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CHAPTER SIX

The Burden of Sickle Cells

AT SURGICAL PATHOLOGY CONFERENCES, cells are the focus, not patients. Lecturers project photomicrographs of tissue slides onto large screens so that everyone can see the magnified images of cells; it is part of the learning process to sit in the dark and witness unusual cellular features, patterns, dramas that illustrate the lecture. A trained eye can readily identify the rogues and heroes, the plot twists. Although these are stories about the mechanisms of human disease, they seldom explore the cages of human illness.

Purpose
subject

Nadler Spencer. 2001. The Language of Cells. Random House, N.Y.

In an effort to stay tuned to the larger implications of my surgical pathology practice, I attend clinical gatherings and listen to the findings of internists, surgeons, or pediatricians. At one such conference on sickle cell disease at the Hyatt Regency in Long Beach, California, I am surprised to see mothers of sickle cell children. Though I have never before seen patients' families at medical meetings, it seems to me a compassionate strategy. Aspiring to learn about the plight of sickle cell disease, I introduce myself to one of the mothers, Kim Holland, and her affected son, Comille Begnaud.

Comille suffers the pain of his disease about every second day, Kim tells me as we sit down to lunch and wait for our food. It is capricious pain and often intractable, usually arising in his chest, back, belly, or joints with varying intensity. On occasion, the pain can occur in his head, even his penis. Seemingly no part of him is spared.

"If the pain is mild, he gets that look on his face and his eyes drop real low," Kim says. "He stops playing Nintendo, or playing outside, and lays around the house. I ask him if he wants his pain medicine because I know how he's hurting, but he usually says no."

"Why don't you take your pain medicine, Comille?" I ask. He takes Motrin, or Tylenol with codeine if the pain becomes more severe.

Kim sits between us, so Comille leans in to her shoulder, talks to me across her chest. His rich chocolate eyes—the color of his skin—are enhanced by steel-rimmed glasses precariously perched on his tiny, upturned nose.

"I don't want to be a baby," he says.

"He's trying to learn to deal with the pain by himself, without medicine. So he lays down with a hot pad instead," Kim says. She has a pretty, angular face that contrasts with Comille's softer, broader features. "When the pain is severe and doesn't go away with the medicine, he comes crying to me. I know he can't take it anymore. He's grunting and he'll let out a yell." She is speaking faster now and louder as if it is her pain, too. But her cells have contributed only one defective gene to Comille's recessive disease; she has the sickle cell trait and remains pain-free. The other defective gene had to come from his long-absent father. "I panic because I know that he needs a morphine drip, that he has to go to the hospital. But he's calm as he cries. He tells me it's okay, he's just hurting. *He's* calm-

ing *me* down. I try to be strong for him and he's being strong for me."

"Women aren't strong. It's the men who are strong," Comille says. He is eight years old.

And pain is not the only leitmotif in this disease; disordered immunity allows seemingly harmless infections to fulminate. Comille has been hospitalized more than fifty times in his short life for pain or fever or both.

His outward appearance, like so many sicklers, is unremarkable; this makes it harder to garner sympathy and compounds his predicament. But the smile on his face is so ebullient that I am caught up in it, and I grapple for a way to help.

"Have you ever seen sickle cells?" I ask.

Kim and Comille look surprised.

"Under a microscope."

They shake their heads. "No."

"Come to my office sometime. I'll show them to you."

"Wow!" Comille says. "Can we go?"

Kim nods her approval. The thought of seeing the cause of Comille's illness has never occurred to them; nobody has ever suggested it.

Will the sight of his sickle cells brace him against his illness? I do not know. I can only show him these tiny aberrances in the best possible light.

OF ALL THE HUMAN CELLS I see, none is more pragmatic than the mature red blood cell. Pierce your finger with a sterile lancet and steer one oozing, sanguine drop onto a clean glass slide. Smear this precious grume thinly and evenly and, when it has dried, stain it with Wright-Giemsa. Place the slide on a microscope stage and behold an abundant uniformity of mature red blood cells. They are orange-colored disks, biconcave as Rolaids, as near and apart from one another as checkers on a board.

