

Fred Apple

Fred Apple was born in June 1953 in the Hudson River Valley city of Troy, New York, just 20 miles from the Vermont border. Every summer, his parents would pack him and his brothers into the family car, cross into Vermont, and then head northeast toward the White Mountains and the town of Bethlehem, New Hampshire. Once a sleepy mill town, Bethlehem, with its mountain air and views, was transformed into a glittering resort during the waning decades of the 19th century, the so-called Gilded Age. Wealthy patrons—along with presidents and poets like Robert Frost—came by train to fill the elegant hotels and mansions that lined the streets. With the rise of cars, they began visiting other spots and the grand buildings fell into disuse. Around 1916, Jewish families seeking relief from hay fever began flocking to Bethlehem—and they and their descendants kept coming.

“You have to picture all these people moving into the town for the summer. There were kids everywhere,” Apple said. For him, Bethlehem would be a kind of Shangri-La. “We had a community there that was just kind of an escape from the real world,” he said. His grandparents had a modest bungalow where he and his family stayed, though Apple was rarely indoors. Naturally outgoing and intensely athletic, he would spend his days shooting hoops and playing softball with friends, some of whom he still sees. They would hike and camp in the White Mountains 2 or 3 times a week. And every day, Apple would golf. He learned to play at the age of 7 and was, by all accounts, a natural.

“Fred has always had one of the prettiest golf swings that anybody’s ever seen,” said his younger brother Gary Apple, who works as a sportscaster in New York City. “He was born with this really magical, in tempo, never changing swing that has never really left him. It’s sort of a part of who he is. I think it goes back, in many ways, to his personality—he’s somewhat unflappable. I think that’s pervasive in a lot of avenues in his life.”

Apple has pursued other passions over the years—rock and roll, cooking, opera, and running. His penchant for running—he would run 12 marathons in 6 years—is the stuff of legend. He runs through wind, sleet, and rain—in the wee hours of the coldest, darkest Minneapolis morning and in the midst of snowstorms. Once, while living in St. Louis, he jumped out of a taxi and ran all the way home—7 miles through a driving blizzard—when he heard what the driver wanted to charge him. “He didn’t get into an argument,” said Jack Ladenson, the Oree M. Carroll and Lillian B. Ladenson professor of clinical chemistry at Washington University School of Medicine. “He said, ‘I’m getting ripped

off. I’m not going to do it—and pops right out of the car.’”

Apple revealed an almost uncanny flair early in his profession as a clinical chemist. In 1980, after a few rudderless years—he turned down a graduate program at Princeton and a postdoc at Harvard—he came to work with Ladenson. He quickly made a splash when he and a colleague, also a runner, drew their own blood and found that the reigning biomarker for heart attacks, creatine kinase-MB (CK-MB), was elevated after intense exercise—an observation that helped transform the field of cardiac biomarkers. Over the following years, as medical director of clinical laboratories at the Hennepin County Medical Center in Minneapolis, he set out, along with Ladenson and others, to develop a new kind of assay based on measurements of the troponin I protein. Partnering with industry, he helped to refine and implement an array of troponin I tests so exquisitely sensitive that they could measure the minutest fluctuations in protein levels—which brought its own set of challenges: how do you distinguish between normal and elevated concentrations of troponin I? What does it mean to be normal? What does it mean to be at risk for a heart attack?

Intellectually curious and energetic, Apple has tackled these and other scientific challenges—he is also medical director of the toxicology laboratories at Hennepin—with relish. At the same time, he is intensely hands on and practical. Helping patients is a critical part of the bargain.

“Fred was one of the first to recognize the value of the troponin assay for myocardial infarction,” said Scott Sharkey, a cardiologist at the Minneapolis Heart Institute Foundation and an old colleague and friend of Apple. “Once you make that diagnosis it easily translates into millions of lives saved.”

It’s tempting to link Apple’s professional success, and his renown is worldwide, to that golf swing. “He is calmly competent and calmly on top of things though sometimes when you talk with him you wonder, ‘Is he really going to pull something off?’ And then he always does,” said Ladenson. Part of it may go back to the game—in golf, decorum is prized over showmanship. But the fact is, Apple still can’t quite believe his luck. “Never in



my wildest dreams would I have thought that this type of work would've allowed me to see the world and contribute to science in the field worldwide," he said.

