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Carbon Fibers

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"What are you doing?" I asked.

"I'm showing you that people from Africa have one arm shorter than the other, it's from swinging on trees."

Strover had done a surgical rotation in England where he met an orthopaedist named David Jenkins. According to Strover, Jenkins had been in a bar in Singapore and happened to sit on a stool next to a man who had just sold carbon fibers to a company that used them to reinforce tennis rackets. The salesman had ruptured a knee ligament years earlier; as a consequence of that injury his knee would give way unexpectedly. Jenkins explained that it was a common problem for which there was no good solution; reconstructing the ligament using pieces of tendons or ligaments

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taken from other places in the body often gave poor results, and there were no artificial knee ligaments. At this point the salesman gave Jenkins some samples of carbon fibers and said, "You ought to try this."

Jenkins had used the carbon fibers in experiments with sheep and then with patients, leading to what he concluded were successful results. Strover told me that ruptured ligaments atrophy, and disappear from the joint, but that the carbon fibers induced growth of a new ligament in place of the original, as if the fiber bundle was a riverbed along which new tissue flowed.

After he had returned home from England, Strover went to a local supplier to buy carbon fibers, intending to cut sections to length and implant them in patients. Hourahane, who had a small plastics company in Johannesburg, had gone to the same supplier the same day, also to buy carbon fibers, which he used to reinforce the products he made.

Hourahane said to me, "The clerk told me he had just sold the last of his stock to a doctor from Wits who was going to implant them in people, so I went there to try to find him."

"Why?" I asked.

"Because I wanted to stop him from hurting somebody," he said. "Carbon fibers sold for industrial purposes can't be implanted in the body because they have a special chemical coating that's poisonous."

Hourahane had found Strover in time, and they began working together on Strover's project. Hourahane obtained carbon fibers that had never been coated, and fabricated them into artificial knee ligaments which Strover used to treat patients who had an unstable knee joint. Hourahane had designed and built special instruments to facilitate the surgery because ordinary instruments would have damaged the carbon fibers, and he invented devices to attach the fibers to bone.

Strover's patients did well, and other orthopaedists in South Africa and Australia began using the carbon-fiber implant, instruments, and fixation devices, which Hourahane made and sold. Strover said that Hourahane's system allowed a cruciate to be repaired successfully with a greater degree of reliability than was previously possible.

Hourahane had patented his inventions and wanted to gain access to the huge American market, but he had not received much help at the other U.S. orthopaedic departments that they had visited. Some orthopaedists were opposed to the idea of using artificial materials to repair ligaments.

Others had committed to one of the companies that was already trying to bring an artificial ligament implant to market. Someone had suggested to Strover and Hourahane that they visit Jim Albright, who had recently published a book entitled *The Scientific Basis of Orthopaedic Surgery* and who had a national reputation as an innovative man and a lover of research.

During their visit Jim learned about the clinical results and became interested in the project. I initially had no interest, but my attitude changed when I saw Jim's reaction, and I offered to help in any way I could. I hoped to give back something to the man who had given me so much, and perhaps even to earn a profit.

Jim and I went to South Africa to see first-hand what had been accomplished. In Johannesburg we saw Strover implant carbon fibers in the knee of a man who had been injured in an automobile accident. It was deft surgery, done in a fraction of the time normally needed when such injuries were repaired using tendons taken from some other area of the patient's body. At Baragwanath Hospital in Soweto a surgeon told me that his carbon-fiber patients were able to walk the day following surgery. In Pretoria I met Hourahane's biggest customer, an Afrikaner orthopaedic surgeon who told me that before he had started using carbon fibers he had never been able to successfully repair anterior cruciate injuries. At a hospital for gold miners in the Transvaal I visited an orthopaedist who had been especially meticulous when implanting the carbon fibers, and his results were the best of all – although, of course, not perfect.

Hourahane proposed that we go into the business of making and selling the carbon-fiber implant system in the United States, and Jim and I agreed. I incorporated our new company in Louisiana and became its president, with the major duty of doing what was necessary to obtain a license to sell the implant. Hourahane agreed to wire me the money I would need.

I went to the Food and Drug Administration in Washington, D.C., to learn exactly what was required for the license. When I entered the building I saw a huge room filled with desks piled high with stacks of paper; people swirled around like smoke in a wind tunnel. Someone directed me to a conference room and told me to wait there. The room was drab, almost depressing. Most of the formica on the edge of the table was missing, and there was a half-inch step between the halves. Ripples in the rug ran at right angles to a path that had been worn by the traffic in countless previous meetings. I sat in the least comfortable chair, no two of which

were alike, directly opposite a picture of President Bush. After a while a dark-skinned man with a repellent body odor entered the room, along with three other people.

"I am Nirmal Mishra," he said. "I am in charge of applications for artificial ligaments, these people are on my team. How can I help you?"

"I would like to sell a carbon-fiber knee implant," I said. "What do I have to do to get a license?"

"Give us evidence that your device will be safe and effective," he replied.

"What kind of evidence?"

"You must prove that it is strong. You need to do animal studies. Then you must prove that it works in people and doesn't have any side effects."

"I'm unclear about exactly what I need to provide. For example, I can put the carbon fibers in a machine and measure how much force it takes to break them. Is that what you mean about proving strength?"

"Yes, that would help, but you should do other studies as well."

"What studies?"

"Studies that show how strong it will be."

I began to feel uneasy. "How strong does it have to be?" I asked.

"Strong enough so that it will be safe and effective," he replied in an impatient tone.

"Suppose it took a hundred pounds to break the carbon fibers, would that be strong enough?" I asked.

"The situation can't be oversimplified. The device must be strong enough that it won't ever break, however strong that is, well, that's your answer, that's the number you want."

He seemed annoyed, so I lied and said, "I think I understand what needs to be done."

I began to tell him about what I thought was important data from over three hundred patients in South Africa who had received carbon fibers and had generally done well. But as I was speaking he started shaking his head from side to side.

"We can't rely on the opinions of surgeons, they often don't admit bad results. You will need to do a clinical study in the United States, according to our specifications," he said.

He gave me a booklet entitled *Guidance Document for the Preparation of Investigational Device Exemptions and Pre-Market Approval Applications for Inter-*

Articular Prosthetic Knee Ligament Devices and said, "Follow this." Then he rose from his seat, and the people on his team immediately shot up as if they were connected to him by springs. He walked toward the door, and when he reached it he turned and said, "You need to continue this dialogue with us so that we can tell you what we expect;" I quickly agreed to do so.

As soon as I returned home I planned a study in which the anterior cruciate ligament in the knee joint of goats would be cut out and replaced with carbon fibers. When I called Mishra's expert in charge of animal studies to obtain his approval I told him, "We will assess the quality and strength of the new tissue that grows."

He was a friendly young man who had just graduated from college. "That sounds reasonable," he replied.

"How long should I let the goats live before I kill them and test the ligaments?" I inquired. He asked for my opinion, so I told him that I thought three months was long enough, and he agreed.

"I expect to have some problems because no one else has ever done the kind of surgery we are planning, but in most cases we anticipate that the implant will hold up well," I said. "Realistically, that's all that could be expected."

"Yes," he said.

When the experiment was over I reported the results, but this time the young man was less realistic. He flipped through the pages of data and said, "Two goats didn't do well."

"Yes, but that's more or less what you would expect."

"Nevertheless, the fact that some goats can get bad results indicates that the device can be risky."

I thought about telling him there are always risks, but I said nothing for fear that I might give offense.

The strange mechanical properties of carbon fibers intrigued me. They were stronger than steel when pulled at each end, but broke easily if bent at an acute angle. Their apparent ability to grow a new ligament seemed marvelous, and I took it as my goal to understand this process. I hoped that moving the subject of artificial ligaments from the realm of speculation and anecdote into the realm of science would relieve Mishra's anxiety about granting me a license, so I did many experiments on rabbits, mice, and rats. During that time I also did experiments that Mishra had insisted upon, though I saw no merit in them.

One day the secret of how the carbon fibers worked became apparent to me. I discovered that the tissue which grew around the fibers didn't actually stick to them, but rather that each fiber could slip out of its tube of tissue as if the fiber had been coated with grease. The reason the carbon fibers strengthened an injured ligament was that the new tissue that grew around them joined the ligament's original tissue and insertion points on the femur and the tibia, thereby reinforcing the injured ligament. Each implant contained forty thousand carbon fibers, so there were forty thousand tubes of tissue that grew to strengthen the injury site, many times more than grew in response to the artificial materials being developed by competitors who were using other materials. The strength of the carbon fibers was not what mattered, but rather the strength of the new tissue. Moreover, most materials could spontaneously trigger an attack by the immune system but carbon never did, so carbon fibers were twice blessed.

