Murray Korc, M.D.: The piano tuner

By Nancy Marie Brown

Murray Korc likes to be baffled and busy. He likes puzzles and problems and figuring out what makes the body tick. "Look at a *Tyrannosaurus rex*," he says, leaning back in his chair and lacing his fingers together in his lap. "Look at his bone structure: He has a femur, a pelvic bone, and he stands on his toes! Just like we do. Those genes have been conserved over many, many years. Or look at a giraffe, with its long neck. How many [neck] vertebrae does it have? Seven. All mammals have seven [neck] vertebrae—a cat, a dog, a giraffe, or us. Isn't it amazing?"

Equally amazing is where this schoolboy fascination with anatomy has led Korc: into endocrinology—the treatment and study of hormone-related disorders, including diabetes, pancreatic cancer, and osteoporosis.

Grew up: Born in Germany and grew up in Brooklyn, N.Y.

Education: Brooklyn College '68 (B.A.); Albany Medical College '78 (M.D.)

Training: Albany Medical Center (internal medicine); University of California at San Francisco (endocrinology and metabolism)

Previous position: Chief of the Division of Endocrinology, Diabetes, and Metabolism at the University of California at Irvine (1989-2003)

Positions at DHMC: Chair of the Department of Medicine; Joseph M. Huber Professor of Medicine; professor of pharmacology and toxicology

Favorite leisure activity: Reading funny mystery novels by writers such as Susan Isaacs

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"I wound up liking every single clinical rotation I went through—psychology, surgery, ob-gyn," he says of choosing a specialty in the late 1970s. "But in medicine you needed to make an initial diagnosis when it wasn't apparent early on what the problem was. Belly pain could be caused by something benign, something major, or something very unusual. Trying to play detective was what made it interesting to me. I chose endocrinology, finally, because of the really unusual presentation of diseases."

Take the case of the tall young man, apparently healthy, who had lost three and a half inches in height in just nine months. Korc determined that he had severe osteoporosis, so his vertebrae were collapsing. But what was the cause? It turned out that a tumor in his pituitary gland had metastasized to his liver, where it produced the hormone corticotropin-releasing factor (CRF). The hormone coming from the liver was normal and natural—but there was way too much of it. The cancer cells had no "stop" mechanism.

"Hormones are controlled by a feedback loop," Korc explains. Since his postdoctoral days at the University of California at San Francisco, where he researched the physiology of pancreatic cancer cells, he has studied the signaling pathways of these control loops. "If the normal gland produces too much, there's a signal that says, 'Make less.'" In a cancer cell, that signal never comes. Production of the hormone runs amok.

The result? Cacophony, says Korc. "I look at it as a large symphony orchestra. Music is a combination of many signals, coming from many instruments, played by many maestros. Are they all doing the same thing? No. But it's all music. That's where I see the connection to cancer. When cancer cells hijack the making of hormones, they don't make music, they make a cacophony of signals." The work of the doctor is to fix the piano—or teach the pianist to play better—so the music of the body can resume.

As he talks about his work, Korc exudes a sense of calm optimism. He's relaxed but alert. "It's kind of difficult for me to call what I do 'work,' since I enjoy it so much," he wrote in in an essay titled "The Joy of Discovery" for the July 2006 issue of *Cancer Biology and Therapy*. "Or," he continued, "is that the definition of a workaholic?"

He had wanted to call his essay "The Ecstasy of Discovery," but the editor thought that word choice was a little too emphatic. Yet Korc *is* emphatic—albeit in a quiet, professorial way. He calls his academic career "an accidental joyride" and refers to the "seductive" pleasures of research. He finds it "exhilarating" to be the chair of medicine at Dartmouth, a position he took in 2003, after 14 years at the University of California at Irvine.

At DHMC, Korc practices clinical medicine, seeing mostly osteoporosis patients (though in California his emphasis was on diabetes), and he also runs a very active research lab, focusing on pancreatic cancer. He has published more than 230 scientific papers in peer-reviewed journals, plus over 50 book chapters and numerous reviews, and has given nearly 100 invited talks. He is a member of the Association of American Physicians, the premier society for physician-scientists. At Dartmouth, in 2006, he was instrumental in the creation of the Program in Experimental and Molecular Medicine to train more physician-scientists, seeing it as a way to more quickly translate research findings into patient care. A former president of the American Pancreatic Association, Korc founded the Dartmouth Pancreas Club in 2004 to improve the diagnosis and treatment of pan-

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creatic diseases by fostering collaboration among clinicians and researchers.

Anything else? "I used to be a soccer referee, but I don't seem to have enough time to do that now," he says.

He is also married to Antoinette Korc, M.D.—a DHMC dermatologist who specializes in surgical treatments for skin cancer—and they have three children, the eldest of whom is in his last year of medical school.

How is Korc able to accomplish so much? "I only sleep five hours a night," he quips. Then he gives a more serious answer: "Tenacity, serendipity, hard work, intellectual curiosity, and the desire to help."

