John Mulvihill, M.D., '67: Still in genes

By Alissa Poh

Grew up: Wethersfield, Conn.

Education: College of the Holy Cross '65 (B.S. *magna cum laude* in biology), DMS '67 (bachelor of medical science), University of Washington School of Medicine '69 (M.D.)

Training: Johns Hopkins (residency in pediatrics)

Current academic title: Kimberly V. Talley/Children's Medical Research Institute Chair in Genetics, University of Oklahoma Health Sciences Center

Activity he enjoys: Doing his own car maintenance—"a nice, difficult thing to do."

Recent read: *Cutting for Stone* by Dr. Abraham Verghese—"a wonderful saga of a British surgeon in Ethiopia and his son, who also became a doctor. . . . The ending brought tears."

"We are all a unique set of genes interacting with a unique environment," Mulvihill said to *USA Today*.

The best decision John Mulvihill ever made, he says—other than marrying his high school sweetheart, Charlotte—was taking the advice of Dr. Kurt Benirschke, chair of pathology at DMS from 1960 to 1970. It was 1967, and Mulvihill was about to graduate from DMS, which then had a two-year preclinical program. Benirschke recommended that Mulvihill complete his medical education 3,000 miles away, at the University of Washington in Seattle.

Benirschke was one of two professors whom Mulvihill credits as having been particularly inspiring during his time at DMS. The other was Dr. O. Ross McIntyre, then an oncologist and cancer researcher and later the director of Dartmouth's Norris Cotton Cancer Center. "I admired Dr. McIntyre's commitment to cancer research, especially multiple myeloma, and how he approached his work with such humility," Mulvihill says. And "Dr. Benirschke became—and still is—a real mentor; he taught me the joys of mentoring others."

So while most of his classmates headed to Harvard Medical School, Mulvihill drove cross-country to the Pacific Northwest. "Washington was better for studying genetics and pathology, which were my chief interests," Mulvihill explains. "I eventually lost interest in pathology, but my passion for genetics never waned."

That was a turbulent time in U.S. history, when many newly minted doctors were being drafted into the Vietnam War. So Benirschke advised his protégé to discharge his military obligation by joining the uniformed Public Health Service Commissioned Corps. Through its associate training program, Mulvihill became a research associate in epidemiology at the National Institutes of Health (NIH).

"I landed at Dulles Airport," Mulvihill recalls, and "by the time I made it to Bethesda, four of the five research possibilities on my list were taken." The only remaining option was to work for Dr. Robert Miller, then chief of the NIH's epidemiology branch. "So I got into epidemiology by accident, really," Mulvihill says.

It was a very fortuitous accident. "At the time, we were looking at the viral and chemical origins of cancer," he explains. "But we had also found cancer families, inbred strains of mice with cancer, and viral oncogenes in human tumor DNA. Geneticists were beginning to achieve real insights into the biology of human disease." Mulvihill soon realized that the fusion of genetics and cancer fit his interests well.

In 1974, after completing his residency at Johns Hopkins, Mulvihill returned to the NIH. He stayed for 16 years, as chief of clinical genetics in the National Cancer Institute's clinical epidemiology branch. "Most academic health centers claim the tripartite mission of service, teaching, and research," he says, "but the NIH unabashedly emphasized research, research, research. For me, it was a privilege to focus on scientific discovery."

Mulvihill helped found the InterInstitute Medical Genetics Program in 1983—the NIH's first fellowship in the field. His own research, meanwhile, focused on gene mapping. In 1987, he helped localize to chromosome 17 the gene for neurofibromatosis type 1—an inherited disorder, originally called von Recklinghausen's disease, in which nerve tissue sprouts tumors. Two years later, the National Neurofibromatosis Foundation presented him with its first Friedrich von Recklinghausen Award in recognition of this achievement.

Mulvihill's office at the NIH was just down the hall from that of Dr. Mitchell Gail, a biostatistician. Working with Mulvihill, Gail came up with the statistical equations for the Breast Cancer Risk Assessment Tool, which uses a woman's medical and reproductive history to estimate her risk of the disease. They published the Gail Model, as it is known, in 1989; of the nearly 300 scientific papers bearing his name, Mulvihill still considers it his best.

In 1990, Mulvihill decided to explore academic life in a more traditional setting, at the University of Pittsburgh. He was named the founding chair of its Department of Human Genetics and co-director of the Pittsburgh Genetics Institute.

