring where my curiosity led—until I emerged years later at the other sid with a better understanding of what we know and don't know about cancer. I was in for som remarkable surprises.

Many people helped along the way. First I thank the scientists who devoted so much tim —sitting for interviews, answering e-mails, reviewing parts or all of the manuscript: Davi Agus, Arthur Aufderheide, Robert Austin, John Baron, José Baselga, Ron Blakey, Timoth Bromage, Dan Chure, Tom Curran, Paul Davies, Amanda Nickles Fader, William Field, And Futreal, Rebecca Goldin, Anne Grauer, Mel Greaves, Seymour Grufferman, Brian Henderso Richard Hill, Daniel Hillis, Elizabeth Jacobs, Scott Kern, Robert Kruszinsky, Mitchell Laza Jay Lubin, David Lyden, Franziska Michor, Jeremy Nicholson, Elio Riboli, Kenneth Rothma Bruce Rothschild, Chris Stringer, Bert Vogelstein, Robert Weinberg, Tim White, and Micha Zimmerman. In addition I consulted more than five hundred papers and books about canc and sat in on dozens of lectures. Most of these sources are listed as references in my endnot along with interesting information that didn't make it into the main text. George Demetri an Margaret Foti kindly allowed me to sit in on a private workshop in Boston organized by th American Association for Cancer Research. Thanks to them and the staff of AACR, includin Mark Mendenhall and Jeremy Moore, who welcomed me to the organization's fascinatin annual meeting in Florida. I am also grateful to the Keystone Symposia and the Society fo Developmental Biology for accommodating me at some of their events.

Just as I was getting my boots wet, David Corcoran at *The New York Times* enthusiastical commissioned and published two of my early reports. Thanks to him and other colleagues- Christie Aschwanden, Siri Carpenter, Jennie Dusheck, Jeanne Erdmann, Dan Fagin, Louis Gilder, Amy Harmon, Erika Check Hayden, Kendall Powell, Julie Rehmeyer, Lara Santor Gary Taubes, and Margaret Wertheim—for their reactions and advice on the manuscript.

Several recent alumni of the Santa Fe Science Writing Workshop read early version offering their good sense and expertise: April Gocha, Cristina Russo, Natalie Webb, Shanno Weiman, and Celerino Abad-Zapatero. Bonnie Lee La Madeleine and Mara Vatz helped wi library research and the endless checking of facts. The manuscript was in constant flux an any errors that survive are my own. This will be the seventh book I have done with Jo Segal, my editor at Knopf, and the fourth with Will Sulkin of Jonathan Cape and Bodley Hea in London. Thanks to them and their colleagues—including Victoria Pearson, Joey McGarve Meghan Houser, and Amy Ryan, a superb copyeditor—and to Esther Newberg, my age almost from the start.

Special thanks to Cormac McCarthy, who read an early version of the book, and to Jessi Reed, whose literary sensibility and encouragement were an inspiration. More than once m friend Lisa Chong read through the book sentence by sentence, page by page, helping to appl

the finishing touch.

Finally my deep thanks to Nancy Maret and the family of my brother, Joe Johnson, wh
allowed me to tell their stories.

I wonder now, though, if the steady presence of music around me didn't contribute importantly to my sense of the cancer as a thing with its own rights. Now it sounds a little cracked to describe, but then I often felt that the tumor was as much a part of me as my liver or lungs and could call for its needs of space and food. I only hoped that it wouldn't need all of me.

—Reynolds Price, *A Whole New Life*

Tuberculosis used to be called "consumption" because it consumes. It dissolved a lung or bone. But cancer produces. It is a monster of productivity.

—John Gunther, *Death Be Not Proud*

Chapter 1

Jurassic Cancer

As I crossed a dry, lonesome stretch of the Dinosaur Diamond Prehistoric Highway, I tried t
picture what western Colorado—a wilderness of sage-covered mesas and rocky canyons-
looked like 150 million years ago, in Late Jurassic time. North America was breaking awa
from Europe and Asia—all three had formed a primordial supercontinent called Laurasia. Th
huge land mass, flatter than it is today, was drifting northward a few centimeters per yea
and was passing like a ship through the waters of what geographers would come to call th
Tropic of Cancer. Mile-high Denver was near sea level and lay about as far south as whe
the Bahamas are today. Though the climate was fairly dry, webs of rivulets connectin
shallow lakes and swamps covered part of the land, and vegetation abounded. There were n
grasses or flowers—they had yet to evolve—just a weird mix of conifers commingling wit
ginkgos, tree ferns, cycads, and horsetails. Giant termite nests soared as much as thirty fe
high. Splashing and stomping through this Seuss-like world were *Stegosaurus, Allosauru*
Brachiosaurus, Barosaurus, Seismosaurus—their bones buried far below me as I made my wa
from Grand Junction to a town called Dinosaur.

Occasionally one can glimpse outcroppings of the Jurassic past, exposed by erosio
seismological uplift, or a highway department road cut—colorful bands of sediment that for
a paleontological treasure house called the Morrison Formation. I knew what to look for fro
photographs: crumbling layers of reddish, grayish, purplish, sometimes greenish sediment-
geological debris piled up over some 7 million years.

Just south of the town of Fruita on the Colorado River, I hiked to the top of Dinosaur Hil
stopping for a moment to pick up a pinch of purplish Morrison mudstone that had fallen nea
the trail. As I rolled it in my fingers it crumbled like dry cookie dough. On the far side of th
hill, I came to a shaft where in 1901 a paleontologist named Elmer Riggs extracted 6 tons o
bones that had belonged to an *Apatosaurus* (the proper name for what most of us call
Brontosaurus). Alive and fully hydrated, the 70-foot-long reptile would have weighed 30 ton
Riggs encased the bones in plaster of paris for protection, ferried them across the Colorado o
a flat-bottom boat, and then shipped them by train to the Field Museum in Chicago, whe
they were reassembled and put on display.

