Peter Kwiterovich '64: Battling cholesterol

By Laura Stephenson Carter

He's spent his whole career unraveling the biochemical and genetic mysteries underlying heart disease, but he might never have enlisted in the cholesterol wars if he had followed in his father's footsteps and become a psychiatrist. Peter O. Kwiterovich, Jr., M.D., founder of the Lipid Clinic at Johns Hopkins University Medical School, was curious as a boy about what made people sick and how doctors made them better. He and his father would have long chats about medicine and mental illness as they strolled along the Susquehanna River in Danville, Pa. Later, as a premed at Holy Cross in Worcester, Mass., and a summer worker at the Danville State Mental Hospital, he yearned to discover the biochemical processes that might be responsible for abnormal behavior.

"It was pretty clear that these people were sick because they had some biochemical abnormality that would cause such extreme forms of abnormal behavior," he says. "[I] was considering trying to get an M.D.-Ph.D. to pursue whether there were molecules in the brain that were responsible for this behavior, whether there were receptors in the brain, or what the basis for these abnormalities may be."

After graduating from Holy Cross in 1962, Kwiterovich entered the two-year program at Dartmouth Medical School, where studies in a new field of medicine, human cytogenetics, had been underway in the Department of Pathology since 1960. Kwiterovich's interest in genetics blossomed at DMS; he also spent a summer working with a genetics researcher at the Geisinger Medical Center in Danville. "I got exposed [to] and interested in genetics. I did a lot of reading, set up cell culture systems, and began to do chromosomal karyotypes, which were in vogue at the time, and took different patients who had been in the hospital, did their karyotypes, and found some abnormalities," he says.

Kwiterovich went on to complete his M.D. at Johns Hopkins, where one of the world's first distinct divisions of medical genetics had been established under Victor McKusick, M.D., the man now known as the father of medical genetics.

"After I graduated from Dartmouth . . . I spent that summer with Victor McKusick," says Kwiterovich. "I started a project [with] the Holmes County, Ohio, Amish." Geneticists were interested in the Amish because they seldom marry outside their group, which makes them more likely to suffer from inherited diseases. McKusick had identified an inherited form of hemolytic anemia among these people, as well as certain liver diseases and forms of inherited dwarfism. That summer, his research involved Down's syndrome, a congenital condition characterized by mild to severe mental retardation.

"Was there a gene in the Amish that predisposed [them] to Down's syndrome?" asks Kwiterovich; that's the question his summer job was intended to answer. "I went to these farmhouses, and drew blood on children in barns [by] candlelight," he explains. But the prevalence of Down's syndrome was no higher in the Amish than in the population at large. Nevertheless, Kwiterovich found it "a very interesting experience, because it involved the lab—growing the cells and doing the karyotyping—and also interacting with the patients. The path that I've followed since then is . . . laboratory research related to human disease."

Kwiterovich figured that if human disease is inherited, "it's likely to present in childhood." So he decided to go into pediatrics, a field that he felt would give him a chance to intervene earlier rather than later. After a one-year internship in pediatrics at Children's Hospital in Boston, he spent three years in the molecular disease branch of the National Heart and Lung Institute (NHLI), where he really delved into genetic research and "got interested in cholesterol and inherited disorders of cholesterol metabolism. . . . [I had] changed my thrust from originally being interested in [the] biochemical basis of mental illness to the biochemical basis of cholesterol and heart disease."

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Kwiterovich published his first two papers in the field based on his work at the NHLI: one, published in 1973, showed that familial hypercholesterolemia could be diagnosed in cord blood at birth in families at risk for high cholesterol and heart disease; the other, published in 1974, showed that familial hypercholesterolemia could be expressed in children between two and 18 years of age.

"I was more attracted to the preventative aspects of the cholesterol field and heart disease," he says. "[I] saw the potential of diagnosing people who carried these genes making them at risk for heart disease later. I think that sort of turned me on rather than . . . [caring for] somebody who already had fairly far-advanced disease."

From 1970 to 1972, he completed his residency at Hopkins. And even before he was appointed an assistant professor of pediatrics there in 1972, he had received an NIH grant funding the establishment of a state-of-the-art lipid lab that he has directed ever since. Among other projects, the new lab would be involved in a big clinical trial aimed at proving the cholesterol hypothesis: "If you took somebody with high cholesterol and lowered it, you could prevent heart disease."

Today, the Hopkins Lipid Clinic is a national leader in offering patients the most sophisticated technologies to evaluate protein and fat levels in their blood so that medication and diet plans can be tailored to meet individual needs.

