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SECOND OPINION
How does a doctor tell a gravely ill man that another doctor's advice may kill him?

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Alex Orkin, a thirty-eight-year- old physicist at a university in New York, was told by his doctor that he had less than six months to live unless he underwent a bone-marrow transplant. He called on me for a second opinion, and one cold day in February, 1994, he arrived at my office in Boston. He was a short, stocky man, with receding black hair, a broad nose, and darting eyes behind thick glasses. A couple of months earlier, at a faculty Christmas party, he had felt dizzy and nearly fainted. He had been exhausted for several months and assumed it was the long hours at work and the rigors of parenthood—he had two young children. But when a blood test revealed that he had severe anemia his doctor sent him to a specialist.

Dr. Frank Hochman, a senior hematologist at a medical center in New York, had performed an extensive evaluation of him. I'd met Frank at scientific meetings, and knew that he was a distinguished clinician and researcher, who led the marrow-transplant program at his hospital. (For reasons of confidentiality, I've changed names and identifying details.) He had found that Alex Orkin's marrow was largely depleted of cells, extensively scarred, and, evidently, incapable of producing sufficient blood. He had been unable to arrive at a definitive diagnosis, but he recommended that Orkin receive a bone-marrow transplant, despite the fact that no compatible donor had been found. It was an extremely aggressive and risky form of treatment; still, Hochman believed that not to pursue it would be even more dangerous. Orkin, a man whose training and temperament ill suited him to uncertainty, decided to get a second opinion.

Second opinions are common in cases like Orkin's, where the illness is serious and the diagnosis is uncertain. Orkin had a life-threatening condition, and the treatment he faced would itself be life-threatening. But seeking a second opinion can be awkward, for both the patient and the doctors. The patient sometimes worries that he will insult or alienate his primary doctor—that the doctor might abandon him out of pique. For the doctor who is being second-guessed, there is the issue of pride: a second opinion tacitly highlights your limits and your fallibility. And when you're the one giving the second opinion all these issues come to the fore. You're evaluating a patient, but you're also, inevitably and uncomfortably, evaluating a colleague.

Orkin had brought his medical files with him to Boston, and I looked through them. “Marrow failure state—myelodysplasia? aplastic anemia?” Hochman had written in his notes. He was uncertain why the marrow had failed, but myelodysplasia is a frequent cause. In myelodysplasia, damaged marrow cells appear distorted in size and shape. (“Dysplasia” is from the Greek for “distorted form,” and “myelo” refers to marrow.) The condition can be caused by toxic chemicals, drugs, or radiation, any of which can damage the cells’ DNA and so deform their appearance. In many cases, myelodysplasia evolves into acute leukemia. Aplastic anemia is a disorder in which the marrow appears nearly empty, with very few cells to be seen. (“Aplastic” is from the Greek for “without form.”) Patients with this condition seldom live long, because their marrow produces so little blood. Aplastic anemia can result from the same factors that produce myelodysplasia—chemicals, drugs, and radiation—and also from certain viruses and autoimmune diseases, such as lupus.

But which condition did Orkin have? The sparse numbers of marrow cells, Hochman wrote, could signal aplastic anemia; the changes in their appearance suggested myelodysplasia. There were too few cells in Hochman’s biopsy to analyze for DNA damage, which, if present, might have supported the latter diagnosis. Other tests were inconclusive.

Under Hochman’s care, Alex Orkin received transfusions of red blood cells to help treat his anemia and transfusions of platelets to prevent bleeding. A course of treatment with immunosuppressive drugs, which was sometimes effective in aplastic anemia, didn’t seem to help.

If a patient is less than forty years old and his or her marrow has failed because of myelodysplasia or aplastic anemia, a bone-marrow transplant is the best chance of a cure. But Alex Orkin had no related donors, and no good matches had turned up on the national registry of donors. So Dr. Hochman had recommended that he undergo an unmatched transplant. As in a standard transplant, all of the marrow cells would be destroyed by high doses of chemotherapy and radiation. Then a donor’s stem cells—cells that have the ability to form the various cellular components of blood—would be infused; they would repopulate the marrow cavity and start producing red cells, white cells, and platelets. Unfortunately, the white cells produced by an unmatched donor would perceive their host as foreign and start to attack Orkin’s own tissues. He could expect his liver and bowel and skin to be ravaged. Many patients die from the condition—known as graft-versus-host disease—and most of those who survive are permanently debilitated.