"His career path has surprised even him," said his brother Gary. Serendipity may have played a role but it is possible to discern in the arc of his career another kind of motivation. Coming to work with Ladenson after turning down other offers—and then joining clinical chemistry with his love of running—it's as though Apple was waiting to find the right moment to swing. He makes his own decisions, in his own time—when he feels a personal connection. He has travelled the world and yet he has stayed at the same job for 31 years—he loves the hospital where he works. It goes back to his golf game but what drives him may also be a desire to recapture the feeling of community that he found in Bethlehem.

Certainly the Apple family roots run deep in the Northeast and, in particular, the Hudson River Valley. The Gilded Age, with its promise of opportunity and wealth, drew waves of Jewish immigrants from the far corners of Europe, including Apple's grandparents. They were less than 5 years old when they arrived in Ellis Island during the 1890s. After a short stay in New York City, Apple's paternal grandmother and grandfather moved with their families to Troy, which by then was fast becoming a melting pot of tightly knit communities. They met there and married. Raised in the Orthodox Jewish tradition, they passed the same customs of observing sabbath and keeping kosher to their son Ira, Apple's dad.

Ira, it turned out, had terrible hay fever. He heard about an organization, the Hebrew Hay Fever Relief Association, located in Bethlehem. In the summer of 1947, he met Apple's mother, Anna, there. They married the following year and had their first son, Leslie, a year later. Fred arrived 4 years after that. They had 3 more sons and raised them in a hybrid version of Judaism, less orthodox and more conservative, but always with the focus on family. "We were brought up to be extremely close. It reverberated in my mind, 'Be your brother's keeper,'" said Gary Apple. "I can't tell you how many times Fred has been there for me."

Ira, an accountant—and a strict but open-minded man—had another saying that stuck with his sons. "He essentially instilled in us that you go after your dreams," Apple said. Apple took that lesson to heart, too, though not always in the way that his father intended. "I was very much an explorer. I liked to open doors which I shouldn't have opened." He had 2 groups of friends—his close friends and "the rabble rousers." He would shoot hoops with the first and then run 2 miles across town to meet the other. "They were fun—different, more exploratory," he said.

He found ways to ease the tension between his adventurous spirit and his parents' expectations. One was to not tell them everything he was doing. He would say that he was going golfing with his friend, Rich—they were both members of the high school varsity team, which won 3 New York State Championships—and instead hop a train to Manhattan. "We'd hang out in the city all day and be home by 8 o'clock and they wouldn't even know. I spent every other Saturday in New York City," said Apple.

He let his father in on his plans on at least one occasion. It was the summer after his sophomore year, when he was 15. His friend had gotten him tickets to a music festival happening an hour down the road, which he showed his dad. "My father plucked the tickets from my hands and said, 'You're not going to a concert, hitchhiking down the thruway.' He handed them to my friend Bobby and said, 'You need to get someone else to use these,'" said Apple. There is a brief scene in the movie *Woodstock* showing his friends Eugene and Bobby. "I would've been with them," said Apple.

He soon made up for it. That same year, he heard the Grateful Dead for the first time and was instantly hooked. He would get into his Volvo 120S—which his father had received in exchange for his accounting services—and drive 10 hours to hear them. When he was in college, he spent 5 days hitchhiking cross-country to see them play San Francisco. "There was just something about the energy," he said. "It was your family."

In 1970, he was at the March on Washington, the culmination of an extraordinary decade. "You can't describe to people what it was like growing up on the edge of such a counterculture," he said. By then he was a student at Rensselaer Polytechnic Institute in Troy. He liked science but did not think he would go into it professionally, which made his college years a bit unfocused. "If you didn't have a dream of what you wanted to do, you just muddled along and took courses," he said.

In his junior year, the chair of the chemistry department invited him to work in his laboratory. The chemical reactions reminded him of cooking, which he loves. He majored in biology because they didn't have a degree in biochemistry and decided he wanted to be a college professor. He was accepted into a graduate program at Princeton. Meanwhile, his girlfriend—whom he was hoping to marry—had her heart set on a graduate program at the University of Minnesota. He turned down Princeton and applied to Minnesota. "We broke up. She ended up going to Columbia," he said. He went to Minnesota.