After making my way north to Dinosaur (population 339), where Brontosaurus Boulevar
intersects Stegosaurus Freeway, I stood at an overlook and watched Morrison stripes in
canyon reddening with the setting sun. But it was a little farther west, along the Green Rive
in the western reaches of Dinosaur National Monument, that I saw the most beautif
example: a cliffside of greenish grays slumping into purples slumping into browns. It indee
resembled, as the woman at the park headquarters had told me, melted Neapolitan ice crean

It was somewhere in these parts that a dinosaur bone was discovered that displays wh
may be the oldest known case of cancer. After the dinosaur died, whether from the tumor o
something else, its organs were eaten by predators or rapidly decomposed. But the skeleton-

at least a piece of it—gradually became buried by windblown dirt and sand. Later on, a expanding lake or a meandering stream flowed over the debris, and the stage was set fo fossilization. Molecule by molecule minerals in the bones were slowly replaced by minera dissolved from the water. Tiny cavities were filled and petrified. Several epochs lat dinosaurs were long extinct, their world overlaid by lakes and deserts and oceans, but th fossilized bone, encased in sedimentary rock, was preserved and carried through time.

That hardly ever happened. Most bones disintegrated before they could become fossilize And of the fraction that survived long enough to petrify, all but a few remain buried. Th specimen, now labeled CM 72656 and housed at the Carnegie Museum of Natural History Pittsburgh, was a survivor. Unearthed by a rushing river or exposed by tectonic forces somehow it was delivered to the surface of our world where, 150 million years after th animal died, it was discovered by some forgotten rockhound. A cross-section was cut with rock saw, polished, and after passing through who knows how many human hands, the foss found its way to a Colorado rock shop where it caught the eye of a doctor who thought h knew a case of bone cancer when he saw one.

His name was Raymond G. Bunge, a professor of urology at the University of Iowa Colleg of Medicine. In the early 1990s, he telephoned the school's geology department to ask someone would come evaluate a few prize specimens in his collection. The call made its wa through the switchboard to Brian Witzke, who on a cold autumn day bicycled to the doctor house and was presented with an attractive chunk, 5 inches thick, of mineralized dinosau bone. Viewed head-on, the fossil measured 6.5 by 9.5 inches. Lodged inside its core was a intrusion, now crystallized, that had grown so large it had encroached into the outer bon Bunge suspected osteosarcoma—he had seen the damage the cancer can do to huma skeletons, particularly those of children. Oval in shape and the size of a slightly squashe softball, the tumor had been converted over the millennia into agate.

The fragment was too small for Witzke to identify the bone type or the species of dinosau but he was able to provide a geological diagnosis: The reddish-brown color and the agatize center were clues that it came from the Morrison Formation. Bunge remembered buying th souvenir somewhere in western Colorado—burnished pieces of petrified dinosaur bone wer a favorite among collectors—but he couldn't remember the precise location. He gave the roc to the geologist, asking that he seek an expert opinion.

Other projects intervened, and so the fossil sat almost forgotten atop a filing cabinet Witzke's office, until the day he sent it to Bruce Rothschild, a rheumatologist at the Arthrit Center of Northeast Ohio who had expanded his practice to include dinosaur bone disease. H had never seen a clearer or more ancient example of prehistoric cancer. His next step was determine just what kind of cancer it was.

The tumor, it turned out, didn't exhibit the ill-defined margins or the layered, onion-sk look of an osteosarcoma, the cancer Bunge had suspected, or of another malignancy calle Ewing's sarcoma. Rothschild also felt confident in ruling out myeloma, a cancer of plasm cells that leaves bone with a "punched out" appearance. The fact that the tumor, gnawing i way outward, had left intact a thin shell of bone was reason to exclude the more invasiv multiple myeloma. Every skeletal disease leaves a distinct engraving and, one by on Rothschild eliminated the possibilities: "the superficial solitary and coalescing pits leukaemia," "the expansile, soap bubble appearance of aneurysmal bone cysts," "th

epiphyseal 'popcorn' calcifications characteristic of chondroblastomas," "the 'ground glas appearance of fibrous dysplasia."

For an outsider reading Rothschild's observations, the medical jargon might be somewhe between translucent and opaque, words that gain a grim familiarity only as one strives understand the sudden disruption of cancer. What is clear from the beginning is th confidence with which a specialist in the obscure discipline of dinosaur pathology can provi a likely diagnosis for a 150-million-year-old tumor. Rothschild went on to rule out th "sclerotic-rimmed lesions of gout," the "zones of resorption characteristic of tuberculosis and the "sclerotic features of gummatous lesions of treponemal disease." Unicameral bon cysts, enchondromas, osteoblastomas, chondromyoxoid fibromas, osteoid osteom eosinophilic granuloma—who would have known that so much can go wrong inside wh appears to be solid bone? None of these seemed like candidates. To Rothschild's eye th lesion had the markings of a metastatic cancer, the deadliest kind—a cancer that ha originated from cells elsewhere in the dinosaur's body and migrated to establish a colony the skeleton.