To purify their purpose, these cells discard their nuclei like unwanted tumors and stuff the newfound space with added hemoglobin. This pigment binds oxygen from the lungs and releases it to every vital body part. The binding and releasing of oxygen is the red cell's raison d'être; each cell travels some 700 miles in its 120-day life span, coursing the body's ubiquitous vascular network, discharging its vital element. Red cells travel easily; in larger arteries and veins where

they mass, they are carried in the course of plasma like fry teeming in a stream; in the narrowest capillaries, they readily deform to half their diameter and squeeze through single file. Pliancy enables these acrobatics, keeps the blood flowing. Sometimes I close my eyes and meditate: Aware of my breathing—feeling my breath come in . . . feeling my breath go out—I picture the billions of red cells percolating my system, and try to tune in to their harmony.

So perfectly adapted is the red blood cell and so vital its function that the smallest flaw can be destructive. A single point mutation in the hemoglobin molecule is responsible for Comille's pain. The normal hemoglobin A in each red cell is virtually replaced by an abnormal hemoglobin S in sickle cell disease. When red cells filled with hemoglobin S release their oxygen, hemoglobin polymers build slowly and stretch the cells like kites into the rigid, crescent shape of a sickle.

Within the asylum of small vessels, younger sickle cells and vessel-lining endothelial cells can run amok. Aided by biologic modifiers, they can wax adhesive, embrace in torrid intravascular tangos, and narrow vessel lumens. In larger vessels, lining cells are less inclined to take part in the dance. They burgeon as wallflowers, thicken vessel walls, and also narrow lumens. When older rigid sickle cells are trapped in these dwindling vascular spaces, the blood can clot.

And blood clot deprives distal tissues of oxygen. It is the fierce pain of this deprival that can squeeze the spleen, heart, bones, muscles, liver, and lungs like a vise until sickle cell patients howl.

I have looked at sickle cells in countless blood smears over the years and never once have I thought about the pain; it starts to enforce its limitations within months after birth, to propel its host through a guarded childhood into a wary adolescence. And the longer the host prevails, the more organ damage from oxygen deprivation he sustains, until organ failure or infection or both cause a premature demise. The average male lives only forty-two years, the average female forty-eight; if the fierce distractions of illness are subtracted from their lives, their allotted time is much less still.

Reynolds Price, in his affecting memoir, *A Whole New Life*, describes a postoperative bout as "one long fling at the end of a tether of pain." When I think about Comille's "long fling," how pain can rise inside him, I see his body as a fire and his sickle cells as hematologic arsonists. I imagine Comille's early

memories filled with pain, repeated and random intrusions that fire his cranial wires until they flare in the heat of it.

"COMILLE IS TEASED in class because he's so short," Kim tells me the following morning. We are standing in the hotel lobby drinking coffee, awaiting the start of the conference's second day. Comille's sickle cells have a reduced life span, and the chronic anemia that results can delay physical maturation, retard growth.

"Mickey Washington, the man that lives with me, makes Comille laugh at his shortness," Kim says. "He'll tell Comille to walk under the car and see if anything's leaking."

"I can ride free on the bus," Comille says. He is laughing as though he is part of the joke. "I can get into movies at half price."

There is something else he can do. Act. His shortness allows him to play a five-year-old, gives him an edge in the TV-commercial business. He has made a peanut butter commercial that airs next month on the Fox network. When the producer asked him if he wanted to work in commercials, he said, "Yep, I need a job."

But pain crises and infections do not allow Comille to live his life in an ordinary eight-year-old way; they obligate him to focus deeper. Some days, when this deep focus depresses him, he tells Mickey to "take good care of my mom." Such talk scares his mother. With Mickey, she tries to accede to Comille's great burden, help him cope with the flagrant unfairness of it. Most days Comille seems resolute; he can also be idealistic, infinitely practical. "I want to be a doctor when I grow up," he tells me. "I want to cure sickle cell disease."