"You make decisions," he said. "I'm a big fan of Robert Frost," referring to his famous poem "The Road Not Taken." He moved to Minneapolis in 1975 and

spent the next 4 years working on a project on membrane fluidity and *trans* fatty acids. He decided to “shoot for the stars” for his postdoc and wrote to the Harvard lipid chemist Konrad Bloch, who won a Nobel Prize for his work synthesizing cholesterol. Bloch invited him to come to Harvard. “Again, I was dating someone who I liked, it was serious, and she didn’t want to move to Boston,” he said. He called Bloch and told him he wasn’t coming. Ten minutes later, his dean called, screaming. “I said, ‘You know, I’ve made my own decision. I’m not going to do this,’” Apple said. “At that point, I was kind of rudderless.”

He took a job teaching physics in the Minneapolis school district and then one across the river at the University of Wisconsin–River Falls, and was not enjoying it. He called his old graduate student friend Mary Ellen King. “I said, ‘What are you doing with your life?’” he said. She told him about her career in clinical chemistry and that it offered a real job on hard money.

Apple applied to several programs and was about to leave for the University of Utah but—wanting to keep his options open—decided to check out the University of Miami’s program in marine chemistry. His uncle, a cardiologist, happened to live in Miami. Apple was sitting at his uncle’s pool having a beer when he got a phone call. It was Ladenson, calling from Washington University, where Apple had applied. “He said, ‘Listen, you’re probably sitting around the pool in Miami, having a beer. I need you to come up here. We have one slot open and we want to look at you.’ I looked around—I would’ve thought he was in a bush. He described exactly what I was doing,” said Apple.

“What else are you going to do when you’re visiting your uncle?” said Ladenson. Apple moved to St. Louis in 1980. He and his girlfriend had split up, a good thing given the intensity of the Washington University program. “It was like doing a medical residency,” he said. He fell in love with the place—“You were judged on what you had to offer,” Apple said—and the field of clinical chemistry. It was during his first rotation that he and his colleague made their observation about CK-MB, a discovery that set the course for his entire career.

In 1982, he took a job at the Hennepin County Medical Center, which was a kind of homecoming. “I really had fallen in love with Minneapolis,” he said. Girlfriends had helped define his early career but he remained single for the next decade. “He had no trouble finding a date. But he was looking for the right person to marry and he couldn’t quite find that,” said Sharkey. “And then boom, he met Jan.”

They met in 1992. She was doing a psychiatry residency at the University of Minnesota. “It was love at first sight,” he said. He found his match in Jan—

intelligent, outdoorsy, artistic, and extremely adventurous. On their second date, he called his mom and told her he’d met the woman he was going to marry. On their honeymoon, they went hang-gliding in New Zealand—it was Jan’s idea. “We were 5400 feet off the ground for about 8 minutes,” he said.

Years ago, they bought a house on an acre of land in the suburb of Minnetonka, 9 miles from downtown Minneapolis, which is where they raised their 2 daughters, Liz, now 25, and Molly, 18, both talented artists. Apple adores spending time with them—running, hiking, reading poetry. But living in a house of females can sometimes flap the unflappable Apple. “I grew up in a male family and now I live in a female family. I have to understand the sensitivities of the women in my life on a daily basis. That’s a huge challenge because sometimes as a male, you lose track of that,” he said.

Apple rises at 5:30 am and after a run comes back to read *The New York Times* over breakfast. After work, he returns home, where he and Jan might concoct a fabulous dinner. They might watch TV or listen to music in the living room, where the walls are lined with paintings and family photos going back a hundred years, to the early days in Bethlehem. They also have a condo in Bretton Woods, not far from the White Mountain town where he spent all those summers.

When asked where he feels most alive, it is in those mountains. “If I could be with my family up in New Hampshire, hiking up Mt. Madison or Mt. Washington, I’d be in heaven.” Apple said, “If the 4 of us could go hiking and camping up there just for a couple of days, I’d be happy if I died on the spot.”

Author Contributions: *All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.*

Authors’ Disclosures or Potential Conflicts of Interest: *No authors declared any potential conflicts of interest.*

**Sponsored by the
Department of Laboratory Medicine
Boston Children’s Hospital**

Misia Landau
e-mail misia.landau@gmail.com

DOI: 10.1373/clinchem.2013.217968