There had been scattered references in the journals to other dinosaur tumors—osteoma (clumps of overeager bone cells outgrowing their rightful bounds) and hemangioma (abnormal effusions of blood vessels that can form within the spongy tissue inside bone). Lik cancer, these benign tumors are a kind of neoplasm (from the Greek for "new growth")—cel that have learned to elude the body's checks and balances and exert a will of their own. Th cells in a benign tumor are multiplying rather slowly and have not acquired the ability invade surrounding tissue or to metastasize. They are not necessarily harmless. Occasionally benign tumor can press dangerously against an organ or blood vessel or secrete destructiv hormones. And some can become cancerous. These were rare enough. But sightings malignant dinosaur tumors were especially scarce. A cauliflower-like growth in the forelim of an *Allosaurus* was thought for a while to be a chondrosarcoma. But on close examinatio Rothschild decided that it was just a healed fracture that had become infected. Bunge's foss was the real thing. In a terse, five-hundred-word paper written with Witzke and anoth colleague and published in *The Lancet* in 1999, he came to a bold conclusion: "Th observation extends recognition of metastatic cancer origins to at least the mid-Mesozoic [th Age of the Dinosaurs], and is the oldest known example from the fossil record."

I'd first heard of Raymond Bunge's fossil earlier that summer when I began working m way through the literature on the science of cancer. There is something sickly fascinatin about the way a single cell can break from the pack and start multiplying, creating somethin alien inside you—like a new organ suddenly sprouting in the wrong place or, even mo gruesome, a vicious, misshapen embryo. Teratomas, rare tumors that arise from misguide germ cells (the ones that give rise to eggs and sperm), can contain the rudiments of hai muscle, skin, teeth, and bone. Their name is from the Greek word *teras,* for "monster." young Japanese woman had an ovarian cyst with head, torso, limbs, organs, and a cyclopea eye. But these cases are very rare. Tumors almost always evolve according to their ow impromptu plan. The most dangerous ones become mobile. Once they have establishe themselves in the immediate vicinity—your stomach, your colon, your uterus—they mov on, metastasize, to new ground. A cancer that began in the prostate gland can end up in th lungs or the spinal column. There was no reason to believe that cancer hadn't occurred

dinosaurs. But considering the tiny fraction of paleontological remains that humans have ha the opportunity to examine, coming across an actual example seemed almost miraculous.

Consider the size of the field: From Dinosaur National Monument in Utah and Colorad the Morrison Formation reaches north into Wyoming, Idaho, Montana, the Dakotas, ar southern Canada. It spreads east to Nebraska and Kansas, and south to the panhandles Texas and Oklahoma, and into New Mexico and Arizona. It covers approximately half million square miles. Erosion and excavation, natural or man-made, have only nicked th edges, barely sampling the 7-million-year accumulation of dinosaur bones, and only thos that happened to become fossilized. If it hadn't been for Raymond Bunge's sharp eye, th earliest solid evidence of prehistoric cancer would have been missed. How many other cas were crushed inside those lightless layers? And among the bones that have been retrieve how many malignancies had been overlooked? Paleontologists were hardly ever looking f cancer—few would recognize it if they saw it—and the only tumors they had a chance finding would be those that had tunneled their way outward to a bone's surface or had bee revealed by a random fracture or the blind cut of a lapidary saw.

One of the most elusive questions about cancer is how much is timeless and inevitable- arising spontaneously inside the body—and how much has been brought on by pollutio industrial chemicals, and other devices of man. Getting a rough sense of the frequency cancer in earlier epochs might provide important clues, but only with a larger sample of dat His interest piqued by Bunge's fossilized tumor, Rothschild began looking for more.

With a portable fluoroscope, he began x-raying his way through the museums of Nor America. In people, cancers that metastasize to the skeleton most commonly lodge in th spine, so Rothschild concentrated on vertebrae. By the time he was done he had examine 10,312 vertebrae from about seven hundred dinosaurs collected by the American Museum Natural History in New York, the Carnegie Museum in Pittsburgh, the Field Museum Chicago, and other institutions throughout the United States and Canada—every specime north of the Mexican border that he could get his hands on. He inspected loose vertebrae an using ladders and a cherry picker, the soaring spines of whole skeletons. (There is a picture him wearing a dinosaur T-shirt and leaning backward inside the rib cage of a *Tyrannosaur rex*.) Bones that appeared abnormal under x-rays were scrutinized more closely with a C scan.

In the end, his diligence paid off. He found another bone metastasis, and this time it wa possible to identify the victim: an *Edmontosaurus,* a duck-billed titan (the family name Hadrosauridae) that lived toward the end of the Cretaceous, right after the Jurassic, whe dinosaurs began to go extinct. Other Hadrosauridae also had bone tumors, all of them benig an osteoblastoma, a desmoplastic fibroma, and twenty-six hemangiomas, but there were nor among the other beasts. That perhaps was the biggest surprise. Although Hadrosaurida vertebrae made up less than one-third of the bone pile—about 2,800 specimens from few than one hundred dinosaurs—they were the source of all the tumors. The approximate 7,400 vertebrae that were not hadrosaurs—*Apatosaurus, Barosaurus, Allosaurus,* and so forth- exhibited no neoplasms, either malignant or benign.

It was the kind of anomaly epidemiologists of human cancer confront all the time. Why c some people get more cancer than others? Some evolutionary twist may have le *Hadrosaurus* with a genetic predisposition for tumors. Or the reason might have bee

metabolic. These dinosaurs, Rothschild speculated, may have been more warm-blooded tha other ones. Warm-blooded metabolisms run faster—it takes energy to maintain body heat- and that might accelerate the accumulation of the cellular damage that leads to malignancy.