MINE IS A RESEARCH-QUALITY German microscope made by Zeiss. It occupies the center of my desk and, truth be told, the center of my life. I fiddle gently with the coarse- and fine-adjustment knobs that sit like ears above its rectangular foot, run my fingers up the elegant curve of its arm to its flattened, mobile nose where finely ground lenses hang like walrus tusks. I hold the binocular body in my hands and search the eyes; in them, if I look deeply, I see malignancies that undermine their hosts, benignancies that whelm them with joy. My microscope and I are intimates; together, microcosms open to me with awe-

some clarity. I feel like a virtuoso exhorting sweet notes from a grand piano, or a stunt pilot at the helm of his aircraft, artfully furling contrails.

Today, to my right, sits my microscope's little sister, a Wesco monocular student microscope with ample resolution; it is Christmastime and I have purchased it for Comille. Before he arrives with Kim and Mickey, I place a slide of sickle cells on his microscope stage, set the pointer on a classic crescent.

"Apples and bananas," Comille shouts as he looks through the eyepiece of his new Wesco. He is looking through the high-power objective—a magnification of four hundred; his little hands deftly work the adjustment knobs, focus in on the shapes of his pain.

Mickey Washington, a gentle man, sits quietly in his wheelchair. A few years back, he unknowingly drove his car into a Hispanic gang's turf. The shooters never said a word; he was a black man and that was reason enough. A bullet pierced his spine at the fourth thoracic vertebra, made him a paraplegic. Kim sits by his side, holding two-year-old Kentrel, who is free of sickle cell disease.

"Suns and moons," Comille continues. He is excited as he sits at his new microscope, carefully taking the measure of the misshapen, miscreant red cells that so reduce the quality of his life.

"What do you say to Dr. Nadler, Comille?" Kim says.

"Thank you very much." Then he says, "What are the big cells?"

With the pointer I show him the different white cells: Lymphocytes have round purple nuclei and wear their skimpy cerulean cytoplasm like short skirts; they are responsible for immunity. Granulocytes have multilobated lilac nuclei and faint pink cytoplasm peppered with granules; they are the first lines of defense at the site of bacterial infections.

"It's the red cell bananas and crescent moons that cause your pain and infections," I say.

"Yeah. They look kinda weird. Wow!"

Perhaps he will visualize, in his own creative way, what his sickle cells can do to him. Can these flaws beget a positive purpose, a grace?

Now Kim sits at the Wesco; she, too, is excited to see the real thing. Then she tells me about her own paraplegia. While she and her four-year-old daughter (Comille's older sister) were walking to school in 1991, they were hit by a speeding car that had run a

red light. Her daughter was killed. Kim was left a paraplegic and remained that way for a year and a half until regaining her ability to walk. Comille was two years old when he lost his sister.

I am struck by the violence that shapes their lives. For Mickey and Kim the destruction is external, random, abrupt; for Comille it is internal, ongoing, Mendelian. Yet there is a cohesiveness that shapes this family, a pride they seem to acquire in one another's company. They handle the gravest vitiations in their lives with quiet confidence.

ABOUT ONE IN TEN Black Americans has the sickle cell trait and one in four hundred has sickle cell disease. People of Hispanic, Mediterranean, Indian, and Middle Eastern origin are also afflicted. The only cure for this disease to date is a bone marrow transplant. In theory, this procedure is a godsend; the patient's marrow is destroyed with drugs and replaced with that of a normal, genetically matched sibling. The sad reality is that genetically matched siblings are not available to most sicklers. And when a match *is* available, there may be a lack of financial or psychosocial support; at times, parents and doctors themselves refuse this treatment option, fearing that it is still too experimental, that the patient is not sick enough to take the transplant risk. A marrow transplant can fail despite a genetic match. The patient can die.

For Comille, marrow transplant from a sibling is not an option; he no longer has a sister whose marrow might be compatible. Kentrel is adopted.

GROWING UP IN CANADA, I thought the difference between blacks and whites was simply a matter of color. If one color seemed unnatural or inefficient, it was my own pink-white that produced insufficient melanin to protect me from the sun's ultraviolet rays; I would simply turn red and peel.