JON GILBERT FOX

Murray Korc finds working with students and residents—those who represent the future of medicine—to be one of the most satisfying parts of his job. He also oversees the Department of Medicine and a research lab and cares for osteoporosis patients.

It was a feeling of helplessness that inspired him to combine research with clinical practice in his first years out of medical school. He realized, he wrote, that "in spite of many wonderful scientific advances, there was still so much more that we did not know or understand. Medical ignorance all too often meant that as a physician I was helpless in too many circumstances."

The treatment of diabetes—the focus of his practice then—was totally different before the invention of blood glucose meters and insulin pumps, before today's many varieties of insulin and other new medications. The mystery of diabetes had supposedly been solved in the 1920s, when a team of Canadian scientists discovered insulin and used it to treat a 14-year-old boy who had been a "hopeless invalid," according to the Nobel Prize announcement for 1923. Yet insulin was a treatment, not a cure, "and that boy died at age 33 of coronary artery disease," Korc says. "The doctors then didn't know what side effects to look for."

Learning about the link between diabetes and another disease, pancreatic cancer, launched Korc in 1984 on the trajectory that has defined his career. A conscientious reader of the medical literature, he used to spend hours in the library. (Now, thanks to the internet, he can read relevant journal articles well before their official publication date.) Japanese researchers had found that patients with type 2 diabetes mellitus were at greater risk of developing pancreatic cancer. "Eureka!" Korc wrote in his 2006 essay. "As an endocrinologist with an interest in diabetes who had trained in laboratories that studied pancreatic physiology and pancreatic gene regulation, and who was yearning to do translational research, I suddenly discovered my calling." He would investigate the role of growth factors in pancreatic cancer—something no one had yet looked at. And what he learned might help his patients with diabetes, too.

Now, 20 years later, it is widely known that growth factors are overexpressed in pancreatic and other cancers, causing tumors to grow and metastasize. The "stop" signals for growth factor production are also out of order.

"I have another analogy I like to use to explain it," Korc says. "Imagine you're driving a car and the accelerator is stuck to the floor. And the brakes don't work. Not only that, the brake pedal has been converted into a second accelerator."

Korc and his 10-member research team have discovered chemicals that are able to restore the brakes in some pancreatic cancer cells; several of their ideas are now in clinical trials. Urging his fellow endocrinologists nationwide to be more optimistic, he wrote recently that "the nihilism regarding the potential for prolonged survival of pancreatic cancer patients is no longer an option, and that is a tremendous change in perspective."

Curing pancreatic cancer is more difficult than repairing the brakes on a car—you can't put a cell up on a lift and get out your wrench. In addition, each cell's accelerator and brakes are broken in slightly different ways. "The cancer arose because the checks and balances fell apart that controlled the fidelity of what's going on inside the cell," Korc says. "Once that's gone awry, all the cells will go in a slightly different direction. Each cancer cell will be different, and each cancer will be different between different people. We're now talking about personalized therapy."

A futurist might see the solution in genomics—looking toward a day when every patient will have his or her gene profile recorded onto a microchip and inserted under the skin of the upper arm (maybe leaving a pucker like an old-fashioned vaccine). Then the doctor will be able to look at the profile and design a personalized treatment.

But Korc is not a futurist. "There are huge problems with privacy, ethics, insurance," he says. "Do you want to know you'll get pancre-

continued on page 57

Faculty Focus: Murray Korc

continued from page 53

atic cancer when you're 40? Some people will refuse the microchip. Some people refuse to have a flu shot today. Or to wear a seatbelt. Or to wash their hands. All these things complement each other. Sometimes it's the simplest and most basic things that will prevent the most problems."

That first-things-first approach is evident in how Korc treats his osteoporosis patients. First, he checks for a secondary cause of the condition, such as an overactive thyroid or a calcium leak. Then he starts a program of education and motivation.

"Bone is a living tissue," he tells them. "There's a constant balance between bone-building and bone-chewing. Bone constantly goes through stresses." Although most people start losing bone after age 30, there are many things you can do to keep your bones strong or to protect bones that have already become fragile, Korc says. "Throw away the cigarettes. Start exercising. Take vitamin D if you're deficient. Eliminate slippery surfaces in your house. Do you have a tendency to go for walks at night? If so, bring a flashlight. Wear hip pads so if you fall—and you will eventually fall—you won't break a hip."

Why does Korc try to do everything—motivating patients, researching growth hormones, managing the huge Department of Medicine, and training new doctors? "There's a great sense of fulfillment," he wrote in his 2006 essay, from seeing a patient get better. But when he thought about giving up research at one point, he decided that "the joy of scientific discovery had become too seductive. I found that I simply could not help myself, and that I absolutely had to write manuscripts and give presentations at national meetings because it was fun and exciting."

Training the next generation of physicians provides a different sort of satisfaction. "One of my favorite parts of the day is the Morning Report," Korc says, referring to an hour in which residents get together to discuss puzzling cases. Watching from the audience, Korc says, "is always a humbling experience. You have medical conditions that present in such unusual ways. You learn from the process—but you also realize you can't know everything. Nobody can." ■