My good feelings about the knowledge I had gained were tempered by discouragement about the time and money wasted in performing all the experiments Mishra had required. Had he and his team left me alone, I could have gained my understanding more quickly and inexpensively; their suggestions and opinions – really commands – were rarely useful. He called those on his team "scientists" – they weren't, but that didn't stop them from giving me rote advice concerning how experiments should be performed, like medieval monks braying out memorized psalms they don't understand. Mishra himself often preached to me about "risk." One time he sweated for an hour and stunk up the place even more than usual, but succeeded only in showing that nobody could objectively define "risk," although of course he thought he had done it. Nevertheless I always did as I was told by Mishra. I hated the way my desire for the license made me act. It was as if I were limp, like my carbon fibers.

After many delays, Mishra finally approved my plan for a clinical study to determine whether carbon fibers were safe and effective for repairing the anterior and posterior cruciate ligaments in the knees of humans. The plan had to conform to his *Guidance Document,* so there was much in the plan that had little to do with science but rather was intended to generate interlocking patterns of data that would make it difficult to fabricate data favorable to my interests which, it seemed, the FDA assumed any company trying to obtain approval for a device would do.

The clinical data I collected on each of the patients who took part in

my study was supposed to come together to support Mishra's judgment regarding the issuance of a license, but I didn't understand quite how, which put me in the position of a man searching for something but having no way of knowing whether what he found was what he was looking for.

"How will you know from the data I collect whether the implant is safe and effective?"

"I'll know when I see the data," he replied.

During the next year I collected thousands of pieces of information about each study patient, some of whom received carbon fibers and others of whom received conventional ligament reconstruction with tendons harvested by the surgeon from elsewhere in the body. I had to hire bookkeepers to keep track of the data, and I struggled constantly with the orthopaedic surgeons who performed the periodic follow-up examinations on each patient, which I needed in order to evaluate whether the carbon-fiber treatment was successful. They resented the length and prolixity of the follow-up form Mishra had required, and often omitted data they thought meaningless but Mishra considered important. His term for each blank line was "protocol violation," and he construed every such instance as evidence against the idea that the implant was safe and effective.

As the study went on I saw things that could have been done differently and likely would have helped the patients, but Mishra denied me permission to make any changes in the experimental procedure he had approved at the inception of my study. He too learned of things that could have helped the patients in my study, knowledge he obtained from studies being done by my competitors, but he refused to share it with me because, he said, it was against the policy of the FDA to require competitors to share scientific data. "Why should they pay for information for you to use in your business?"

While I was performing my study, which was taking place at my institution in Shreveport, Brooke Army Base in San Antonio, and the University of Iowa in Ames, Hourahane continued to sell carbon fibers to orthopaedic surgeons in South Africa, Australia, Canada, Israel, and Europe, which he was free to do because the system in those countries placed primary responsibility for the choice of medical treatment on the doctor and his patient, not the government. Many hundreds of patients received Hourahane's carbon fibers with generally good results, at least in the opinions of the surgeons and the patients.

As the implant became progressively more popular, Hourahane began

receiving phone calls from veterinary surgeons who expressed an interest in using carbon fibers. The application he judged to be most promising involved the treatment of lameness in racehorses. Although the topic had been far from my mind, I learned that when one of the large tendons in the horse's leg stretched too much, the result could be swelling that deformed the leg into a backward-pointing bow. Then the horse couldn't walk, much less run.

I asked how he planned to repair the horses' injuries.

"I remembered that a young man in Louisiana discovered that no bonding took place between carbon fibers and tissue, and that the tissue that formed along the carbon fibers was aligned by them. I'll make a pointed cannula that can enter the tendon through a quarter-inch incision and then pass up to the top of the tendon. The vet will be able to pass the carbon fibers through the injury site by means of the cannula."

South African veterinarians implanted carbon fibers in more than fifty racehorses and show jumpers, and many of the horses returned to competition. I then performed two studies in the United States in which veterinary surgeons implanted carbon fibers in bowed tendons of thoroughbred racehorses, and did standard therapy in another group of injured horses – more than 100 horses in all. The results showed that use of carbon fibers was an effective treatment; I published a report about the experiment in the *Journal of Equine Veterinary Science.*

Meanwhile, the other companies that were trying to develop a ligament implant avoided all basic science research, and did only the experiments Mishra told them to do – or at least what they thought he had told them. One by one, the companies received an education at the public meeting the law required prior to a licensing decision. That's when each company learned its path had been only a big circle.

The first presentation was made by a company whose implant was made of polyethylene. After the company had presented results involving mechanical tests of its implant, a panel of experts Mishra had appointed to the FDA's review panel told the company's president, "We think the device is not strong enough."

"Compared with what?" he asked.

"Compared with a normal ligament," he was told.

"But that's not what we are trying to do. The patients we operated on had no ligament left. We were only trying to improve the patient's condi-

tion, not return him to mint condition. We don't know enough yet about how to make a device that's as strong as the original ligament. We have to take this a step at a time."

"I think you should make a better device and then do more studies," the panel chairman replied.

At the same meeting, other companies requested approval for their devices. One company described a tongue depressor, which was said to be an improvement over present models on the market because it was thinner and shorter, making it more suitable for depressing the tongues of children. Another company described an adhesive bandage that was said to result in less pain upon removal from the patient. Both devices were approved by the panel.

The last presenter that day described an implantable total-knee prosthesis, and illustrated its use with graphic slides that showed it being placed in a patient in France, where it had been developed. The surgeon cut off the knobby ends of the femur and tibia, and replaced them with devices made of titanium and polyethylene, which were attached to the bone with a special glue. The presenter then said, "We request approval of our implant because it is substantially equivalent to an implant that was legally sold in the United States prior to May, 1976," and the panel quickly approved the application. At that time I did not understand why manufacturers of such lowly devices as tongue depressors and band-aids were striving to improve their product, yet the manufacturer of a device whose use requires major surgery would go to great lengths to emphasize that his product was no different than one that had been marketed for a long time.

Six months later, a company that had developed an artificial ligament made from the tendons of pigs presented its invention to the panel. After a spokesman had finished explaining the company's animal and human studies, the panel chairman told the company president that patients might eventually reject the implant because it was foreign tissue.

"We treated the implant to reduce that possibility," the spokesman told the panel, "and we have not had any instances of bad reactions in patients."

"Have you looked inside the knees of these patients to see what is going on?" a panel member asked.

"Of course not," the president said. "We couldn't justify operating on a patient who had no problem simply to see what the ligament looks like."

The panel told him that using animal tissue was a bad idea because it might activate the immune system.

"Why didn't you tell us that when we started?" the company president asked. "Why did you wait until we had worked for three years and spent $5 million?"

He might just as well have saved his breath because the panel ignored him. Why Mishra had assembled such a panel of fools had not yet become apparent to me.

Other companies at that meeting who were seeking approval for their devices fared much better. In short order, the panel approved a new design for a hospital bed that had larger wheels, making it easier for the nurses to move, and a new formulation of plaster of paris that hardened into casts 20% faster. The sponsoring companies assured the panel that there were no risks associated with their products as long as they were used according to label instructions. The panel then approved a total hip consisting of a cobalt chrome stem designed to be hammered down into the bone's canal after it had been exposed by cutting off the top part of the bone, and an articulating ceramic component that was attached to the pelvis. Again, a company spokesman told the panel that the hip was "substantially equivalent to a device that had been marketed prior to the enactment of the device law." By then I'd learned the reason for that formula. Scientific evidence of safety and efficacy was not needed because any implant on the market before the 1976 device law had been deemed to be safe, like BHT. Consequently, for the sake of consistency, a new implant that was exactly like one of the old implants also had to be deemed safe.

Several months later the device panel held another meeting. The first presenter was a company seeking a license to sell a Teflon ligament. The panel chairman told the spokesmen for the company that small particles could flake off the device and cause an inflamed and painful knee.

"That's why some of the patients in your study did poorly," he asserted.

"Some patients in every surgical series do poorly," the company representative replied. "That alone is no reason to deny us a license." But that's what the panel did.