Heavy sheets of freezing rain began to fall as Alex Orkin and I reviewed his medical history. Orkin spoke in a dry, professorial tone, as if his way of dealing with his condition were to turn himself into a research paper. Still, when he told me of the six-month prognosis that Frank Hochman had given him, he clasped his hands tightly to arrest a growing tremor.

Alex Orkin was born in Brooklyn to a middle-class family. Nobody in his family had suffered from a blood disease. Orkin was a scientist, but the work he did was theoretical, not experimental, and he knew of no exposure to radiation or chemicals or pathogens that could have injured his marrow.

I recall him listing his risk factors in a detached, expressionless voice; he'd obviously gone through this several times before. "I don't use illicit drugs," he said. "I have no tolerance for alcohol. I never had a venereal disease. My wife, Sandra, and I met in college—she's an electrical engineer. I've been monogamous ever since."

Occasionally, autoimmune diseases, like lupus, can suppress the marrow. But Orkin had never had any signs of such a disease—arthritis, urinary problems, skin rashes, visual difficulties. He did have some low-back strain from lifting his children.

"You didn't take medications like Butazolidin for the strain, did you?" I asked. Butazolidin is a painkiller and anti-inflammatory that has been associated with aplastic anemia.

"Just Tylenol," he said.

Was he certain?

"Of course I'm certain," he said, gazing at me stonily. "I have a near-photographic memory." Then he handed me a computer printout he'd prepared for me. At the top of the page was "December 17, 1993," the date of the faculty Christmas party at which he first fell ill. Dr. Hochman's office address and telephone and fax numbers followed. Then there was a graph with three colored lines, one for red blood cells, one for white blood cells, and the third for platelets. It charted their levels over the weeks since the party.

Alex Orkin's physical examination, except for the pallor from his anemia, was normal. While he dressed, I took the slides of the bone-marrow biopsy done in New York to the microscope room next to the clinic.

I began the examination of the marrow biopsy under low magnification. Instead of a rich field of growing cells amid nourishing fat, which you see in healthy marrow, it looked like a desert landscape. Large, desolate tracts extended from the rough borders of bone. Several wide bridges of scar tissue crossed these tracts. I increased the magnification to search for signs of life, and slowly marched down the empty tracts. Finally, I found a few groups of immature marrow cells, clustered along deposits of fat, like bands of desperate nomads clinging to drying oases.

I wasn't quite sure what to make of what I saw—it didn't seem to fit with either diagnosis—and so I took the slides to Ned Waterman, the pathologist at my hospital who specialized in blood diseases. Waterman carefully studied the biopsy, shifting from low to high magnification, as I had done. Finally, he said, "It's not myelodysplasia and it's not aplastic anemia." He explained that the few marrow cells he'd found lacked the characteristic distortions of myelodysplasia, and he doubted it was aplastic anemia because of another feature he'd noticed. "Too many nests of marrow cells around the fat deposits," he said. "My best guess is that something outside the marrow's stem cells is suppressing this man's capacity to produce blood. Intrinsically, I believe his marrow cells may be healthy."

I walked slowly back to the hematology clinic, feeling unsettled. The diagnostic reasoning in New York had been complete, but there was a critical difference of opinion between Hochman and me, and it was based upon a subjective interpretation of the same marrow biopsy.

“I’ve reviewed your biopsy with Dr. Waterman,” I told Orkin. “We’re seeing marrow failure. But we don’t believe it shows myelodysplasia or aplastic anemia.”

“Believe?” he replied. “Or know?”

“Diagnostic tests like the bone-marrow biopsy are inexact,” I said. “They’re open to varying interpretations.”

This sort of uncertainty didn’t sit well with him, as I recall. “How inexact?” he pressed. “Is the test ‘open to interpretation’ on the order of one per cent or ten per cent or fifty per cent?”