Maybe the difference was not endemic but environmental—something about wh *Hadrosaurus* ate. Plants in an ecosystem engage in endless chemical warfare, synthesizin herbicides and insecticides to fight off pests. Some of these chemicals are mutagens: they ca change DNA. Modern descendants of the fernlike cycads that grew in Mesozoic times produc poisons that can induce liver and kidney tumors in laboratory rats. But why woul *Hadrosaurus* eat more cycads than, say, *Apatosaurus*? Another possible source of carcinogens- needles from conifer trees—had been discovered in the stomachs of a couple *Edmontosaurus* "mummies," whose remains had been buried under the right environment conditions to fossilize instead of rot. But that wasn't much evidence to go on.

There were other curiosities to explain. When *Hadrosaurus* tumors did occur it was onl among the caudal vertebrae—those nearest the tail of the spine. What was it about th bottom of the reptile that was more susceptible than the top? If only dinosaurs could be r created from ancient DNA as they were in *Jurassic Park* and made available for medic research. At the great cancer centers—Dana-Farber in Boston, MD Anderson in Houston, an others around the world—a scientist can consume a career studying the role a single molecu plays in malignancy. Just the data from Rothschild's survey suggested dissertations' worth questions. The overriding one was how to put his findings into perspective. Human bon cancer of any kind—metastatic or originating in the skeleton—is a rarity. Was one cas among seven hundred dinosaur skeletons a little or a lot?

In a third paper, Rothschild considered the odds. He had been approached by tw astrophysicists who were hoping to support their theory that the end of the dinosaurs' earth reign was hastened by a spike of radioactive cosmic rays. Ionizing radiation—the kind stron enough to damage DNA—can cause cancer, and bone marrow is particularly susceptible. If cosmic event had unleashed unusually strong rays, the effect on the dinosaurs would hav been like being x-rayed from outer space.

But how would you do the epidemiology? In an earlier study Rothschild and his wif Christine, had x-rayed bones at the Hamann-Todd Human Osteological Collection at th Cleveland Museum of Natural History, a repository of three thousand skeletons from medic school cadavers—homeless souls who would otherwise be in pauper's graves. Thirty-three them had metastatic bone tumors, which amounts to 1.14 percent. Autopsies at the San Dieg Zoo suggested that reptiles have a bone cancer rate about one-eighth that of humans, or abo 0.142 percent. One cancerous *Edmontosaurus* among seven hundred fluoroscoped dinosau yields almost precisely the same number. One would have to look elsewhere for evidenc that cancer had been a factor in the extinction.

For months factoids like this had been accumulating in my notebook and metastasizin through my mind. Every question raised about cancer inevitably spawned more. Ho representative was the Hamann-Todd Collection of the overall cancer rate? The indigen whose bones were there may have suffered from poor nutrition and haphazard diets, possibl increasing their susceptibility. Yet many of them probably had comparatively short life span dying from violence or infectious diseases before there was time for a cancer to grow. Mayb it all balanced out. And maybe not. The study of the animals in the San Diego Zoo raise

more questions. Animals in captivity tend to get more cancer than those in the wild, mayb because they are exposed to more pesticides or food additives, or maybe just because the survive longer, get less exercise, and eat more. Of all the risk factors associated with huma cancer two that are seldom disputed are obesity and old age.

The most troubling question was how much one can extrapolate about dinosaur cancer- and the ultimate origins of the disease—from what little evidence has survived. If yo included in the sample only the one hundred tumor-prone *hadrosaurs,* their bone cancer ra would be 1 percent, about the same as for the human skeletons. But you have to wonder ho many other specimens are waiting to be discovered. Just one more with a malignant tume would double the cancer rate. Finally there was the question of how many cancers migh have spread to unexamined parts of the skeleton or to softer organs—cancers that neve reached bone. Once the tissues decomposed the evidence would be gone.

There are reports of a possible exception. In 2003, the year the Rothschild surve appeared, paleontologists in South Dakota announced the discovery of what might be dinosaur brain tumor. They were preparing the skull of a 72-million-year-old *Gorgosaurus,* close relative of *Tyrannosaurus rex,* when they found "a weird mass of black material in th brain case." Analysis with x-rays and an electron microscope indicated that the rounded lum had consisted of bone cells, and veterinary pathologists diagnosed it as an "extraskelet osteosarcoma," a bone-cell-producing tumor that had taken up residence in the cerebellu and brainstem. Maybe that explains why the *Gorgosaurus* appeared to be so battered, a though the animal, suffering from a loss of motor control, had stumbled and falle repeatedly. "It certainly would take a bizarre event to have created this appearance Rothschild speculated at the time. "The position and character may well be a tumor, but still needs to be proven that this is not simply broken skull fragments that fell in."

Continuing along the Dinosaur Diamond Highway, thinking about cancer, I made my ow rare sighting: a Sinclair gasoline station with its green dinosaur logo—another relic of earli times. Along the road, rocking oil wells pumped the fossil fuels derived, as best we know from prehistoric organic matter, a puree of tiny plant and animal life, perhaps with some o of dinosaur splashed in.

It was almost dusk when I reached the Yampa Plateau in northern Colorado, a 300-millio year pile of geology. Eons of seismic turmoil—the thrusting and tilting, the slipping an sliding of great crustal masses—had made a mess of the timeline. For miles the road skimme the surface of rock laid down in the Jurassic and Cretaceous, mid to late dinosaur time. The without so much as a bump of the tires, the mesa top abruptly changed to Pennsylvanian- whole epochs sheared off to expose an older world, 150 million years before the Morriso dinosaurs, when primitive cockroaches crawled the land. Crushed a couple of strata beneat the Pennsylvanian would have been the Devonian, a 400-million-year-old countryside. I Devonian rock 1,600 miles east of the Yampa, a jawbone of a primitive armored fish wa discovered near what became Cleveland, Ohio. It is pitted with what some scientists take t be a tumor and others dismiss as an old battle wound.