In training, when I first glimpsed black skin under the microscope, I readily saw protective granules of melanin pigment tucked into the basal layer of the epidermis. I subsequently saw the magnification of my own white skin; melanin granules were barely visible, and the pigment-synthesizing melanocytes seemed languid.

The number of melanocytes in human skin is relatively constant, irrespective of race; it is the amount of melanin these cells synthesize that largely deter-

mines skin color. Black is just like white, but with more of nature's sunshade dispersed in it.

In my practice I see, in skin biopsies, the endless variety of normal pigment scatter; it is my job to see beyond this pigment, to focus in on the real conundrums in the biopsy—inflammation, benign and malignant proliferations. This is what surgical pathologists do. It is only in the larger world where every eye can spot melanin disparities that such differences are intuited as larger differences.

And what of Comille? Most of the sickle cell patients at his clinic are black, the doctors white. Kim is aware that some of the black mothers distrust white doctors, but she is grateful for the care Comille gets. And she sees bigger issues—a lack of awareness of sickle cell disease, insufficient testing for it by hemoglobin electrophoresis, inadequate genetic counseling, and paltry fund-raising.

I receive the following e-mail:

Dear Dr Nadler

this is Comille. I will go to beauty and the beast tomorrow at 11 in the morning then I will go with my mom . . . to take some tests that Dr Groncy ordered. they wont hurt its just a lot. And I like having all my doctors. I dont care if they are black or white they are my friends and they love me like I love them. well I have to get off now because I am supposed to do my homework and study from 3–4 then I can play on the computer until 8 and then it's time to wind down (that's what my mom calls it) and then go to bed at 9. My mom says I have to keep a regular routine. ok I have to go before she gets back or she takes 30 minutes off my computer time. bye bye Dr Nadler I love you.

Comille

IT IS A CURIOUS THING that an organ configured so largely of nerve cells—the brain—itself is without nerve endings for pain. Within the sanctum of its vessels, sickle cell clots can deprive nerve cells of oxygen, painlessly ravage them. These attacks (strokes) can come on silently, without warning, as vague as the haze of a morphine drip.

Is Comille at risk for such a cataclysm? Psycho-

logical tests show a discrepancy between his high IQ and his reading, visual memory, and visual processing skills. Such disparities in a sickle cell child whose nervous system is otherwise intact suggest a narrowing of his cerebral arteries, possible early brain damage.

In the black-and-white images of magnetic resonance and ultrasound, the narrowed curlicues of his cerebral arteries are confirmed. Although his brain appears as yet undamaged, the diminished blood flow (and oxygen) it is receiving puts Comille at risk for a stroke.

It is possible to reverse these vascular changes, to reopen his lumens and resume a full blood flow. The solution is not simple.

THE PALE BLUE CURTAINS and linoleum in the day-care room at Long Beach Memorial Medical Center teem with multicolored polka dots, the white paper walls with pastel-colored fish. At the far end, an array of toys—building blocks, trains, trucks, puzzles, crayons, stencils, soldiers, Barbie dolls—is scattered about. Giant video games hug the wall. TV screens face downward from elevated brackets. It is the olive-green vinyl reclining chairs, spread uniformly across the floor, each with its own IV pole, that give the room its medical purpose: to infuse chemical agents into children with cancer, to transfuse blood into children with thalassemia and sickle cell disease.

Comille is the first patient to arrive. His short hair is done up in tiny twisters, his smile guarded. He will require a unit of packed red blood cells every three to four weeks of his life to markedly reduce his chance of a stroke. He has had occasional blood transfusions before when his hemoglobin got too low, and remembers how good the infusion of normal red cells and the elevation of his hemoglobin made him feel.

He climbs onto the first reclining chair with Kim and Mickey by his side. The nurse has difficulty sticking an IV catheter into a vein in his left hand. He is calm, his face inscrutable, his hand gilded with blood. The nurse apologizes, seems flustered as she cleans his skin and connects him to a packet of sodium chloride solution that hangs from the IV pole; it will flush his vein, keep it open to receive the foreign blood. She secures the catheter in place and supports his hand with a splint.