Alex Orkin was a hard scientist. He solved problems using sharp, quantitative information. But here numbers weren’t easy to come by. “It’s difficult to say just how inexact,” I said, aware that the words sounded evasive. “So we look to other tests to refine the diagnosis. But those couldn’t be done, because you had a ‘dry tap.’” That is, when Hochman’s team drilled into Orkin’s pelvic bone they hadn’t been able to extract any fluid, or aspirate, which normally contains a whole range of marrow cells. “We should try again and repeat the aspirate.”

“There aren’t any other tests you can do?”

Waterman and I had discussed this question. Confirming his hypothesis would require special experiments—not something to be undertaken lightly. Such experiments are time-consuming and expensive, requiring researchers to divert their attention from ongoing work. All the same, we’d already decided to design a small study. As Orkin knew, the biology of bone-marrow growth was a major research focus in my laboratory; if we could collect enough cells, we’d try to grow them in a petri dish and experiment on them. “It’s a long shot, but it might give us insights we don’t have from standard tests.”

“I like that—an experiment,” Alex Orkin replied, his face brightening for the first time. And he asked how long it would take.

Cultures of marrow are usually assessed at twenty-one days. So, conservatively, we would have data in less than a month. I warned him, though, that research assays were even less exact than clinical tests.

“And in the meantime?”

“Continue the transfusions for your anemia and your low platelets. Your white count is low, and you’re at risk for major infection. I would begin injections of G-CSF. It’s a protein that might boost your white-blood-cell count.”

“That’s it?”

“For now, yes.”

Orkin pointed out that my recommendation contradicted Hochman’s. Hochman had scheduled Orkin for chemotherapy next week, to be followed by an unmatched transplant.

“A third opinion might be helpful,” I said.

Alex Orkin shook his head. Both Dr. Hochman and I were experts; he didn’t see the point in getting another subjective interpretation of the same data.

Then I brought up an issue that had been bothering me. “Even if we confirm one of Dr. Hochman’s diagnoses,” I said, “I disagree with the statement that you have less than six months to live. No one can say that, because of the inherent variability in how diseases behave. There is a distribution of outcomes of any illness. Most patients with a certain type of brain tumor live six to nine months. I’ve seen patients with it live more than two years. Sure, living two years is several standard deviations from the mean—some small percentage of cases. But it’s not zero. What’s false is to say that you have only some arbitrary time to live.”

Orkin looked away. He was a theoretical physicist, trained to view variability and inexactness as enemies. “It does make a difference to hear that,” he finally said. Then he asked me to explain the experiment I had in mind.

We would try to extract a sample of his marrow cells, isolate them from whatever poisons or antagonists might be present in his body, and see how those cells grew. If the stem cells themselves were healthy, then the most obvious culprit would be some component of his immune system: either specially targeted proteins, the so-called antibodies, or a type of white blood cell, the lymphocytes. We could investigate these possibilities by adding either his antibodies or his lymphocytes to cultures of growing marrow cells from a healthy donor. That way, we could get more evidence about whether antibodies or lymphocytes in his system were hostile to marrow cells.

Orkin smiled. He saw a checkerboard of possibilities, he said, with two variables in play, his antibodies and his lymphocytes. “How might growing my marrow show your interpretation to be incorrect—and Dr. Hochman’s to be right?” he asked.

“There’d be some evidence for that if your stem cells, freed in the culture dish from your immune cells and antibodies, still didn’t grow properly.” It wouldn’t be proof, of course; as I explained, there’d still be the possibility that an antibody was at work, one whose effects could not be diluted by the isolation procedure.

“So it’s inexact,” he observed. “Like most of medicine.”

I said I would show the biopsy to my colleagues and ask their opinion—a so-called "curbside consult." Then I'd call Dr. Hochman and discuss my thinking with him. I hoped there might be a meeting of the minds, that Frank Hochman would tell me of something I'd missed, or vice versa.

"Ready for another marrow biopsy?" I asked.

Alex Orkin lay on his abdomen. His head, turned to the side, rested on a thin pillow.