The road ended at Harpers Corner—the far tip of the plateau. I walked to the edge whe deep below me the Green and Yampa Rivers come together, having sawed though all th hardened time. I stood there flummoxed by the thought of all that vanished past. After th

disappearance of the dinosaurs came the Laramide orogeny, when the peaks that became th Rockies soared from the earth, reaching as high as 18,000 feet, only to become buried their necks in their own debris. With the Exhumation of the Rockies (these names sour almost biblical), the infill began washing away. In early Pleistocene time, just 2 million yea ago, the great glaciations followed, leaving behind the geography we know toda Throughout all of these cataclysms life kept evolving. Stowing away on the journey was th interloper called cancer.

Hints of benign neoplasms have been found in the fossilized bones of ancient elephant mammoths, and horses. Hyperotosis, or runaway bone growth, appears in fish from the genu *Pachylebias,* which seem to have put the tumors to good use. With the ballast provided by th increased bone mass, the fish could graze deeper in the salty Mediterranean waters, givi them an edge over their competitors. What began as a pathological growth may have bee adopted as an evolutionary strategy.

Malignant tumors have been suspected in an ancient buffalo and an ancient ibex. There even a report from 1908 of cancer in the mummy of an ancient Egyptian baboon. Th examples are scant and sometimes controversial. But as with the dinosaurs, absence evidence is not evidence of absence. Maybe cancer was a great rarity before man bega messing with the earth. But a core amount of cancer must have existed all along. For a boc to live, its cells must be constantly dividing—splitting into two cells, which split into fou then eight, doubling again and again. With each division the long threads of DNA—th repository of a creature's genetic information—must be duplicated and passed along. Ov the course of time mechanisms have evolved to repair errors. But in a world awash wi entropy that is naturally an imperfect process. When it goes wrong the result is usually just dead cell. But under the right circumstances the errors give rise to cancer.

Even a lone single-celled bacterium can spawn a mutation that causes it to replicate mo vigorously than its neighbors. When that happens to a cell within a tissue the result is neoplasm. Plants and animals—two variations on the theme of multicellularity—ultimate sprang from the same primordial source. Plants are our very distant cousins, and they do g something resembling cancer. A bacterium called *Agrobacterium tumefaciens* can transfer fragment of its own DNA into the genome of a plant cell, causing it to multiply into a tum called crown gall. A remarkable paper published in 1942 demonstrates that in sunflowe these tumors can spawn secondary tumors—a primitive analog of metastasis. In the inse world larval cells can give rise to invasive tumors—the same phenomenon, perhaps, th carried over to the vertebrates.

Cancer (sarcomas, carcinomas, lymphomas, these clinically depressing names) has bee described in carp, codfish, skate rays, pike, perch, and other fishes. Trout, like people, g liver cancer from a carcinogen, aflatoxin, produced by the fungus *Aspergillus flavus.* Rumo that sharks don't get cancer led to a mass slaughter by entrepreneurs hawking cancer-fightin shark cartilage pills. But sharks do get cancer. None of the classes of the animal kingdom a exempt. Among reptiles, there are cases of parathyroid adenoma in turtles and of sarcom melanoma, and lymphatic leukemia in snakes. Amphibians are also susceptible to neoplasm but some offer a strange variation on the theme. When injected with carcinogens, new rarely develop tumors. They are more likely to react by sprouting a new, misplaced limb This ability to regenerate body parts has been all but lost by other animals over the course

evolution. Could this be another clue to the origins of cancer—damaged tissues tryi frantically to regrow themselves, only to find that they no longer know how?

None of these creatures walk, swim, or slither to a clinic seeking care. But from th haphazard sightings of naturalists and zoologists, patterns have emerged. Mammals appear get more cancer than reptiles or fish, which in turn get more cancer than amphibian Domesticated animals seem to get more cancer than their cousins in the wild. And people g the most cancer of all.

One afternoon during my roadtrip, I stopped for a while at the Dinosaur Journey Museu Given the current state of science museums—so much show biz—I expected the place to b infested with animatronic dinosaurs and hands-on exhibits resembling video games. B plenty of good science was there. I peeked through the picture windows of the Paleo La where live men and women sat on display, leaning over worktables and chipping embedde fossils from surrounding stone. I walked among reconstructed skeletons towering toward th ceiling—*Allosaurus, Stegosaurus.* I saw a neck vertebra from an *Apatosaurus* so large th without the label I wouldn't have guessed the rocky mass had once been living tissue. It wa all impressive, but over the years I had seen enough dinosaur skeletons to feel a little jade It wasn't until I stopped at a display with a full-size outline of a *Brachiosaur*'s heart standi as high as my chest that I really felt how enormous these beasts had been.

I thought again about Rothschild's survey of dinosaur tumors. There is a close relationsh between size and life span. Though there are exceptions, larger species tend to live long than smaller ones, and by some reckonings, the largest dinosaurs had very long life spans—s much time and space for mutations to collect. Wouldn't that have made them high susceptible to neoplasms? At least in the mammalian world the issue is not clear-cut, a observation that goes by the name of Peto's paradox. It was named for Sir Richard Peto, a Oxford epidemiologist. He was puzzled that large long-lived creatures like elephants don't g more cancer than small short-lived creatures like mice. The mystery was succinctly posed the title of a paper by a group of biologists and mathematicians in Arizona: "Why Don't A Whales Have Cancer?" Except for belugas in the polluted St. Lawrence estuary, whale canc appears to be uncommon. For mice the cancer rate is high.