The last presenter in the morning session asked the panel to approve a total knee implant. Hoping to gain an advantage in the marketplace, the company had advertised in trade journals that an innovative porous coating on the surface of the implant would encourage bony ingrowth, leading to

a longer-lasting implant. A controversy ensued when some panel members expressed the opinion that the coating was technologically impossible in 1976, and therefore the FDA should not deem the implant to be safe. In the end, the company convinced the panel that the claim had been made by its marketing department, and shouldn't be taken seriously. The company got its approval without needing to run the FDA gauntlet I was running and that any manufacturer of a new implant is forced to run. None had ever survived, but I hoped I would be the first.

While sitting in the audience I met people from various companies that hoped to someday obtain a license for their products. A young woman from a start-up company in Phoenix told me about a device she had invented that was powered by a watch battery and produced a tiny EMF that made fractures heal twice as fast as normal. She had gone deeply into the biology of bone healing and learned that the EMF did not alter the amount of proliferation of the stem cells of bone caused by the injury, but rather increased the rate at which they differentiated into the kind of cells that actually build bone. She showed me a report entitled "A new theory of the biology of bone healing." Across the title page Mishra had written "Not recognized," which he underlined twice. The opinion of others at that meeting who also heard her story was that it was madness to present novel scientific results to the FDA.

Of all the companies trying to get a license to sell ligaments, Hexcel Medical was the most aggressive. Its product was also made from carbon fibers, and the company kept trying to pin down Mishra regarding exactly what evidence would convince him they were safe and effective. Somebody from the company visited or called Mishra every day but, according to what I was told, he never allowed himself to be trapped into giving an answer.

Thinking to strengthen its position in its dealing with Mishra, Hexcel hired David Jenkins as one of its experts. He had learned about the toxic coating on carbon fibers that were sold for ordinary purposes such as reinforcing tennis rackets, and he attempted to remove it with a solvent. Unfortunately, he had not rinsed the carbon fibers well enough to remove all of the solvent which, it turned out, was more toxic than the coating. Some of Jenkins's patients developed chronic inflammation due to the solvent residue, and their fate came to light in a paper published by a surgeon named Dandy who had examined Jenkins' patients. To prove his point, Dandy himself implanted carbon fibers that contained solvent residue; unsurpris-

ingly, his patients developed chronic inflammation.

At the FDA meeting where Hexcel presented its scientific evidence, the panel chairman asked where the data was that showed chronic inflammation in the patients in the study. But Hexcel, like me, had obtained pure carbon fibers, thereby obviating the error committed by Jenkins and then aped by Dandy in the so-called interests of science. Nevertheless the panel accused the company of hiding data that showed bad results, and Hexcel was denied a license.

I avoided the mistakes in judgment and the errors in science I perceived in the way Hexcel had gone about its effort to obtain a license. I had discovered the biological basis of the action of carbon fibers implanted in the body, and I had proved that they could be used successfully in animals. Hexcel Medical had done neither. My system for implanting carbon fibers included specialized surgical tools for grasping the carbon fibers and threading them through the joint, and specialized devices for attaching the implant at each end to bone. Hexcel lacked these instruments; consequently the surgeon often broke some of the carbon fibers when he grasped them with ordinary surgical forceps or routed them over the sharp edge of an unchamfered bone hole. Hexcel had no means of attaching the carbon fibers to bone, so the surgeons had attached them to soft tissue using sutures, which often resulted in a fatally weak repair. Worst of all was the design of the clinical study. Carbon fibers were used to repair an instability anywhere in the body, from the foot to the shoulder, and without any control group. My study, in contrast, specified that only ligaments in the knee would be repaired using carbon fibers, and I had included a control group consisting of patients who received standard surgical treatment. Thus the ability of my clinical study to reveal whether carbon fibers were effective was focused on a single problem, not diffused across many different problems. It was the first controlled study in the history of orthopaedic implants.

When I reached the point where I had a year of follow-up data on the last of the 145 patients in my study, I evaluated the data and I saw that I had proved my point. I went to Washington to show my results to Mishra. We met in the same drab conference room, but the contrast between my surroundings and how I felt inside couldn't have been more dramatic. I thought I had reached my goal, and that my rewards would soon be coming. When he entered we exchanged greetings, and then I told him of my intentions.

"I am ready to make my formal application, I have all the requisite evidence."

"I think longer follow-up is needed to insure that carbon fibers are safe and effective," he replied.

When I heard those words I started to see flashes of red and blue light. I could see that he was continuing to speak, but I couldn't hear anything. Then I couldn't see him, or feel anything, as if gravity had ceased and I were floating in space. After a while, how long I didn't know, I could feel the uncomfortableness of the chair, and I recovered sufficiently to blurt out, "But you said one year's follow-up would be enough. I have it in writing."

"Well, the state of the art changes. We now know that implants which look good after one year may not be good after two years. The health of the public is at stake here. We must be certain."

"You said one year's follow-up would be enough," I said again. "I have it in writing."

"I make the rules, Dr. Marino," he said, "and I can change the rules."

Obtaining the follow-up data had always been difficult and expensive, but now it became a nightmare. Some of the patients had been athletes at the University of Iowa; after graduation they moved all over the country, making it difficult to locate them and arrange for a physical examination by an orthopaedic surgeon where they lived. The situation was even worse with the servicemen who had been stationed at Brooke Army Base in Texas when they entered the study. The patients at my institution frequently failed to return for the yearly examination because they felt well and saw no need to take the trouble to do so. Some patients at all three locations sensed our desperation to obtain the follow-up information, and demanded to be paid large sums of money for allowing themselves to be examined.

Hourahane finally reached the point where he could no longer supply money to maintain the study. So I told Mishra that I would make a formal application for a license, as I had the right to do under the law.

"Why don't you put together all your data and present it to me informally, and we'll take it from there," he replied.

The meeting with Mishra and his team took place in the same room as our other meetings.

"Well, what do you have?" he asked, and I began at the beginning.

"My first animal experiments were on mice. We wanted to show that carbon fibers were well tolerated, so we implanted them in muscle and fat,

and near nerves, and we found that the fibers were well tolerated by all the tissues."

"How long were they implanted?" he asked.

"Three months," I replied.

"Suppose you left them in longer. What would have happened?"

"Probably nothing, but I don't know because that's not what I did."

"So you don't know if there would have been problems."

"I had no reason to implant them for longer than 3 months."

"Safety is a paramount concern. It's your responsibility to answer all the questions."

"What questions?" I asked.

"My questions."

I continued. "In rabbits, we removed the Achilles tendon and replaced it with carbon fibers; nylon was the control. We discovered that the amount of new tissue that grew depended on the surface area of the material. Carbon fibers have several hundred times the surface area of nylon, so they produce several hundred times more tissue. The additional tissue added strength to the injury site. That is our rationale for carbon fibers."

He rocked back in his chair and looked up at the ceiling. Through his usual frozen smile he said, "It was an interesting experiment, but what does it prove as far as safety is concerned?"

Before I could reply he said, "What else do you have?"

"In goats we took out the ligament and replaced it with carbon fibers."

"Was the result as strong as the original ligament?" he asked.

"Of course not," I said. "The purpose of the study was …." He interrupted, "Well, that's what people will expect."

"Well, we'll just tell them the truth," I said, but he waved me off saying, "They won't listen. What else?"

"We thought that carbon fibers would work in injured tendons, and we proved it in racehorses."

"That kind of a study has to be evaluated by veterinarians," he said.

I told him it was, and that it was published in their journal. He nodded, pursed his lips, and asked a question he surely knew I could not answer, "Were there any carbon particles in the lymph nodes?"

"I don't know. We didn't look. The horses didn't belong to me. They were very expensive animals, and their owners wouldn't let me operate on them just to remove tissue. I did examine the lymph nodes in other animals."

"But not in the horses, right?"

"Right," I said.

"What did the human studies show?" he asked.

"By any reasonable interpretation of the data, the patients who received the carbon fibers did better than the control surgery," I replied.

"What about side-effects?" he asked.

"The number of infections and complications was the same in the carbon-fiber and control groups."

"What about the strength of the carbon fibers. If you pull on them, how much force does it take to break them?" he asked.

"About 100 pounds," I replied.

"The average strength of the cruciate ligaments is 500 pounds, so the fibers are much weaker than normal tissue," he said.

"That's comparing apples and oranges. The original ligament is gone, so the strength of what remains is zero. We shouldn't make the perfect the enemy of the good."

"How much strength do you get eventually?"

"I can't possibly answer such a question unless I remove the new ligament from the patient and test it."

"How about the animal studies?" he asked, and I gave the only answer that was possible. "Animal studies can't be done to answer that kind of a question because people and animals are different."