"First, the iodine," I said. Ialways narrate what I'm doing in these procedures. I applied the sterilizing solution to the posterior crest of his pelvis, which would be the entry point for the large-bore trocar. "I'm going to anesthetize the area with lidocaine, like at the dentist. It's a bee sting."

The needle was twenty-four-gauge, very thin, and drew only a single drop of blood. I raised a small mound under the skin, and then rubbed it so the anesthetic was dispersed into the tissue. I then inserted the needle deeper, all the while releasing anesthetic, until it hit the fibrous sheath covering the pelvis. I injected a large amount of lidocaine into the sheath.

"Let's wait a few minutes for the anesthetic to work," I said. "Tell me more about what you're currently working on."

Orkin told me that he was part of a team of physicists trying to increase the speed of computing. He worked on the theoretical side, creating models for the flow of electrons in a variety of microchip materials and designs, which other people would assemble and test.

"Any successes?" I asked.

"Some encouraging results, but still preliminary. I think we're on the right track, but it needs to be significantly better to be competitive, and we're far from that." He explained that he would prefer to work in purely theoretical physics, continuing his doctoral project on the behavior of subatomic particles. But he had to compromise. His current research topic was considered "hot," he said; he had to "follow the money" to be sure of support.

I took the trocar and placed a thin metal rod inside it. The rod would displace connective and fatty tissue as the knifelike tip of the trocar cut from the skin to the bone. I pressed downward and the bevelled edge of the trocar sliced straight through the flesh to the sheath of the bone. Alex Orkin did not move or cry out.

"Now I'm going to bore the trocar in and aspirate out the marrow. Women say the sensation is like menstrual cramps, a deep ache in the pelvis."

I pushed hard and felt a snap as the thick bone gave. I pushed farther, and, feeling no resistance, was sure that I was inside. I removed the inner rod of the trocar and attached a large syringe to the handle. I pulled on its plunger.

A trickle of viscous marrow slowly crept into the bottom of the syringe. I let the syringe's plunger down halfway, and then pulled upward again, maximizing the force of the vacuum. Fragments of the inner lattice of the bone marrow, called spicules, flew up into the syringe.

"We've got some good marrow," I said.

"I felt that," Orkin said wanly.

"Sorry. It's impossible to anesthetize inside the bone."

I reinserted the thin metal rod into the trocar and pushed still deeper into the cavity. Beads of perspiration trickled down Orkin's face onto the pillow. "We're almost done," I said. "Just the biopsy and then the trocar comes out."

"I now have more sympathy for menstrual cramps," he said.

I removed the rod and twisted the open trocar, feeling the inner lattice grate along the sharp edge of the instrument. I twisted again, and then quickly pulled the trocar out. Blood welled from the hole the instrument had made in Orkin's skin, and I quickly applied a pressure bandage.

"Take slow, deep breaths," I told Orkin. Sweat now streamed down his cheeks.

I teased out a core of marrow from inside the trocar. It looked like a calcified worm. This was the biopsy. Part of it would be placed in fixative, and the rest put in a sterile saline solution for special tests to be done by Ned Waterman.

Alex Orkin was still breathing hard. The procedure always hurts.

"I've had eight marrows done on myself," I told him.

"Into S & M?" he asked weakly.

"No, but when I was a research fellow in the lab we would aspirate marrow from each other for experiments. Now we pay donors."

"How much do they get?"

The going rate was seventy-five dollars, I told him.

"Times must be very hard in Boston," he said. "You couldn't get away so cheap in New York."

Three days later, Ned Waterman and I again sat at the microscope. Our conclusion was the same: it was marrow failure, but it didn't look like myelodysplasia or aplastic anemia. The DNA studies on the aspirated marrow cells would take more time. I called Hochman.

"Are you coming to the stem-cell meeting next week?" he asked. "I'd like to take you down the mountain with me." The year before, at a winter meeting on hematology research held at a ski resort, Hochman and I had shared a chairlift. When we reached the top, he challenged me to follow him down his favorite double-black-diamond expert trail. It was far beyond my abilities, and I went for an easier run.

"I think I'll keep living as a coward, with intact limbs," I replied. Then I told him about Ned Waterman's assessment of Alex Orkin's biopsy and our opinion of the case.