At first that didn't seem so strange. There is an inverse correlation between life span an pulse rate. During a typical lifetime an elephant and a mouse will each use up roughly billion heartbeats. The mouse will just do it much faster. With a metabolism on so high burn, it seems sensible that mice might get more cancer. But what is true for the mouse is n true for other tiny mammals. Birds, despite their frenzied metabolic rate (a hummingbird heart can beat more than a thousand times a minute) appear to get very little cancer. If yo graph mammalian size against cancer rate there is no telltale sloping line, just a scattering dots. In our ignorance, each species seems like an exception.

Scientists have proposed several reasons for why cancer doesn't correlate smoothly wi size. While larger animals may indeed get more mutations, they might also have evolve more effective means for repairing DNA, or for warding off tumors in other ways. Th authors of the Arizona paper suggested how that might occur: hypertumors. Cancer is phenomenon in which a cell begins dividing out of control and accumulating genetic damag Its children, grandchildren, and great-grandchildren go on to spawn broods of their own-

subpopulations of competing cells, each with a different combination of traits. The strong contenders—those that have evolved an ability to grow faster than the others or to poiso their neighbors or to use energy more efficiently—will gain an upper hand. But before the can dominate, the authors proposed, they might become susceptible to "hypertumors clusters of weaker cancer cells opportunistically trying to latch on for a free ride. Thes parasites would sap energy continuously, destroying the tumor or at least keeping it in chec In large, long-lived animals cancer develops gradually enough for the leeches to form. The may indeed get more tumors, but they are much less likely to grow to a noticeable siz Cancer that can get cancer. For all the time I'd spent immersing myself in the literature, th was the first I had heard of that.

That still left me wondering about the hummingbirds, and a footnote in the paper abo Peto's paradox led me to yet another of cancer's mysteries. It is well known to zoologists th virtually all mammals, no matter how tall or short, have precisely seven vertebrae in the necks: giraffes, camels, people, whales. (Manatees and sloths are exceptions.) Bird amphibians, and reptiles are not bound by the rule—a swan can have twenty-two to twenty five neck vertebrae. They also appear to get less cancer. Frietson Galis, a Dutch biologis thought there must be some kind of connection. She considered what happens in ra instances when fetuses sprout an extra rib right where the seventh vertebra would normall be. As a result, children born with the defect have only six vertebrae in their necks. They a also more likely to die from brain tumors, leukemias, blastomas, and sarcomas. Galis sugges that it is why variation in the number of neck vertebrae is slowly being weeded out of th mammalian population.

I spent my last night on the road in Vernal, Utah, where a giant pink *Brontosaurus* (I mea *Apatosaurus*) with long flirtatious eyelashes held up a sign welcoming visitors. It was abo nine o'clock and the town was already shutting down. I found a restaurant with a Wild We theme barely open on Main Street. After a long day of driving I was looking forward to glass of wine. I tried to keep up with the latest studies on how this vice, in moderation, mig conceivably be good for the circulatory system, staving off heart attacks and strokes. Th most wishful research even suggested that the antioxidizing effects of the elixir might he suppress tumors and extend life. But the longer you live the more likely you are to g cancer. Every meal presents a calculus of probabilities: Alcohol increases the risk for som cancers (mouth, esophageal) but may decrease the risk for kidney cancer.

In a file on my laptop I had been keeping a list of headlines from recent news:

"Natural Compounds in Pomegranates May Prevent Growth of Hormone-dependent Breast Cancer"

"Green Tea Could Modify the Effect of Cigarette Smoking on Lung Cancer Risk"

"Soft Drink Consumption May Increase Risk of Pancreatic Cancer"

"Bitter Melon Extract Decreased Breast Cancer Cell Growth"

"Seaweed Extract May Hold Promise for Non-Hodgkin's Lymphoma Treatment"

"Coffee May Protect Against Head and Neck Cancers"

"Strawberries May Slow Precancerous Growth in Esophagus"

I knew by now that the effects, if real, would be minuscule. How can anyone sensib weigh the trade-offs, based inevitably on imperfect information—on findings that could b overturned tomorrow?

The carcinogenic effects of red wine turned out not to be an issue that night. This was Uta and there was nothing alcoholic on the menu. My fried chicken cutlet sandwich was washe down with lemonade made with powder from a jar and tap water. Back at my room at th Dinosaur Inn (guarded over by another smiling *Apatosaurus*), I thought again about thos layers extending miles and millennia below me. Someday more layers would pile on top o us, and I wondered how much cancer would be there. It had been seven years almost to th day since Nancy, the woman I was married to, was diagnosed with a rabid cancer tha sprouted for no good reason in her uterus and burned like a flame along a wick down th round ligament and into her groin. She lived to tell the tale, but ever since, I have bee wondering how a single cell minding its own business can transmogrify into a science fictio alien, a monster growing within.

Chapter 2

Nancy's Story

She always ate her vegetables. Obsessively, it sometimes seemed. Breakfast, lunch, dinne throughout the day she would keep mental count. Never mind if it was 10:30 p.m., halfwa through a *Simpsons* episode or a DVD. If she hadn't consumed two or three servings vegetables (some green, some yellow) and three or four servings of fruits, nuts, grains- whatever the food pyramidologists were recommending—she would slice up an apple or ope a bag of carrots.