When the bloody poke is over, Comille climbs off the recliner and wheels his IV pole over to the toys. I tell Kim and Mickey of the mounting evidence

that repeated blood transfusions in sickle cell children with narrowed brain vessels may not only prevent a stroke, they may, in a small number of these kids, cause the narrowed brain vessels to appear reopened.

They nod. The clinicians have already informed them of these hopeful possibilities.

I am reluctant to tell them about the risks of repeated blood transfusions, the immunization to foreign red cell antigens, the iron overload in body tissues that can occur. As a surgical pathologist, it is not my place to discuss therapeutic complications. I try to draw the line between demonstrating the microscopic alterations of a disease—the apples and bananas of it—and clinical management. I hope the depictions themselves, the vivid red cell aberrances, will help mollify, for Comille, his disease's hard edge. Pain is more than a stimulus transmitted by nerves; it is a complex perception largely influenced by emotion. If the sources of his pain—sickle cells—can be perceived as positive images, perhaps he will feel more assured in his illness, less fearful, his pain more tolerable.

I have been so engrossed—a unit of cross-matched blood now hangs on Comille's IV pole and trickles through the catheter into his hand vein—that I have failed to notice the other children. Now I see six of them cheerfully interacting and moving about, each tethered to an IV pole, each receiving chemotherapy or a unit of blood. They are playing with the toys, eating their lunch—macaroni and cheese, ham sandwiches, potato chips, chocolate pudding—laughing, seemingly oblivious of their ongoing therapies. The day-care center has the feel of a giant pit stop on the road of life; refueling and maintenance checks are a necessary routine, a fragile ingenuity.

The hours go by and Comille remains in a Super Nintendo trance: Ever so slowly, normal blood seeps into his blood vessels, diluting the sickle cells, sufficiently elevating his hemoglobin to turn off the marrow's flow of new sickle cells. Sitting beside him as though tethered to his pole, I am awed by this stay of his illness, swept up in his new and congruous flow.

It is still uncertain how sickle cells bring about clotting, how vessels narrow, how chronic transfusions seem to reopen the narrowings. These murky complexities add mystery to the misery of sickle cell disease. And yet there is hope: In a decade's time, perhaps more, Comille will donate the stem cells of his marrow to genetic engineers; these cells will be grown in tissue culture, spliced with normal genes, and returned to him. Cured at last, his marrow inca-

pable of making new sickle cells, he will be given a hug and sent on his way.

In the meantime, Comille endures his disease. He dutifully gets his blood transfusions and lives his life as best he can. And we keep in touch.

I receive another e-mail:

Dear Dr. Nadler,

I got a lot of blood at the hospital and I didn't leave until late at night. The next day I was dizzy at school and got rushed to the hospital because the doctors thought I could have a stroke but I didn't. they kept me over night to watch me and I was scared because everything got really dark but I was strong for my mom. I can't wait for the Torch Run and I can't wait to run with you it will be fun. How is your wife and dogs please tell them I said hello and my mom says hello and Mickey too. well I will go now to Dr. Groncy's office for my checkup.

I love you Dr. Nadler. Your friend forever.

Comille

The old *Queen Mary* has been docked at Pier J in the port of Long Beach for twenty-eight years, functioning as a hotel and museum. Beneath its imposing bow is the newly completed Queen Mary Events Park, the sight of this year's Torch Run. I go with my wife, as I regularly do, to honor the valor of children with cancer and blood disorders, to help raise funds to defray medical expenses. It is a grassy park packed with children, parents, siblings, friends, dogs, all participants wearing the kelly-green Torch Run T-shirts. Each sick child, in turn, with torch in hand and parents and sponsors in tow, runs, walks, or rolls in a wheelchair a quarter lap around the track. It is a victory lap for all, and each winner is celebrated with loud kudos and the vigorous applause of spectators thronging the track. These are spiritual moments as kids get to momentarily forget their illnesses in a positive environment.

It is Comille's turn to carry the torch. He explodes from the starting line, the torch held high in his right hand. His little legs pump like pistons as the crowd cheers. He is soaring now, pushing his limits, bravely confronting misguided genes. I jog happily in his wake, his pride playing over me, and know that I will sponsor him until he is cured.