"We'll have to agree to disagree," Frank said, polite but firm. "The senior man down here is as accomplished a pathologist as any. I've followed this patient now for nearly two months. The longer we delay, the riskier it gets. Professor Orkin needs definitive treatment, and he needs it now."

I asked if there was any progress on identifying compatible donors.

"We're going ahead with an unmatched transplant," Hochman said.

My stomach tightened. "What about a trial of growth factors to boost his blood counts, as a temporizing measure?" I asked. G-CSF, the white-cell growth factor, and erythropoietin, a red-cell growth factor, might increase his marrow production.

"If it's aplastic anemia, they don't work," Hochman said, his tone cool. "And if it's myelodysplasia G-CSF may spark full-blown leukemia. This isn't the time for 'temporizing measures.' I know the risks here—an unmatched transplant might succeed one out of four or five times, maybe less. And he'll have some form of chronic graft-versus-host disease if he survives. But I've seen countless cases of severe marrow failure in my years of practice. It's a bad disease. A fatal disease. As I like to tell my trainees, desperate diseases require desperate measures."

As he spoke, I recalled something that an attending physician once told me during my medical-student days. I had been on the wards at Columbia Presbyterian Medical Center with Dr. Linda Lewis, a statuesque woman who was raised in rural West Virginia. One day on rounds, I presented a complex case to her. She repeated my physical examination and then suggested we retire to a conference room to discuss the patient. I admitted that I wasn't sure of the diagnosis. Dr. Lewis, who was among the most respected clinicians at the hospital, said she wasn't sure, either, and couldn't think of other tests likely to clarify the case. There was, she told me, an edict she abided by in situations like this: Don't just do something—stand there.

I chafed at the advice. It ran counter to my clinical training, which urged us to use the technologies we had at hand. Moreover, we understood that patients wanted us to act, that taking action in itself had a therapeutic effect. A passive doctor revealed his

ignorance and risked undermining his credibility in the eyes of patients and their families. It took a while before I saw the wisdom of Dr. Lewis's recommendation.

"Frank, I'm going to advise Professor Orkin to wait," I said.

There was silence on the line.

I had no solid evidence that Hochman's advice was wrong. But the risks seemed too great.

"I'm seeing the patient today," Hochman said icily. "And I'll urge him to do what's needed."

Alex Orkin telephoned me later that afternoon with a barrage of questions: How could there be such disagreement about the same biopsy? What would I estimate as the probability that my analysis was wrong—one per cent, ten per cent, fifty per cent? What if the experiments in my laboratory were inconclusive—would that change my opinion? What if they suggested an intrinsic problem in the marrow stem cells—would I then agree with Dr. Hochman that he proceed with an unmatched transplant?

Sandra Orkin was also on the line. She mainly listened, only occasionally adding a few words to extend her husband's questions.

I answered each of the questions as concretely as I could. In essence, though, there was one reply to them all: intuition can weigh as heavily as raw data in clinical judgment.

"But we have to go one way or the other," Alex Orkin said.

Once again, I suggested that he seek a third opinion.

"I don't see this as a tie-breaker vote," he said. "And Dr. Hochman would direct me to someone of his philosophy, and you might refer me to someone of yours."

I told the Orkins that Ned Waterman was going to send the marrow slides to other pathologists.

"That could take weeks," Sandra Orkin said. "And Dr. Hochman told us we had no time to wait."

"But, honey, he also said, again, that I had less than six months to live," her husband told her.

I didn't say anything.

"And today," Orkin went on, "when I asked him how he calculated this—specifically, in my case—he said, 'I know.' He said he was the professor of hematology, and patients like me who keep questioning his every statement can see his curriculum vitae. I don't

like statements like that. I am not going to accept his opinion as a fiat, based on his credentials or reputation. So I pushed him further, asking for a set of confidence limits around his estimate of my survival. He told me I was 'in denial.' I told Dr. Hochman I am painfully aware I have a life-threatening condition." Alex paused. "But then again I don't fully trust my thinking."

I waited several days for the Orkins' answer, and during that time the case stayed in the front of my mind. I kept trawling through Alex's medical history and tests, searching for some overlooked clue. I found nothing.