In the spirit of Pascal's wager (there is no downside to believing in God), none of th probably hurt. It is often said that two-thirds of cancer cases are preventable—one-third b eliminating smoking and the other third by getting more exercise and eating healthier meal But the evidence associating any particular diet with cancer is discouragingly thin. We wer told, Nancy and I, to eat our spinach because it is rich in folates, and folates are a cruci ingredient used by cells to synthesize and repair the intertwining helices of DNA. That sound great in theory, but the argument is weak at best that consuming more folate reduces the ris of three of the most common cancers: colorectal, breast, and prostate. For breast cancer, th effect, if there is one, may be primarily of benefit to alcoholics. Other research suggests tha too much folic acid (the synthetic form of folate found in vitamin pills) can increase cance risk. Once a neoplasm has taken root, extra doses might even accelerate its growth, addin fuel to the fire. Some cancers are combated by administering antifolates, which are amon the oldest chemotherapeutic drugs. The most persuasive reason for eating spinach is tha sautéed with garlic or tossed in a salad, it tastes so good.

Just as dubious is the mythology surrounding antioxidants like vitamins C and E, which ar consumed in fruits, vegetables, and pills and smeared on the face in the form of antiagin cosmetics. The hope is to counteract free radicals—products of cellular combustion that eat the insides of cells. It is far from clear that the body needs help on that front. To blunt th impact of free radicals (the name conjures images of bomb-throwing anarchists), living cel come equipped with a built-in system of antioxidizing mechanisms, a finely strung molecula web crafted over the eons since life began. That is not the kind of thing you want to me with. And no creature would want to eliminate free radicals. They are scavengers tha prevent the inevitable accretion of cellular poisons, garbage collectors for the cells. Bet carotene, an antioxidant that gives carrots, mangoes, and papayas their color, has bee promoted as having anticarcinogenic powers. But in a clinical trial in Finland, smokers give beta-carotene supplements were more likely to get lung cancer. A similar trial in the Unite States was curtailed at an early stage when it also appeared that the supplements wer increasing the risk of the disease. "To go beyond the bounds of moderation is to outrag humanity"—Pascal again—and to outrage our cells.

These days grocery store packaging has descended to a new level of detail, luring shoppe with produce and other goods rich in phytochemicals, naturally occurring ingredients

plants reputed to help detoxify carcinogens, repair DNA damage, or otherwise discourag cells from going wild. Lycopene, quercetin, resveratrol, silymarin, sulforaphane, indole-carbinol—they go in and out of style. In a laboratory dish these substances might affe biochemical pathways believed to be involved in the numbingly complex processes carcinogenesis. Far less clear is whether consuming more of them actually prevents anyon from getting cancer. Unless a person is severely malnourished there is little reason to believ that a shortage of any specific molecule is throwing the cellular processes seriously out whack. You can hedge your bets by taking multivitamins, but the evidence here is als meager. If life were so delicate we probably wouldn't be here worrying about what we eat.

There is so much that science doesn't know about the molecular clockworks, and it possible that substances in fruits and vegetables confer synergistic advantages whose logic yet to be uncovered. Throughout the 1990s, the news was filled with reports of miraculou anticarcinogenic effects from consuming nature's bounty. The National Cancer Institute bega pushing its 5 A Day program. Eat that many servings of fruits and vegetables and you wou be a long way toward beating the odds against cancer.

The evidence, alas, came mostly from case control studies in which people with an without cancer were asked to remember what they ate. Epidemiological studies like these ar prone to error. Grasping to explain their predicament, cancer patients might be more likely overestimate how badly they neglected their diets, while healthy people might remembe eating more fruits and vegetables than they really did. Since cancers can take decades develop, great feats of memory are required. Skewing things further, those most likely volunteer for the control group may be relatively affluent health-conscious citizens who, addition to eating nutritious meals, exercise more often and are less likely to binge on alcoh or cigarettes. A good study will try to strike a balance between the cases and the controls, bu the best that retrospective epidemiology can do is hint at associations to be investigated mor rigorously. In prospective cohort studies, large groups of people—the cohorts—are followe for years and interviewed regularly to see if patterns emerge among those who do and do no get cancer. Though these too suffer from biases, the evidence is considered stronger than fo retrospective epidemiology. The largest prospective study on diet and health has found so fa that eating fruits and vegetables has, at most, a very weak effect on cancer prevention. There are suggestions of possible benefits with a few cancers, but nothing that has lived up to th earlier hopes.

We were told to eat our fiber, and when Nancy went shopping she would bring hom breakfast cereals that tasted like pieces of the cardboard box. Intuitively it made sense. Yo could imagine all that fiber scouring clean your intestines on its way through the digestiv tract. Fiber was also said to nurture a mix of bacteria that reduces the risk of colon cance The case for fiber may be a little stronger than for other foods, but the evidence has bee controversial. One big prospective study found an association while another did not.

This all might be less ambiguous if foods could be subjected to the same kind of rigorou trials used to test new drugs. A large group of people is randomly assigned to an experiment group, which receives the treatment, or a control group, which does not. In the end th results are compared. But these studies are rare in cancer nutrition research. It is hard enoug to force people to arbitrarily eat or not eat a certain food. And to clinch the case, th enforcement would have to last for the decades it can take a cancer to develop. When a fou

year controlled trial was carried out with a low-fat diet that was high in fiber as well as frui and vegetables it found no evidence of a reduction in colorectal polyps, which are precurso to colon cancer. Another randomized trial of about equal duration found that a fibrous di had no effect on the recurrence of breast cancer.

Reading these less than ringing endorsements, I was reminded of the biochemist Bruc Ames, who has reported that brussels sprouts, cabbage, broccoli, cauliflower, and othe staples of the farmer's market contain naturally occurring carcinogens, built-in pesticides lik the ones that might have killed the poor *Edmontosaurus*. People apparently don't ingest thes foods in quantities that would cause a public health problem—or maybe we have acquired natural resistance. But how did the superstition arise that plants have the opposite effec conferring us with the power to beat back cancer? Fruits and vegetables evolved to promo their own propagation. Then people started eating them.