"What scientific basis is there for the hypothesis that the ingrowth of tissues bears a load or has any strength to it? What's the basis for that hypothesis?"

I plowed the same ground again, telling him, "We showed that new connective tissue grew in animals. We showed that it added mechanical strength and that it led to improved function, as evaluated on the basis of the ability of racehorses to return to racing. Then we did the clinical study. The results couldn't have been as good as they were unless there was new tissue."

"You have not given us any scientific data to show that in fact there's any tensile strength to that stuff that grows in. Sure, fibrous tissue grew, but what's the strength of it?" he asked, even though he knew exactly what my answer would be.

"I can't answer all that," I said.

"Well, my question is pertinent," he said, "because you're saying that

you put carbon fibers in there and suddenly tissue grows in, and I'm saying, where is the proof?"

He paused for a moment and then said, "It's too bad, because you've got independent ideas of your own, I almost envy you. Nevertheless, carbon fibers cannot be accepted by the Food and Drug Administration because such an implant might lead to harm. The review process must be very conservative. Everything must be understood in that light."

"What light?" I asked.

"Any device licensed by the Food and Drug Administration must be free of all risk. Risk leads to harm, and that leads to disrespect for the Food and Drug Administration."

That was such a shocking thing to say I could not believe my ears.

"It is impossible to make a device that has no risk," I said, and after I caught my breath I continued, "Besides, that's not what the law says. It does not say 'possible risks,' it says 'probable risks.' And even if there are probable risks, the law says that I'm still entitled to a license if the probable risks are balanced out by the probable benefits."

"And those are exactly the judgments I shall make," he said, "so that we have happy people." When he said that he motioned for his team to leave the room, so only he, I, and the secretary I had brought to take notes remained.

"Do you know what it takes to make people happy?" I asked.

"Eight hours' work not doing anything very arduous, then beer and television. Then they're happy. They really don't need anything more. What could they ask for?"

"They might ask a doctor to fix whatever ails them," I replied.

"Technically, I suppose, those kinds of problems could be fixed. But would the people be any happier? I don't think so. That experiment was tried. We gave them artificial hips and knees, and what was the result? They began to complain about other problems, and to demand that doctors do even more. My files are stuffed with applications for devices that their proponents claim will do wonderful things. Thousands of such applications. There's not a part of the body that someone hasn't proposed replacing with something made of plastic, metal, or some new space-age material."

"Why don't you license the devices?" I said. "Then we could see if they perform as advertised."

"For the sake of the people themselves," he replied. "It would be sheer cruelty to fix one problem because there will always be another, without

end. We have to think about the stability of society."

"What do implants have to do with the stability of society? What do you mean?"

"Devices create instability by fostering the craving for more and more scientific advances. To do what? To defeat aging and death, which is ultimately impossible. Implants like yours are a menace to the stability of society, so the science that breeds them must be kept chained and muzzled."

As I sat there, too stunned to say anything, he launched a long soliloquy after which he abruptly left the room. I had heard this speech somewhere else. I couldn't remember where, but in my mind I could fill in the argument as I heard it from Mishra.

"People," Mishra said, "had a strange idea about scientific progress. They imagined that it could go on indefinitely, regardless of everything else, as if scientific knowledge were the highest good and truth the supreme value. But ideas began to change and the emphasis shifted to universal comfort, which can keep the wheels turning steadily; truth can't do that. What the masses really wanted was comfort, not scientific knowledge. In spite of that, unrestricted medical research still continued. Big business went right on talking about scientific knowledge as if that was what they sought, but in reality it was only profit which the corporations achieved when they acquired ownership and control of the science of medicine. People finally had enough. They were ready to stop enriching the doctors and the corporations, so the FDA began controlling things. It hasn't been very good for scientific knowledge, of course, but it's been very good for society. What's the point of fixing one pain or ache when you realize that such knowledge only leads to an infinite regress. But one can't have something for nothing. The stability of society has got to be paid for. You will help pay, Dr. Marino, because you happen to be too interested in knowledge."

I complained to President Bush about the FDA. I never received a response, but on the day of my panel meeting the chairman began by saying, "I would like to note for the record my strong exception to the charges you made in your letter to President Bush regarding the integrity of the FDA." The panel members all nodded in agreement, like puppets. Then they took turns chastising me.

The first said, "I am concerned about the very limited amount of animal data, and I am not convinced that Dr. Marino has provided all of the clinical data."

The second said, "I have not seen any probable benefits. I have seen some possible benefits, but not any demonstration of any real benefits."

The third said, "I believe we are dealing with very flawed data, and that there may be long-term problems due to unforeseen difficulties."

The fourth said, "I believe it makes no sense to put foreign materials into the body when perfectly acceptable surgical procedures are already available."

The fifth member of the panel, the chairman, said, "I find this submission does not meet the minimum scientific merit necessary for an experimental study."

That was how my grand effort to sell a medical device ended.

When I had started studying science I thought that it was the truest, most certain thing in the world. I had turned my attention to Dr. Becker's project because it seemed more valuable and important than anything I knew about. As wonderful as it would be to put a man on the moon, how much more wonderful would it be to understand how electrical forces made life. I was certain that there was a canonical method for gaining an understanding of the intricacies of bioelectricity, and that my task was simply to learn that method, and then implement it, like a batter learning how to swing a bat. After I had confronted the issue of health risks from EMFs, I saw that there were intractable differences of opinion and that it would be impossible to resolve the issue with the certainty or reliability that I naively had thought characterized everything that could be called "science." Nevertheless, I had still believed there was such a thing as a canonical method, one that scientists generally agreed upon, even if they disagreed about the meaning of the results they found. But in the wake of my defeat by the FDA, I understood that there was something in science that was deeper than method – there was desire, the reason why anyone makes any effort in the first place. Everything begins with desire. It influences both the choice of a method and the meaning attached to the data spawned by the method.

The heart and soul of the culture at the FDA, its very essence, was fear – fear of the consequences of failure. Now, I could fail; I could be wrong. And it would come as no great surprise to anyone. People would say, "Well, he tried, but it didn't work out. He thought he knew how the body would react to carbon fibers, but he was wrong. He just didn't know enough about biology." On the other hand, if the FDA approved an implant

and then some people were injured because it failed to perform as expected, everybody would be shocked. They would wonder how such a thing could happen, and then you would hear a litany of complaints: "Incompetent bureaucrats;" "They must have been paid off by the company;" "If they really knew anything about science, they wouldn't be working for the government." Everyone at the FDA knew that this was how the public would react because that was how it had reacted in the past. How reasonable, how inevitable, that a culture should develop at the FDA to deny approval to *any* implant, whether of carbon fibers, or Teflon, or polyethylene. An implant that was not approved could not be sold, and an implant that was not sold and placed in the body could not fail and thereby injure a patient. The fault lay not with Mishra and his team. My enemy was the culture that they had imbibed. If someone ignorantly thinks that the science of knee-ligament implants ought to be as predictable as the science of levers or computers, then it is quite understandable when such a person reacts with bewilderment and disgust upon learning that a carbon-fiber implant ruptured and left a patient worse off than before the surgery. The true problem lies in the imagination of such a person, because that is where myths are found. The high opinion that people had of the reliability of knowledge in the life sciences was what had spawned the fear that had shaped the culture at the FDA, necessitating not only my defeat, but that of any proponent of a knee-ligament implant.

Knowledge for Herman Schwan was information that could be sucked out of an equation which, itself, was the law that all things followed. Thibodeaux knew nothing of equations or laws, nor did he care about them. For him the so-called method of science was something that was dominated by assumptions, that is, principles he found desirable – the most grievous one being that anything *real* in biology must reappear in machine-like fashion, must be replicable on command. Mishra differed from Thibodeaux chiefly in that he had different desires. For Mishra, the stability of society was the paramount concern, whereas for Thibodeaux knowledge of mechanisms was everything. After having spent my whole life working in science, and approaching fifty years of age, a coherent picture of what science really was had finally emerged. It was as much about what we wanted the world to be as it was about the world in itself, maybe more. There had always seemed to be another mountain that I had to climb in order to be in a position to look down into the valley of understanding. Now I felt I was there, and I

could see that they were going to have to rewrite the textbooks.