The call came late Friday morning. It was Sandra. "He's in the I.C.U.," she said.

I listened tensely.

"I brought him to the hospital just before midnight. He was delirious—ranting. I've never seen Alex confused before. It was awful."

Alex Orkin had a fever of a hundred and four degrees. Sandra said the doctors had diagnosed pneumonia; he'd been started on antibiotics, and was being given oxygen. "If he doesn't improve quickly, Dr. Hochman thinks he'll need a respirator."

For a patient in his condition, pneumonia was often fatal. Alex Orkin's white-blood-cell count was very low, his immune defenses minimal. Maybe I was the one who was in denial, heeding some cowardly inner voice saying, Wait, wait.

I reached Frank Hochman around noon. His voice had the hoarseness of someone who had spent a sleepless night. "The sepsis is high-grade," he told me. "We've got him on triple antibiotics."

I had little to say, except to ask to be kept informed.

"You call me," Hochman replied acidly. "My nurse is available to update you as needed." He added, "If we pull him through this, I'm going to push the Orkins hard to go immediately to transplant. It's madness to just sit and wait for the next catastrophe."

Alex Orkin was placed on a respirator at the end of that first day in the I.C.U. The pneumonia had blossomed in several lobes of his lung, and he wasn't able to sustain a satisfactory level of oxygen. Over the next week, his red-blood-cell and platelet counts plummeted, which is typical with systemic infection. He received several transfusions, but they hardly kept pace.

I called Dr. Hochman's office twice a day and spoke with his nurse, a pleasant older woman who knew what was happening to Orkin moment by moment. Eight days into the hospitalization, Frank Hochman paged me.

"We may lose him," he said. "We can't keep on top of the pneumonia."

“Should we try to boost his white cells with G-CSF? It may not work if it’s aplastic anemia, and ...”

“And trigger leukemia if it’s myelodysplasia.” Hochman finished my sentence.

“True. But the risk of triggering leukemia seems smaller than the risk of no white cells.” Frank Hochman was silent.

The risk of triggering leukemia, it seemed to me, was only theoretical. Sporadic cases of this had been reported, but they might have been accounted for by the natural evolution of myelodysplasia into acute leukemia. (As it happens, subsequent research has allayed the worry.)I wondered if Frank would be willing to change his mind. I had attended his presentations at hematology meetings, and he sometimes bristled at pointed questions. Finally, I said, “There’s really little we can lose right now.”

“O.K. I’ll start it. At a high dose. If it has any chance of working, it’ll be at a high dose. But if he develops acute leukemia it’s on your head.”

I remembered a case when I was a hematology-oncology fellow at U.C.L.A. in the late seventies. I was working at a clinic devoted to a particular variety of leukemia. An elderly farmhand who worked in the San Joaquin Valley was evaluated with low-grade fevers and skin nodules. I assumed that they were solid nests of leukemic cells within the skin, a common feature of the disorder, and didn’t send him to a dermatologist for a biopsy. After a few weeks of chemotherapy, he developed a raging fever. The nodules turned out to harbor an unusual fungus. We treated him with anti-fungal drugs, but it was too late. He died of the infection. It was one of the most painful experiences I’d had as a doctor. Colleagues assured me that the patient “would have died anyway”; the fungus was often fatal, even with prompt treatment. But I never forgave myself. There was no question of neglect in Alex Orkin’s case: he had been about as thoroughly examined as was medically possible. But Hochman’s words made me question myself. It’s on your head, he’d told me, and it was.

Later that day, I opened the incubator in my lab and retrieved a stack of petri dishes. It was only fifteen days since we had aspirated the marrow from Alex Orkin and obtained a comparative specimen from a healthy donor. But I was desperate for any bit of data on his disease.

Each petri dish was filled with agar, a straw-colored gel. I examined the dishes “blind,” meaning I didn’t know which were holding Alex’s cells and which the donor’s. The dishes were identified only by coded numbers.

The sharp light of the microscope diffused through the thick agar, casting a hazy glow like a corona and illuminating clusters of translucent marrow cells. I studied some twenty dishes, systematically counting the numbers of clustered cells by quadrants. I jotted these numbers in columns on a sheet of lab paper. Yigong Chen, a researcher in my lab who was an expert in the biology of marrow growth, independently counted each dish.