Eight years later, Mulvihill left Pittsburgh and moved to his current position as chair of genetics at the University of Oklahoma. His research still emphasizes the crossroads of genetics and cancer—in particular, understanding human germ-cell mutations by studying reproduction in cancer survivors. He also runs a registry of pregnancies in which the mother was exposed to chemotherapy—the only one in

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CHILDREN'S HOSPITAL FOUNDATION

DMS alumnus John Mulvihill devotes most of his time to research but does still consult, here at Oklahoma Children's Hospital, on clinical cases involving genetics.

the country. He attributes the registry's origin to the influence of Dartmouth faculty members who focused on the study of birth defects, including Benirschke, Dr. Stanley Carpenter, and the late Dr. Vergil Ferm.

"Despite expectations to the contrary, pregnancies exposed to chemotherapy in the first trimester [when organs begin to form] don't necessarily suffer ill effects. There are plenty of normal, healthy babies born," Mulvihill says. "While we don't recommend chemotherapy during pregnancy, it can be quite a poignant counseling dilemma. . . . I like to think this registry is available so doctors and women can better understand the risks."

Mulvihill's group at Oklahoma has also studied more than 40,000 offspring of cancer survivors from the U.S., Denmark, Finland, and Canada and plans to perform total genomic sequencing on blood samples from these subjects. Even a decade ago, such an approach would have been prohibitively expensive. But as molecular genomic technologies become speedier and cheaper, it's "at least discussable now," Mulvihill says.

The dawning age of personalized medicine is certainly one Mulvihill believes in. He cautions, however, that the origins of human disease are so complex that we may be unable to afford to create and match drugs to every individual disease target. "I'm fascinated by the conundrum America has gotten itself into over health care," he says. "At a certain point, we just can't pay for it all; society will have to make choices. But we're so individualistic that we won't empower any government to contribute toward those choices. It comes down to whether basic health care is a right. I say it is. A lot of America says otherwise."

Having worked closely with researchers in Denmark on his genetic studies, Mulvihill particularly admires that country's attitude toward health outcomes analyses. There, a nationwide cancer registry contains basic information on all cases of cancer from 1943 to the present, providing researchers with a wealth of data. "The Danish people don't feel that their informed consent is necessary for properly trained and credentialed researchers to examine available registries and databases," Mulvihill says. "So answering the question 'Do the offspring of cancer survivors have more or fewer chromosome abnormalities than expected?' was a mere computer exercise in Denmark; it took six months and cost $40,000. We've been doing the same study in the U.S. for 17 years and [have spent] at least $15 million."

Since 2006, Mulvihill has also been a scientific advisor to the Radiation Effects Research Foundation (RERF). Established in 1975 by Japan and the U.S., RERF studies survivors of the Hiroshima and Nagasaki bombings. Mulvihill attended RERF's annual meeting in February of this year; as his plane flew over Sendai, he recalls thinking that big waves could damage such a flat area. Not two weeks later, a magnitude 9.0 earthquake and subsequent tsunami devastated Japan's eastern coast, and the American press was seeking out his knowledge of radiation effects in covering the Fukushima power plant's near-meltdown.

Mulvihill was also recently asked to comment for an article in *USA Today* about research showing that two specific genes, CYP1A2 and AHR, come in different forms that affect individual caffeine consumption rates. He hailed this finding as an added boost to the growing awareness that "we are all a unique set of genes interacting with a unique environment."

The interaction of Mulvihill's own genes with his environment apparently led to a love of travel, whether for work or pleasure. Japan is only one of the more than 40 countries that Mulvihill has visited. Frequent plane travel doesn't faze him—in fact, he relishes the "uninterrupted thinking time" that long flights provide.

Whenever his busy schedule allows, Mulvihill also likes to spend time with his family. He and Charlotte have three grown children—sons Peter and William and daughter Kate. None of them followed their father into medicine or science, but they have produced another body of work in genetics: six grandchildren for "Gramps" or "Grampa John" to dote on.

Mulvihill's interest in genetics has also found an outlet in a non-work arena: he's considered writing a play about Gregor Mendel, the Austrian monk who was a founder of the field. "I've read five of his biographies, including Hugo Iltis's *The Life of Mendel*; there are some fascinating bits in the whole collection, and I have the beginnings of a script in my head," he says. Clearly, genetics is more than a job to Mulvihill. In his case, DNA does seem to be destiny. ■