Kwiterovich is also at the forefront of cholesterol-related research. In the 1980s, his lab identified a pair of important proteins—apoB and hyperapoB—that may be even better predictors of coronary artery disease than the traditional HDL (high density lipoprotein, or "good"

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cholesterol) and LDL (low density lipoprotein, or "bad" cholesterol). In the early 1990s, Kwiterovich discovered three new proteins that play a critical role in cholesterol and heart disease.

"I think I was one of the first to focus on the origins of cholesterol problems and atherosclerosis in youth," Kwiterovich adds. American children have become much heavier in the last 10 or 20 years, he explains, and "obese children often have higher blood pressure levels, higher cholesterol, more bad cholesterol, less good cholesterol, higher triglicerides, higher insulin, higher glucose."

Kwiterovich was on the steering committee for a major initiative called the Dietary Intervention Study in Children. It was conducted at six medical centers, including Hopkins. The study focused on changing the behavior of children with moderately elevated levels of cholesterol: the intervention group ate a low-fat, low-cholesterol diet that contained enough minerals, vitamins, and protein to sustain normal growth. The study concluded that the low-fat diet was indeed safe, as well as effective in lowering cholesterol levels.

"The whole nutrition area can be fairly tricky," Kwiterovich says. "It's one of my real frustrations as I practice medicine—[to] try to help people understand nutrition. Not that they can't understand it, it's just that the way our supermarkets and stores are set up they don't provide the information accurately for people to make an intelligent choice."

KEITH WELLER

Kwiterovich has forged a career that is based partly in the lab and partly in the clinic.

In 1989, Kwiterovich wrote *Beyond Cholesterol*, a book for the lay reader containing advice on healthy eating and avoiding heart disease. He plans to update the book in about a year. "I'm going to . . . see if I can do a better job this time: make my book even more practical and a little bit clearer for the consumer than I did the last time." While he may be modest in his assessment of his first effort, the American Heart Association didn't hesitate to present it with the 1989 Blakeslee Award as the year's best book in the field.

Last summer, Kwiterovich caught the attention of the national media for research showing that a diet based on lean red meat was as healthy for the heart as one based on lean white meat. He coauthored the study, which was funded by the National Cattlemen's Beef Association and published in the *Archives of Internal Medicine*, with researchers from the Chicago Center for Clinical Research and the University of Minnesota.

"It's true that, in general, most red meat is too high in saturated fat," he says. "But you can select proper cuts of red meat that are much lower in saturated fat." The trick is to buy lean cuts of red meat and trim off any excess fat. He recommends avoiding regular hamburger, which is 30 percent fat, and, instead, buying round steak, having all the fat trimmed off, and then having it ground. "That's two grams of saturated fat per three ounces," he says.

Kwiterovich has also become interested in the so-called small-for-dates infant syndrome—the term for babies born small for their gestational age—since it may play a role in heart disease. In the 1980s, Dr. David Barker of England's University of Southampton found, by looking at birth records dating back to the early 1900s, that people who later developed heart disease were more likely to have been underweight at birth. While researchers suspect inadequate nutrition in the womb may be to blame, Kwiterovich thinks genetics plays a greater role. "I'm doing some research now to see what the biochemical basis for this is," he says. "Is there some abnormality that might be related [to] both why they're small-for-dates [and] why they get heart disease later? I'm trying to link that with my hyperapoB work."

Another of his interests is Lipid Therapeutics, Inc., a company that he and colleagues are launching to develop new tests for identifying those at risk for coronary artery disease as well as new drugs for treating it. "We have a couple of patents . . . related to metabolism of sugar lipids, and we have identified a couple of enzymes . . . that appear to be important in atherosclerosis," he explains.

Kwiterovich foresees a day when doctors may be able to use diagnostic chips to identify the exact genetic defects that put a given patient at risk for certain diseases. "Maybe a hundred years from now, you'll be able to know what behaviors you should follow in order to avoid disease," he says. "So if you have certain genes, you'd better not smoke. Or . . . you try to avoid becoming heavy because you're much more likely to have diabetes than somebody else. I think . . . eventually, we'll really practice true preventive medicine and it will be based primarily in genetics."

As busy as his work keeps him, Kwiterovich also has interests outside medicine. He has been active with Baltimore's Roland Park Civic League since 1976 and has served as the group's vice president and president. He also enjoys power-boating and fishing and relaxing in his cottage on the northern part of Chesapeake Bay.

Although nearly half a century has passed since the boy and his father strolled along the Susquehanna discussing medicine and its mysteries, Kwiterovich is just as enthusiastic today as he was then in his pursuit of the biochemical basis of disease. ■