After I recovered from my experience with the FDA I realized that my years of dogged effort had unanticipated salutary consequences. First, they had been appreciated by those in my department, particularly Jim Albright, earning for me a repository of good will and affection. The experience I gained doing biomedical research was another benefit. The many studies I had designed and conducted, some better than others, had taught me the trade of doing research on animals and human beings in the only way that skill could be acquired. Those experiments led to many publications, sufficient in number for me to earn promotion to full professor with tenure, which occurred over the lone dissenting voice of Thibodeaux, who thought me undeserving because I had brought in no money from the National Institutes of Health, which by his lights was the only true mark of success in science, and the measure of one's worth as a scientist.

taken from other places in the body often gave poor results, and there were no artificial knee ligaments. At this point the salesman gave Jenkins some samples of carbon fibers and said, "You ought to try this."

Jenkins had used the carbon fibers in experiments with sheep and then with patients, leading to what he concluded were successful results. Strover told me that ruptured ligaments atrophy, and disappear from the joint, but that the carbon fibers induced growth of a new ligament in place of the original, as if the fiber bundle was a riverbed along which new tissue flowed.

After he had returned home from England, Strover went to a local supplier to buy carbon fibers, intending to cut sections to length and implant them in patients. Hourahane, who had a small plastics company in Johannesburg, had gone to the same supplier the same day, also to buy carbon fibers, which he used to reinforce the products he made.

Hourahane said to me, "The clerk told me he had just sold the last of his stock to a doctor from Wits who was going to implant them in people, so I went there to try to find him."

"Why?" I asked.

"Because I wanted to stop him from hurting somebody," he said. "Carbon fibers sold for industrial purposes can't be implanted in the body because they have a special chemical coating that's poisonous."

Hourahane had found Strover in time, and they began working together on Strover's project. Hourahane obtained carbon fibers that had never been coated, and fabricated them into artificial knee ligaments which Strover used to treat patients who had an unstable knee joint. Hourahane had designed and built special instruments to facilitate the surgery because ordinary instruments would have damaged the carbon fibers, and he invented devices to attach the fibers to bone.

Strover's patients did well, and other orthopaedists in South Africa and Australia began using the carbon-fiber implant, instruments, and fixation devices, which Hourahane made and sold. Strover said that Hourahane's system allowed a cruciate to be repaired successfully with a greater degree of reliability than was previously possible.

Hourahane had patented his inventions and wanted to gain access to the huge American market, but he had not received much help at the other U.S. orthopaedic departments that they had visited. Some orthopaedists were opposed to the idea of using artificial materials to repair ligaments.

Others had committed to one of the companies that was already trying to bring an artificial ligament implant to market. Someone had suggested to Strover and Hourahane that they visit Jim Albright, who had recently published a book entitled *The Scientific Basis of Orthopaedic Surgery* and who had a national reputation as an innovative man and a lover of research.

During their visit Jim learned about the clinical results and became interested in the project. I initially had no interest, but my attitude changed when I saw Jim's reaction, and I offered to help in any way I could. I hoped to give back something to the man who had given me so much, and perhaps even to earn a profit.

Jim and I went to South Africa to see first-hand what had been accomplished. In Johannesburg we saw Strover implant carbon fibers in the knee of a man who had been injured in an automobile accident. It was deft surgery, done in a fraction of the time normally needed when such injuries were repaired using tendons taken from some other area of the patient's body. At Baragwanath Hospital in Soweto a surgeon told me that his carbon-fiber patients were able to walk the day following surgery. In Pretoria I met Hourahane's biggest customer, an Afrikaner orthopaedic surgeon who told me that before he had started using carbon fibers he had never been able to successfully repair anterior cruciate injuries. At a hospital for gold miners in the Transvaal I visited an orthopaedist who had been especially meticulous when implanting the carbon fibers, and his results were the best of all – although, of course, not perfect.

Hourahane proposed that we go into the business of making and selling the carbon-fiber implant system in the United States, and Jim and I agreed. I incorporated our new company in Louisiana and became its president, with the major duty of doing what was necessary to obtain a license to sell the implant. Hourahane agreed to wire me the money I would need.

I went to the Food and Drug Administration in Washington, D.C., to learn exactly what was required for the license. When I entered the building I saw a huge room filled with desks piled high with stacks of paper; people swirled around like smoke in a wind tunnel. Someone directed me to a conference room and told me to wait there. The room was drab, almost depressing. Most of the formica on the edge of the table was missing, and there was a half-inch step between the halves. Ripples in the rug ran at right angles to a path that had been worn by the traffic in countless previous meetings. I sat in the least comfortable chair, no two of which

were alike, directly opposite a picture of President Bush. After a while a dark-skinned man with a repellent body odor entered the room, along with three other people.

"I am Nirmal Mishra," he said. "I am in charge of applications for artificial ligaments, these people are on my team. How can I help you?"

"I would like to sell a carbon-fiber knee implant," I said. "What do I have to do to get a license?"

"Give us evidence that your device will be safe and effective," he replied.

"What kind of evidence?"

"You must prove that it is strong. You need to do animal studies. Then you must prove that it works in people and doesn't have any side effects."

"I'm unclear about exactly what I need to provide. For example, I can put the carbon fibers in a machine and measure how much force it takes to break them. Is that what you mean about proving strength?"

"Yes, that would help, but you should do other studies as well."

"What studies?"

"Studies that show how strong it will be."

I began to feel uneasy. "How strong does it have to be?" I asked.

"Strong enough so that it will be safe and effective," he replied in an impatient tone.

"Suppose it took a hundred pounds to break the carbon fibers, would that be strong enough?" I asked.

"The situation can't be oversimplified. The device must be strong enough that it won't ever break, however strong that is, well, that's your answer, that's the number you want."

He seemed annoyed, so I lied and said, "I think I understand what needs to be done."

I began to tell him about what I thought was important data from over three hundred patients in South Africa who had received carbon fibers and had generally done well. But as I was speaking he started shaking his head from side to side.

"We can't rely on the opinions of surgeons, they often don't admit bad results. You will need to do a clinical study in the United States, according to our specifications," he said.

He gave me a booklet entitled *Guidance Document for the Preparation of Investigational Device Exemptions and Pre-Market Approval Applications for Inter-*

Articular Prosthetic Knee Ligament Devices and said, "Follow this." Then he rose from his seat, and the people on his team immediately shot up as if they were connected to him by springs. He walked toward the door, and when he reached it he turned and said, "You need to continue this dialogue with us so that we can tell you what we expect;" I quickly agreed to do so.

As soon as I returned home I planned a study in which the anterior cruciate ligament in the knee joint of goats would be cut out and replaced with carbon fibers. When I called Mishra's expert in charge of animal studies to obtain his approval I told him, "We will assess the quality and strength of the new tissue that grows."

He was a friendly young man who had just graduated from college. "That sounds reasonable," he replied.

"How long should I let the goats live before I kill them and test the ligaments?" I inquired. He asked for my opinion, so I told him that I thought three months was long enough, and he agreed.

"I expect to have some problems because no one else has ever done the kind of surgery we are planning, but in most cases we anticipate that the implant will hold up well," I said. "Realistically, that's all that could be expected."

"Yes," he said.

When the experiment was over I reported the results, but this time the young man was less realistic. He flipped through the pages of data and said, "Two goats didn't do well."

"Yes, but that's more or less what you would expect."

"Nevertheless, the fact that some goats can get bad results indicates that the device can be risky."

I thought about telling him there are always risks, but I said nothing for fear that I might give offense.

The strange mechanical properties of carbon fibers intrigued me. They were stronger than steel when pulled at each end, but broke easily if bent at an acute angle. Their apparent ability to grow a new ligament seemed marvelous, and I took it as my goal to understand this process. I hoped that moving the subject of artificial ligaments from the realm of speculation and anecdote into the realm of science would relieve Mishra's anxiety about granting me a license, so I did many experiments on rabbits, mice, and rats. During that time I also did experiments that Mishra had insisted upon, though I saw no merit in them.

One day the secret of how the carbon fibers worked became apparent to me. I discovered that the tissue which grew around the fibers didn't actually stick to them, but rather that each fiber could slip out of its tube of tissue as if the fiber had been coated with grease. The reason the carbon fibers strengthened an injured ligament was that the new tissue that grew around them joined the ligament's original tissue and insertion points on the femur and the tibia, thereby reinforcing the injured ligament. Each implant contained forty thousand carbon fibers, so there were forty thousand tubes of tissue that grew to strengthen the injury site, many times more than grew in response to the artificial materials being developed by competitors who were using other materials. The strength of the carbon fibers was not what mattered, but rather the strength of the new tissue. Moreover, most materials could spontaneously trigger an attack by the immune system but carbon never did, so carbon fibers were twice blessed.