There was nothing very rigid about Nancy's dietary pursuits. We both loved steaks an hamburgers, but we tried to moderate our consumption. Here the science sounds a little mo persuasive. If the epidemiology can be believed, eating a lot of red meat every single da might have raised our chances of getting colorectal cancer during the next decade by as muc as a third—from 1.28 percent to 1.71 percent. But given those odds, cooking a giant steak o the weekend seemed worth the trade-off. For penance we would have fish sometime Knowing that it is rich in omega-3 fatty acids may have made the salmon and halibut w grilled more satisfying. But any firm connection between fish, fish oils, and colon canc prevention has remained elusive.

Fruits, vegetables, fibers, fish—if nothing else, loading up on these foods promised t reduce one's intake of mammalian fat. Yet even that has come under challenge as a seriou cancer risk, and it is possible that sugar may pose a greater danger by increasing blood insul levels and stimulating the growth of tumors. In the end, it probably doesn't matter so muc what you eat as how much. Obesity—like old age, sunlight, radioisotopes, and cigarettes- has joined the short list of unambiguous instigators of cancer. Conversely there is evidenc that caloric restriction reduces the likelihood of cancer. You lower your metabolism. Like lizard.

Nancy included a variety of vegetables and fruits in our diet mostly because she like them. But she had reason to worry more than some others about cancer. Her mother ha suffered through a mastectomy and chemotherapy shortly before we married. After sixtee years of slumber, the cancer returned. We didn't know if her breast cancer was among thos linked to a familial genetic defect. If so Nancy might have inherited a susceptibility, thoug not a fate.

She had other risk factors. She was forty-three and we had no children, a source of consta contention. The less frequently a woman is pregnant, the more monthly menstrual cycles sh endures. With each period a jolt of estrogen causes cells in the uterus and mammary glands t begin multiplying, duplicating their DNA—preparing for the bearing and the nursing of a chi that may not come. Each menstrual cycle is a roll of the dice, an opportunity for copyin errors that might result in a neoplasm. Estrogen (along with asbestos, benzene, gamma ray and mustard gas) is on the list of known human carcinogens published by the feder government's National Toxicology Program.

Women these days are also exposed to more monthly doses of estrogen because they a

beginning to menstruate at much earlier ages, possibly increasing the risk of breast cancer. A few scientists blame the change on bisphenol A—a chemical in plastic bottles that mimics estrogen—but a more widely accepted explanation involves nutrition. With more food to eat, girls mature more rapidly, accumulating fat, and that may serve as a signal that the body is healthy enough to begin ovulation. Over a century the age of menarche, when menstruation begins, has dropped in the Western world from about seventeen to twelve. At the same time, women are spending less of their fertile life either pregnant or nursing a child. Lactation also appears to hold estrogen in check. The result of all this is that a teenager today may have already experienced more menstrual cycles than her grandmother did during her entire life.

There are other risks in being female. Hormone therapies, administered during menopause or pregnancy, have been associated with some cancers. And obesity, especially in older women, can increase estrogen along with cancer risk. But none of this is straightforward. Strangely enough, excess body fat can actually reduce the chances of premenopausal women getting breast cancer. And while oral contraceptives may slightly raise the odds for cancer of the breast, they appear to reduce the risk of getting ovarian and endometrial cancer. Nancy wasn't using birth control pills and she was far from being overweight, but she worried, just a little, about another factor: the wine we liked to have with dinner. Alcohol might also tip the hormonal scales and has been associated for entirely different reasons with digestive cancers. Snuffed out by alcohol, epithelial cells lining the esophagus must be replaced—more DNA to be duplicated, more chances for error. There is evidence linking alcohol to liver cancer, but more certain is the risk from hepatitis viruses or long-term exposure to aflatoxin, a poison produced by funguses that can invade peanuts, soybeans, and other foods.

You could live your life with a calculator. Consuming two or three drinks a day might increase breast cancer risk by 20 percent. That is not as bad as it sounds. The chance that a woman between the ages of forty and forty-nine will get the cancer is 1 in 69, or 1.4 percent. Alcohol consumption would raise that to 1.7 percent. Even tallness is a risk factor. (Nancy was just five foot three.) An analysis of data from the Million Women Study found that every four inches over five feet increased cancer risk by 16 percent. A clue to the mechanism may be found in Ecuadoran villagers with a kind of dwarfism called Laron syndrome. Because of a mutation involving their growth hormone receptors, the tallest men are four and a half feet and the women are six inches shorter. Life is not easy for them. The children are prone to infections and adults frequently die from alcoholism and fatal accidents. But they hardly ever get cancer or diabetes, even though they are often obese.

When you're healthy and cancer remains an abstraction, enumerating life's hazards can be reassuring. Neither of us were smokers, in whom cancer risk is measured not in small percentages but in factors of ten to twenty. A twentyfold greater chance of getting lung cancer—nothing sounded subtle about that. From all the public service announcements and scary warning labels, I assumed that a large proportion of smokers must die that way. It was surprising to learn that the figure is more like 1 in 8. With a statistic like that, so many details are washed over. Surely the odds are far worse for a lifetime chain-smoker. In search of an answer I came across the online Memorial Sloan-Kettering cancer prediction tool. I plugged in some numbers. A sixty-year-old man who had smoked a pack a day since he was fifteen and now plans to give up cigarettes will have a 5 percent chance of getting lung cancer in the next ten years—and a 7 percent chance if he doesn't quit. I thought the odds would be