“No difference,” I concluded.

Chen agreed.

I returned the dishes to the incubator, and then removed a second stack. These, too, held marrow cells cultured in the agar matrix, but here Chen’s technician had added quantities of serum containing antibodies either from Alex Orkin or from the healthy donor. Again we counted the cultures blind. There were roughly the same numbers in each. The antibodies didn’t seem to make any difference.

I counted the third set of petri dishes, and then Chen did. In these, the technician had mixed the marrow cells with lymphocytes from Alex Orkin’s blood or from the donor’s.

Chen finished his cell count and turned to me excitedly. We’d both found that some of the dishes were nearly barren.

“Break the code now,” I said. In a special file, the content of each dish was listed, together with its identifying numbers. “I’m not waiting a full twenty-one days.”

We learned that the barren petri dishes were the ones where Alex Orkin’s lymphocytes had been mixed with his own marrow cells, or with the donor’s. Evidently, there were lymphocytes in Alex Orkin’s system that inhibited the growth of both his marrow and the marrow of the donor. I couldn’t rule out alternative explanations for what we’d seen, but at the very least we had reason to think that his stem cells might grow under the right conditions.

“There doesn’t seem to be a major intrinsic abnormality in Alex’s marrow cells,” I told Sandra over the phone later that day. “They can grow, given the right environment.”

“That gives me some hope,” she replied, but she sounded drained. “I just keep thinking he’s going to die, and I’ll be alone with the kids.”

For seven days, Alex Orkin’s pneumonia raged. Then the G-CSF began to take effect. The white count slowly climbed to the level needed to combat bacteria, and, over the ensuing week, the infection started to abate. Alex was gradually weaned off the respirator. After a month in the hospital, he had lost nearly thirty pounds and could not walk more than a few steps unassisted. Still, there was no sign of acute leukemia, and he was able to go home.

“I feel very strongly about continuing the G-CSF,” I told Hochman, “given what he just went through, and the fact that it had some effect.”

“We’ve been lucky so far,” he said. “I’m concerned that long-term treatment will exhaust his marrow.” His objection was that long-term G-CSF therapy, driving the fragile marrow stem cells to grow and mature into white blood cells, would deplete them. This

theory was widely aired when growth factors like G-CSF first came into use, and yet there was little evidence that such “marrow fatigue” occurred.

“We found several closer donor matches,” Hochman said, changing the subject.

“How close?”

“Three out of six.”

This meant that half of the genetic determinants were in accord. Transplant was still a high risk. “I’d give him more time,” I said. “I’m intrigued that his marrow cells grew so well in the lab, and that his counts improved on the G-CSF.”

“Honestly, I think you’re chasing rainbows,” Hochman said.

I telephoned the Orkins later that day. Sandra’s voice was tremulous. Alex’s pneumonia was a warning, Dr. Hochman had told her. “He says now is the time to go ahead with the transplant,”she said.

“But there is still no matched donor,” I cautioned.

“He says to just do it, with a partial match, three out of six.”
Alex had come near death and Sandra had been at his side. Now they were both panicked; they wanted to do something. “Let’s step back and look at some of the data,” I said. I mentioned the robust growth of his isolated marrow cells in my laboratory and the rise in his white cells on G-CSF. And, recently, the report that his aspirated marrow cells had no DNA abnormalities.

“Truthfully, we just don’t know what to do, whom to believe,” Sandra said in a quavering voice.

I heard from the Orkins later that week. “Dr. Hochman says I’m ‘diddling around,’ ” Alex said. “And he said there has to be one chef in the kitchen.”

I said that Hochman was right about that.

“But I didn’t like his reply when I asked again for his thinking about the wisdom of a transplant. He said that he has more experience with transplantation than you. When I reminded him that he had opposed the G-CSF, he answered that he still felt it was risky, that it might exhaust my marrow.”