My good feelings about the knowledge I had gained were tempered by discouragement about the time and money wasted in performing all the experiments Mishra had required. Had he and his team left me alone, I could have gained my understanding more quickly and inexpensively; their suggestions and opinions – really commands – were rarely useful. He called those on his team "scientists" – they weren't, but that didn't stop them from giving me rote advice concerning how experiments should be performed, like medieval monks braying out memorized psalms they don't understand. Mishra himself often preached to me about "risk." One time he sweated for an hour and stunk up the place even more than usual, but succeeded only in showing that nobody could objectively define "risk," although of course he thought he had done it. Nevertheless I always did as I was told by Mishra. I hated the way my desire for the license made me act. It was as if I were limp, like my carbon fibers.

After many delays, Mishra finally approved my plan for a clinical study to determine whether carbon fibers were safe and effective for repairing the anterior and posterior cruciate ligaments in the knees of humans. The plan had to conform to his *Guidance Document,* so there was much in the plan that had little to do with science but rather was intended to generate interlocking patterns of data that would make it difficult to fabricate data favorable to my interests which, it seemed, the FDA assumed any company trying to obtain approval for a device would do.

The clinical data I collected on each of the patients who took part in

my study was supposed to come together to support Mishra's judgment regarding the issuance of a license, but I didn't understand quite how, which put me in the position of a man searching for something but having no way of knowing whether what he found was what he was looking for.

"How will you know from the data I collect whether the implant is safe and effective?"

"I'll know when I see the data," he replied.

During the next year I collected thousands of pieces of information about each study patient, some of whom received carbon fibers and others of whom received conventional ligament reconstruction with tendons harvested by the surgeon from elsewhere in the body. I had to hire bookkeepers to keep track of the data, and I struggled constantly with the orthopaedic surgeons who performed the periodic follow-up examinations on each patient, which I needed in order to evaluate whether the carbon-fiber treatment was successful. They resented the length and prolixity of the follow-up form Mishra had required, and often omitted data they thought meaningless but Mishra considered important. His term for each blank line was "protocol violation," and he construed every such instance as evidence against the idea that the implant was safe and effective.

As the study went on I saw things that could have been done differently and likely would have helped the patients, but Mishra denied me permission to make any changes in the experimental procedure he had approved at the inception of my study. He too learned of things that could have helped the patients in my study, knowledge he obtained from studies being done by my competitors, but he refused to share it with me because, he said, it was against the policy of the FDA to require competitors to share scientific data. "Why should they pay for information for you to use in your business?"

While I was performing my study, which was taking place at my institution in Shreveport, Brooke Army Base in San Antonio, and the University of Iowa in Ames, Hourahane continued to sell carbon fibers to orthopaedic surgeons in South Africa, Australia, Canada, Israel, and Europe, which he was free to do because the system in those countries placed primary responsibility for the choice of medical treatment on the doctor and his patient, not the government. Many hundreds of patients received Hourahane's carbon fibers with generally good results, at least in the opinions of the surgeons and the patients.

As the implant became progressively more popular, Hourahane began

receiving phone calls from veterinary surgeons who expressed an interest in using carbon fibers. The application he judged to be most promising involved the treatment of lameness in racehorses. Although the topic had been far from my mind, I learned that when one of the large tendons in the horse's leg stretched too much, the result could be swelling that deformed the leg into a backward-pointing bow. Then the horse couldn't walk, much less run.

I asked how he planned to repair the horses' injuries.

"I remembered that a young man in Louisiana discovered that no bonding took place between carbon fibers and tissue, and that the tissue that formed along the carbon fibers was aligned by them. I'll make a pointed cannula that can enter the tendon through a quarter-inch incision and then pass up to the top of the tendon. The vet will be able to pass the carbon fibers through the injury site by means of the cannula."

South African veterinarians implanted carbon fibers in more than fifty racehorses and show jumpers, and many of the horses returned to competition. I then performed two studies in the United States in which veterinary surgeons implanted carbon fibers in bowed tendons of thoroughbred racehorses, and did standard therapy in another group of injured horses – more than 100 horses in all. The results showed that use of carbon fibers was an effective treatment; I published a report about the experiment in the *Journal of Equine Veterinary Science.*

Meanwhile, the other companies that were trying to develop a ligament implant avoided all basic science research, and did only the experiments Mishra told them to do – or at least what they thought he had told them. One by one, the companies received an education at the public meeting the law required prior to a licensing decision. That's when each company learned its path had been only a big circle.

The first presentation was made by a company whose implant was made of polyethylene. After the company had presented results involving mechanical tests of its implant, a panel of experts Mishra had appointed to the FDA's review panel told the company's president, "We think the device is not strong enough."

"Compared with what?" he asked.

"Compared with a normal ligament," he was told.

"But that's not what we are trying to do. The patients we operated on had no ligament left. We were only trying to improve the patient's condi-

tion, not return him to mint condition. We don't know enough yet about how to make a device that's as strong as the original ligament. We have to take this a step at a time."

"I think you should make a better device and then do more studies," the panel chairman replied.

At the same meeting, other companies requested approval for their devices. One company described a tongue depressor, which was said to be an improvement over present models on the market because it was thinner and shorter, making it more suitable for depressing the tongues of children. Another company described an adhesive bandage that was said to result in less pain upon removal from the patient. Both devices were approved by the panel.

The last presenter that day described an implantable total-knee prosthesis, and illustrated its use with graphic slides that showed it being placed in a patient in France, where it had been developed. The surgeon cut off the knobby ends of the femur and tibia, and replaced them with devices made of titanium and polyethylene, which were attached to the bone with a special glue. The presenter then said, "We request approval of our implant because it is substantially equivalent to an implant that was legally sold in the United States prior to May, 1976," and the panel quickly approved the application. At that time I did not understand why manufacturers of such lowly devices as tongue depressors and band-aids were striving to improve their product, yet the manufacturer of a device whose use requires major surgery would go to great lengths to emphasize that his product was no different than one that had been marketed for a long time.

Six months later, a company that had developed an artificial ligament made from the tendons of pigs presented its invention to the panel. After a spokesman had finished explaining the company's animal and human studies, the panel chairman told the company president that patients might eventually reject the implant because it was foreign tissue.

"We treated the implant to reduce that possibility," the spokesman told the panel, "and we have not had any instances of bad reactions in patients."

"Have you looked inside the knees of these patients to see what is going on?" a panel member asked.

"Of course not," the president said. "We couldn't justify operating on a patient who had no problem simply to see what the ligament looks like."

The panel told him that using animal tissue was a bad idea because it might activate the immune system.

"Why didn't you tell us that when we started?" the company president asked. "Why did you wait until we had worked for three years and spent $5 million?"

He might just as well have saved his breath because the panel ignored him. Why Mishra had assembled such a panel of fools had not yet become apparent to me.

Other companies at that meeting who were seeking approval for their devices fared much better. In short order, the panel approved a new design for a hospital bed that had larger wheels, making it easier for the nurses to move, and a new formulation of plaster of paris that hardened into casts 20% faster. The sponsoring companies assured the panel that there were no risks associated with their products as long as they were used according to label instructions. The panel then approved a total hip consisting of a cobalt chrome stem designed to be hammered down into the bone's canal after it had been exposed by cutting off the top part of the bone, and an articulating ceramic component that was attached to the pelvis. Again, a company spokesman told the panel that the hip was "substantially equivalent to a device that had been marketed prior to the enactment of the device law." By then I'd learned the reason for that formula. Scientific evidence of safety and efficacy was not needed because any implant on the market before the 1976 device law had been deemed to be safe, like BHT. Consequently, for the sake of consistency, a new implant that was exactly like one of the old implants also had to be deemed safe.

Several months later the device panel held another meeting. The first presenter was a company seeking a license to sell a Teflon ligament. The panel chairman told the spokesmen for the company that small particles could flake off the device and cause an inflamed and painful knee.

"That's why some of the patients in your study did poorly," he asserted.

"Some patients in every surgical series do poorly," the company representative replied. "That alone is no reason to deny us a license." But that's what the panel did.

The last presenter in the morning session asked the panel to approve a total knee implant. Hoping to gain an advantage in the marketplace, the company had advertised in trade journals that an innovative porous coating on the surface of the implant would encourage bony ingrowth, leading to

a longer-lasting implant. A controversy ensued when some panel members expressed the opinion that the coating was technologically impossible in 1976, and therefore the FDA should not deem the implant to be safe. In the end, the company convinced the panel that the claim had been made by its marketing department, and shouldn't be taken seriously. The company got its approval without needing to run the FDA gauntlet I was running and that any manufacturer of a new implant is forced to run. None had ever survived, but I hoped I would be the first.