I realized that I was hearing what Alex Orkin had heard, not necessarily what Frank Hochman had said, but it held a kernel of truth. Hochman was more experienced with transplantation than I. On the other hand, his very expertise might have been affecting his judgment, since we all tend to fall back on what we know best when giving advice.

“I’m going to wait on the transplant and follow your lead,” Alex Orkin said. “You are the chef in the kitchen. At least for now.”

“He’s going to die, you know,” Frank Hochman said gruffly. He was bitter about the Orkins’ decision. “They said they still wanted to see me, have him cared for through my office. But I find it difficult to attend to someone who rejects my advice.” Hochman was an eminent man in his field; he had saved many hundreds of lives. And, it was clear, he genuinely believed that his patient would die because I had dissuaded him from accepting the only course of treatment, however ravaging, that had a chance of extending his life.

I told Hochman that Alex Orkin would benefit from his expertise, that they had an established relationship. Finding a new doctor in New York would be disruptive. Besides, transplantation might emerge as the best option if a match was found.

We restarted the G-CSF to try to boost Alex Orkin’s white-cell production, and added erythropoietin to try to do the same for his red cells. Each Monday and Thursday, Alex Orkin sent me a fax. It summarized his current symptoms and his cumulative doses of G-CSF and erythropoietin; it also included an updated graph of his blood counts. They were inching upward. He was still tired, and napped in the afternoon, but was slowly beginning to regain his energy. He had regained some weight, though his appetite was still poor and he had to force himself to eat. I received regular reports from Frank Hochman’s office as well, including copies of the blood tests and physical examinations.

“I’d like to do another marrow biopsy, sometime early this fall,” I said to Orkin. That would be the most direct way to see how his marrow was recovering.

When I next saw him, it was a cool day in early October, a brisk wind testing the autumn leaves. The Harvard medical area was dense with traffic and pedestrians.

Alex Orkin sat in the first row of chairs in the clinic waiting area. He was reading a document. A thick sheaf of papers was on his lap. He didn’t look up until I greeted him by name.

“Oh, sorry,” he said. “It’s this new grant proposal I’m preparing.” He explained that it was on subatomic particles. He had decided to work on what really interested him. It might take several submissions for the application to be funded—if it ever would be. But he figured it was worth the effort.

In the examination room, Orkin undressed. His color was good; he’d lost the anemic pallor he had before. He had regained some more weight. His lungs had not fully healed, but there were no other abnormal findings on physical exam. I prepared to take the biopsy.

“I haven’t been looking forward to this,” he said.

Now it was easy to obtain an aspirate. The thick juice flowed readily into the syringe.

“Any inflation in the price of healthy donor marrow?” Alex Orkin asked as he dressed after the procedure.

“No. This is Boston, very conservative and set in its ways.”

Three days later, I sat in the pathology department with Ned Waterman as he surveyed the specimen under low power and then under high magnification. “Remarkable,” he said. The wide, desolate tracts we’d seen before were now filled with streams of developing blood cells. “There’s hardly even any scar left,” Waterman added.

I left Waterman and called the Orkins with the news. Sandra began to cry.

“How did you know the right thing to do?” Alex Orkin asked, his voice high with elation.

The point, of course, was that I didn’t know; Hochman and I were forced to make our decisions under conditions of uncertainty. This was medicine, not physics—it was a realm, often, of educated guesswork rather than arithmetical precision.

I still was not completely sanguine about Orkin’s prospects. He may have had a reaction to some unknown virus that suppressed his marrow. Perhaps, in the course of the past year, the reaction to the virus spontaneously subsided: if so, the virus might be dormant in his system, capable of reawakening one day and wreaking havoc. Another scenario was that his illness was an early sign of an autoimmune disease, like lupus. Perhaps Dr. Hochman’s initial immunosuppressive therapy had serendipitously contained the disease before it was fully manifest. It, too, could return. Orkin has remained healthy to this day, but the cause of his illness continues to be elusive. There is no way of knowing more until medical science has advanced. Orkin’s antibodies, lymphocytes, and stem cells are still stored in my laboratory. One day we might retrieve them and, using new tools, solve the mystery of his disease. But even then medicine would not be physics; human biology is too variable to be reduced to mathematical calculation. Intuition would still count, and so would luck.