While sitting in the audience I met people from various companies that hoped to someday obtain a license for their products. A young woman from a start-up company in Phoenix told me about a device she had invented that was powered by a watch battery and produced a tiny EMF that made fractures heal twice as fast as normal. She had gone deeply into the biology of bone healing and learned that the EMF did not alter the amount of proliferation of the stem cells of bone caused by the injury, but rather increased the rate at which they differentiated into the kind of cells that actually build bone. She showed me a report entitled "A new theory of the biology of bone healing." Across the title page Mishra had written "Not recognized," which he underlined twice. The opinion of others at that meeting who also heard her story was that it was madness to present novel scientific results to the FDA.

Of all the companies trying to get a license to sell ligaments, Hexcel Medical was the most aggressive. Its product was also made from carbon fibers, and the company kept trying to pin down Mishra regarding exactly what evidence would convince him they were safe and effective. Somebody from the company visited or called Mishra every day but, according to what I was told, he never allowed himself to be trapped into giving an answer.

Thinking to strengthen its position in its dealing with Mishra, Hexcel hired David Jenkins as one of its experts. He had learned about the toxic coating on carbon fibers that were sold for ordinary purposes such as reinforcing tennis rackets, and he attempted to remove it with a solvent. Unfortunately, he had not rinsed the carbon fibers well enough to remove all of the solvent which, it turned out, was more toxic than the coating. Some of Jenkins's patients developed chronic inflammation due to the solvent residue, and their fate came to light in a paper published by a surgeon named Dandy who had examined Jenkins' patients. To prove his point, Dandy himself implanted carbon fibers that contained solvent residue; unsurpris-

ingly, his patients developed chronic inflammation.

At the FDA meeting where Hexcel presented its scientific evidence, the panel chairman asked where the data was that showed chronic inflammation in the patients in the study. But Hexcel, like me, had obtained pure carbon fibers, thereby obviating the error committed by Jenkins and then aped by Dandy in the so-called interests of science. Nevertheless the panel accused the company of hiding data that showed bad results, and Hexcel was denied a license.

I avoided the mistakes in judgment and the errors in science I perceived in the way Hexcel had gone about its effort to obtain a license. I had discovered the biological basis of the action of carbon fibers implanted in the body, and I had proved that they could be used successfully in animals. Hexcel Medical had done neither. My system for implanting carbon fibers included specialized surgical tools for grasping the carbon fibers and threading them through the joint, and specialized devices for attaching the implant at each end to bone. Hexcel lacked these instruments; consequently the surgeon often broke some of the carbon fibers when he grasped them with ordinary surgical forceps or routed them over the sharp edge of an unchamfered bone hole. Hexcel had no means of attaching the carbon fibers to bone, so the surgeons had attached them to soft tissue using sutures, which often resulted in a fatally weak repair. Worst of all was the design of the clinical study. Carbon fibers were used to repair an instability anywhere in the body, from the foot to the shoulder, and without any control group. My study, in contrast, specified that only ligaments in the knee would be repaired using carbon fibers, and I had included a control group consisting of patients who received standard surgical treatment. Thus the ability of my clinical study to reveal whether carbon fibers were effective was focused on a single problem, not diffused across many different problems. It was the first controlled study in the history of orthopaedic implants.

When I reached the point where I had a year of follow-up data on the last of the 145 patients in my study, I evaluated the data and I saw that I had proved my point. I went to Washington to show my results to Mishra. We met in the same drab conference room, but the contrast between my surroundings and how I felt inside couldn't have been more dramatic. I thought I had reached my goal, and that my rewards would soon be coming. When he entered we exchanged greetings, and then I told him of my intentions.

"I am ready to make my formal application, I have all the requisite evidence."

"I think longer follow-up is needed to insure that carbon fibers are safe and effective," he replied.

When I heard those words I started to see flashes of red and blue light. I could see that he was continuing to speak, but I couldn't hear anything. Then I couldn't see him, or feel anything, as if gravity had ceased and I were floating in space. After a while, how long I didn't know, I could feel the uncomfortableness of the chair, and I recovered sufficiently to blurt out, "But you said one year's follow-up would be enough. I have it in writing."

"Well, the state of the art changes. We now know that implants which look good after one year may not be good after two years. The health of the public is at stake here. We must be certain."

"You said one year's follow-up would be enough," I said again. "I have it in writing."

"I make the rules, Dr. Marino," he said, "and I can change the rules."

Obtaining the follow-up data had always been difficult and expensive, but now it became a nightmare. Some of the patients had been athletes at the University of Iowa; after graduation they moved all over the country, making it difficult to locate them and arrange for a physical examination by an orthopaedic surgeon where they lived. The situation was even worse with the servicemen who had been stationed at Brooke Army Base in Texas when they entered the study. The patients at my institution frequently failed to return for the yearly examination because they felt well and saw no need to take the trouble to do so. Some patients at all three locations sensed our desperation to obtain the follow-up information, and demanded to be paid large sums of money for allowing themselves to be examined.

Hourahane finally reached the point where he could no longer supply money to maintain the study. So I told Mishra that I would make a formal application for a license, as I had the right to do under the law.

"Why don't you put together all your data and present it to me informally, and we'll take it from there," he replied.

The meeting with Mishra and his team took place in the same room as our other meetings.

"Well, what do you have?" he asked, and I began at the beginning.

"My first animal experiments were on mice. We wanted to show that carbon fibers were well tolerated, so we implanted them in muscle and fat,

and near nerves, and we found that the fibers were well tolerated by all the tissues."

"How long were they implanted?" he asked.

"Three months," I replied.

"Suppose you left them in longer. What would have happened?"

"Probably nothing, but I don't know because that's not what I did."

"So you don't know if there would have been problems."

"I had no reason to implant them for longer than 3 months."

"Safety is a paramount concern. It's your responsibility to answer all the questions."

"What questions?" I asked.

"My questions."

I continued. "In rabbits, we removed the Achilles tendon and replaced it with carbon fibers; nylon was the control. We discovered that the amount of new tissue that grew depended on the surface area of the material. Carbon fibers have several hundred times the surface area of nylon, so they produce several hundred times more tissue. The additional tissue added strength to the injury site. That is our rationale for carbon fibers."

He rocked back in his chair and looked up at the ceiling. Through his usual frozen smile he said, "It was an interesting experiment, but what does it prove as far as safety is concerned?"

Before I could reply he said, "What else do you have?"

"In goats we took out the ligament and replaced it with carbon fibers."

"Was the result as strong as the original ligament?" he asked.

"Of course not," I said. "The purpose of the study was …." He interrupted, "Well, that's what people will expect."

"Well, we'll just tell them the truth," I said, but he waved me off saying, "They won't listen. What else?"

"We thought that carbon fibers would work in injured tendons, and we proved it in racehorses."

"That kind of a study has to be evaluated by veterinarians," he said.

I told him it was, and that it was published in their journal. He nodded, pursed his lips, and asked a question he surely knew I could not answer, "Were there any carbon particles in the lymph nodes?"

"I don't know. We didn't look. The horses didn't belong to me. They were very expensive animals, and their owners wouldn't let me operate on them just to remove tissue. I did examine the lymph nodes in other animals."

"But not in the horses, right?"

"Right," I said.

"What did the human studies show?" he asked.

"By any reasonable interpretation of the data, the patients who received the carbon fibers did better than the control surgery," I replied.

"What about side-effects?" he asked.

"The number of infections and complications was the same in the carbon-fiber and control groups."

"What about the strength of the carbon fibers. If you pull on them, how much force does it take to break them?" he asked.

"About 100 pounds," I replied.

"The average strength of the cruciate ligaments is 500 pounds, so the fibers are much weaker than normal tissue," he said.

"That's comparing apples and oranges. The original ligament is gone, so the strength of what remains is zero. We shouldn't make the perfect the enemy of the good."

"How much strength do you get eventually?"

"I can't possibly answer such a question unless I remove the new ligament from the patient and test it."

"How about the animal studies?" he asked, and I gave the only answer that was possible. "Animal studies can't be done to answer that kind of a question because people and animals are different."

"What scientific basis is there for the hypothesis that the ingrowth of tissues bears a load or has any strength to it? What's the basis for that hypothesis?"

I plowed the same ground again, telling him, "We showed that new connective tissue grew in animals. We showed that it added mechanical strength and that it led to improved function, as evaluated on the basis of the ability of racehorses to return to racing. Then we did the clinical study. The results couldn't have been as good as they were unless there was new tissue."

"You have not given us any scientific data to show that in fact there's any tensile strength to that stuff that grows in. Sure, fibrous tissue grew, but what's the strength of it?" he asked, even though he knew exactly what my answer would be.

"I can't answer all that," I said.

"Well, my question is pertinent," he said, "because you're saying that

you put carbon fibers in there and suddenly tissue grows in, and I'm saying, where is the proof?"

He paused for a moment and then said, "It's too bad, because you've got independent ideas of your own, I almost envy you. Nevertheless, carbon fibers cannot be accepted by the Food and Drug Administration because such an implant might lead to harm. The review process must be very conservative. Everything must be understood in that light."

"What light?" I asked.

"Any device licensed by the Food and Drug Administration must be free of all risk. Risk leads to harm, and that leads to disrespect for the Food and Drug Administration."

That was such a shocking thing to say I could not believe my ears.

"It is impossible to make a device that has no risk," I said, and after I caught my breath I continued, "Besides, that's not what the law says. It does not say 'possible risks,' it says 'probable risks.' And even if there are probable risks, the law says that I'm still entitled to a license if the probable risks are balanced out by the probable benefits."

"And those are exactly the judgments I shall make," he said, "so that we have happy people." When he said that he motioned for his team to leave the room, so only he, I, and the secretary I had brought to take notes remained.

"Do you know what it takes to make people happy?" I asked.

"Eight hours' work not doing anything very arduous, then beer and television. Then they're happy. They really don't need anything more. What could they ask for?"

"They might ask a doctor to fix whatever ails them," I replied.

"Technically, I suppose, those kinds of problems could be fixed. But would the people be any happier? I don't think so. That experiment was tried. We gave them artificial hips and knees, and what was the result? They began to complain about other problems, and to demand that doctors do even more. My files are stuffed with applications for devices that their proponents claim will do wonderful things. Thousands of such applications. There's not a part of the body that someone hasn't proposed replacing with something made of plastic, metal, or some new space-age material."

"Why don't you license the devices?" I said. "Then we could see if they perform as advertised."

"For the sake of the people themselves," he replied. "It would be sheer cruelty to fix one problem because there will always be another, without

end. We have to think about the stability of society."

"What do implants have to do with the stability of society? What do you mean?"

"Devices create instability by fostering the craving for more and more scientific advances. To do what? To defeat aging and death, which is ultimately impossible. Implants like yours are a menace to the stability of society, so the science that breeds them must be kept chained and muzzled."

As I sat there, too stunned to say anything, he launched a long soliloquy after which he abruptly left the room. I had heard this speech somewhere else. I couldn't remember where, but in my mind I could fill in the argument as I heard it from Mishra.

"People," Mishra said, "had a strange idea about scientific progress. They imagined that it could go on indefinitely, regardless of everything else, as if scientific knowledge were the highest good and truth the supreme value. But ideas began to change and the emphasis shifted to universal comfort, which can keep the wheels turning steadily; truth can't do that. What the masses really wanted was comfort, not scientific knowledge. In spite of that, unrestricted medical research still continued. Big business went right on talking about scientific knowledge as if that was what they sought, but in reality it was only profit which the corporations achieved when they acquired ownership and control of the science of medicine. People finally had enough. They were ready to stop enriching the doctors and the corporations, so the FDA began controlling things. It hasn't been very good for scientific knowledge, of course, but it's been very good for society. What's the point of fixing one pain or ache when you realize that such knowledge only leads to an infinite regress. But one can't have something for nothing. The stability of society has got to be paid for. You will help pay, Dr. Marino, because you happen to be too interested in knowledge."

I complained to President Bush about the FDA. I never received a response, but on the day of my panel meeting the chairman began by saying, "I would like to note for the record my strong exception to the charges you made in your letter to President Bush regarding the integrity of the FDA." The panel members all nodded in agreement, like puppets. Then they took turns chastising me.

The first said, "I am concerned about the very limited amount of animal data, and I am not convinced that Dr. Marino has provided all of the clinical data."

The second said, "I have not seen any probable benefits. I have seen some possible benefits, but not any demonstration of any real benefits."

The third said, "I believe we are dealing with very flawed data, and that there may be long-term problems due to unforeseen difficulties."

The fourth said, "I believe it makes no sense to put foreign materials into the body when perfectly acceptable surgical procedures are already available."

The fifth member of the panel, the chairman, said, "I find this submission does not meet the minimum scientific merit necessary for an experimental study."

That was how my grand effort to sell a medical device ended.

When I had started studying science I thought that it was the truest, most certain thing in the world. I had turned my attention to Dr. Becker's project because it seemed more valuable and important than anything I knew about. As wonderful as it would be to put a man on the moon, how much more wonderful would it be to understand how electrical forces made life. I was certain that there was a canonical method for gaining an understanding of the intricacies of bioelectricity, and that my task was simply to learn that method, and then implement it, like a batter learning how to swing a bat. After I had confronted the issue of health risks from EMFs, I saw that there were intractable differences of opinion and that it would be impossible to resolve the issue with the certainty or reliability that I naively had thought characterized everything that could be called "science." Nevertheless, I had still believed there was such a thing as a canonical method, one that scientists generally agreed upon, even if they disagreed about the meaning of the results they found. But in the wake of my defeat by the FDA, I understood that there was something in science that was deeper than method – there was desire, the reason why anyone makes any effort in the first place. Everything begins with desire. It influences both the choice of a method and the meaning attached to the data spawned by the method.

The heart and soul of the culture at the FDA, its very essence, was fear – fear of the consequences of failure. Now, I could fail; I could be wrong. And it would come as no great surprise to anyone. People would say, "Well, he tried, but it didn't work out. He thought he knew how the body would react to carbon fibers, but he was wrong. He just didn't know enough about biology." On the other hand, if the FDA approved an implant

and then some people were injured because it failed to perform as expected, everybody would be shocked. They would wonder how such a thing could happen, and then you would hear a litany of complaints: "Incompetent bureaucrats;" "They must have been paid off by the company;" "If they really knew anything about science, they wouldn't be working for the government." Everyone at the FDA knew that this was how the public would react because that was how it had reacted in the past. How reasonable, how inevitable, that a culture should develop at the FDA to deny approval to *any* implant, whether of carbon fibers, or Teflon, or polyethylene. An implant that was not approved could not be sold, and an implant that was not sold and placed in the body could not fail and thereby injure a patient. The fault lay not with Mishra and his team. My enemy was the culture that they had imbibed. If someone ignorantly thinks that the science of knee-ligament implants ought to be as predictable as the science of levers or computers, then it is quite understandable when such a person reacts with bewilderment and disgust upon learning that a carbon-fiber implant ruptured and left a patient worse off than before the surgery. The true problem lies in the imagination of such a person, because that is where myths are found. The high opinion that people had of the reliability of knowledge in the life sciences was what had spawned the fear that had shaped the culture at the FDA, necessitating not only my defeat, but that of any proponent of a knee-ligament implant.

Knowledge for Herman Schwan was information that could be sucked out of an equation which, itself, was the law that all things followed. Thibodeaux knew nothing of equations or laws, nor did he care about them. For him the so-called method of science was something that was dominated by assumptions, that is, principles he found desirable – the most grievous one being that anything *real* in biology must reappear in machine-like fashion, must be replicable on command. Mishra differed from Thibodeaux chiefly in that he had different desires. For Mishra, the stability of society was the paramount concern, whereas for Thibodeaux knowledge of mechanisms was everything. After having spent my whole life working in science, and approaching fifty years of age, a coherent picture of what science really was had finally emerged. It was as much about what we wanted the world to be as it was about the world in itself, maybe more. There had always seemed to be another mountain that I had to climb in order to be in a position to look down into the valley of understanding. Now I felt I was there, and I

could see that they were going to have to rewrite the textbooks.

After I recovered from my experience with the FDA I realized that my years of dogged effort had unanticipated salutary consequences. First, they had been appreciated by those in my department, particularly Jim Albright, earning for me a repository of good will and affection. The experience I gained doing biomedical research was another benefit. The many studies I had designed and conducted, some better than others, had taught me the trade of doing research on animals and human beings in the only way that skill could be acquired. Those experiments led to many publications, sufficient in number for me to earn promotion to full professor with tenure, which occurred over the lone dissenting voice of Thibodeaux, who thought me undeserving because I had brought in no money from the National Institutes of Health, which by his lights was the only true mark of success in science, and the measure of one's worth as a scientist.