

## Raymond Alexanian '53: Myeloma pioneer

By Laura Stephenson Carter

**F**atigue and debilitating pain had begun to consume Sarah Newbury. First it was her back; when she bent or stooped it felt like knives were stabbing through her spine. Soon rheumatoid-like pains began clawing at her arms and legs. Two years into her illness, she fell. The pain became so excruciating that she was confined to her room, and her husband had to lift her in and out of bed. One time when he was carrying her, her thighbones fractured. It was two more years before she was hospitalized at St. Thomas's Hospital in London, and by then her body was so grotesquely twisted, broken, and deformed that she looked like a worn and frayed rag doll. The doctors gave her the best available treatment—infusions of orange peel, rhubarb pills, and opiates—but they couldn't save her. On April 20, 1844, the 39-year-old housewife died. An autopsy revealed that the bone in her sternum and her thighs had been replaced by a red, gelatinous substance. Hers was probably the first recorded case of multiple myeloma, or cancer of the bone marrow.

In the century and a half since then, cancer research and treatment have come a long way, thanks to physicians like Raymond Alexanian, M.D. A professor of medicine and the myeloma section chief at M.D. Anderson Cancer Center in Houston, Texas, he has spent his career breaking new ground in the treatment of myeloma.

"I think that seeing patients who used to live only two or three years in older days but who can now live, say, 10 to 15 years—and have a normal quality of life—is very satisfying," says Alexanian.

There is no cure for myeloma, a malignancy of plasma cells in the bone marrow. But earlier diagnosis and better treatments can prolong life and stave off relapses. Myeloma represents about one percent of all cancers and occurs in about four out of 100,000 people in the United States. There are approximately 13,000 new cases of myeloma diagnosed in the U.S. each year.

"Our treatments have become so much more effective that most [patients] can rapidly achieve a remission that is usually of good quality and long duration," says Alexanian. "We are learning better how to prevent one of the serious complications—pathologic fractures." Like the fractures that Sarah Newbury suffered.

And "there are ways of relieving pain—for example, with a procedure called a vertebroplasty, where you inject methyl methacrylate [an acrylic bone cement] into the vertebrae to relieve the pain of compression fractures." Newbury would surely have welcomed that, too.

Earlier diagnosis, better supportive care, better chemotherapy, better quality of life, and longer life span—all of these add up to real improvements, Alexanian points out.

A distinctive protein in the urine of patients with myeloma was discovered in the 1840s, but routine diagnosis of myeloma was not pos-

sible until the 1930s, when serum and urine protein electrophoreses were developed. And treatment didn't become available until the chemotherapy drug melphalan was developed in 1958.

While some of those advances were taking place, Alexanian was growing up in the Bronx in New York City, where he was an honors student at DeWitt Clinton High School. His parents were Armenian immigrants—his father was a grocer—so coming to Dartmouth College in 1948 was a bit of a culture shock for the young New Yorker. "Going from my background in the Bronx to Dartmouth," he says,

"had a huge impact. It's a time in my life that I'll never forget."

Alexanian hoped to become a doctor, following in the foot-

steps of his maternal grandfather, who had been a physician in Turkey. But, he remembers, "I had no idea what sort of physician I wanted to be. At first I wanted to be a general practitioner."

After completing his M.D. at Harvard in 1955, he headed to the University of Washington for a residency in internal medicine and, later, a fellowship in hematology. "I was impressed with the careers of my mentors at that time and thought that it would be appealing to try to be a teacher of students and a researcher," he recalls. Then one mentor—hematologist Clement Finch at the University of Washington—"really impressed me to focus on research in hematology. He was a brilliant and clever person who imparted enthusiasm."

In 1964, after a brief assignment as a research instructor at the University of Washington, Alexanian joined the faculty at M.D. Anderson. At first, his research "included all kinds of hematologic cancer—leukemia, lymphoma, and myeloma," he says.

His early work focused on erythropoietin, a hormone that regulates red blood-cell production. He was one of the first to measure erythropoietin in human beings; research until then had been with animals. "Much of my work laid some of the basic science foundation for the later development of erythropoietin as a treatment for anemia," he says. "It was developed as a commercial product and used to treat anemia—at first patients with kidney failure and anemia, and then patients with anemia from many different causes."

**G**radually, however, he began seeing mostly patients with myeloma and Waldenström's disease, a lymphoma-like disorder characterized, like myeloma, by an unusual protein in the blood. "My research changed from the field of erythropoietin," he says, to "developing treatments that would improve [those patients'] quality of life and life span. Over the past 30 years," he adds, "our group has been involved in most of the advances in the treatment of myeloma."

Indeed, the prospects for myeloma have gone from "essentially no effective treatment prior to 1960, to treatment that is now effective in approximately 80 percent of patients," Alexanian notes.

In 1969, Alexanian showed that melphalan combined with pred-

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nison gave better results than melphalan alone. And in 1984, he and Bart Barlogie, M.D., Ph.D., introduced VAD therapy, named for the drugs it utilized—"V" for vincristine; "A," the symbol for doxorubicin; and "D" for dexamethasone.

Though there is still no cure for myeloma, treatment is now able to "achieve control that can sometimes last for many years," explains Alexanian. "There are more and more patients who have lived more than 10 years than ever before. In order to reach that point, there have been a series of trials of different drugs, different combinations of drugs, and then the use of intensive treatments supported by one's own blood stem cells."

In 1999, a startling discovery was made by Barlogie, who had moved on to the Arkansas Cancer Research Center—that thalidomide could be effective in treating myeloma. "Thalidomide was a drug that was abandoned 30 years ago because of birth defects and was only discovered recently by Dr. Barlogie," says Alexanian. "He found by chance that thalidomide, a drug long abandoned for any purpose, was an active agent in myeloma. The use of this drug, especially in combination with other drugs such as high doses of dexamethasone, has been a very effective treatment."

Similarly, Alexanian continues, "it took us a long while to recognize that high doses of steroids, glucocorticoids such as dexamethasone or prednisone, were active in myeloma. Those drugs had also been around for many years, but we just didn't know how to use them in safe and effective doses."

The VAD therapy may soon "be replaced by a combination of thalidomide and dexamethasone, the 'D' part of the VAD," Alexanian says. "With all these experiences, one step follows the previous one. And then every so often there's a breakthrough."

Alexanian is optimistic about another promising new drug—PS-341, which is being tested now on myeloma patients. It seems to be "effective in about 40 percent of patients with resistant myeloma."

He has also been assessing high-dose chemotherapy combined with autologous bone-marrow transplants. "One of our transplant specialists . . . pioneered using one's own bone marrow or blood stem cells in treating not just myeloma, but leukemia or lymphoma and myeloma," he says. "It turns out that that kind of transplant is much safer than a donor transplant from a sibling who has a matching tissue type."



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*During the course of alumnus Alexanian's career, he has seen—and played a major role in—some significant advances in the treatment of myeloma.*

Certain kinds of double transplants look promising, too. They entail high-dose chemotherapy followed by an autologous transplant and then an allogenic transplant from a matched donor. "Unfortunately," Alexanian says, "not everyone has a matched donor. Matched donor siblings exist in only one-third or one-fourth of patients."

Alexanian is proud of his team's role in advancing treatments for myeloma and Waldenström's. "Our experience has put us on the cutting edge of modern therapies for these diseases," he says. But, he adds, "we're still short of a cure."

Nevertheless, the availability of better treatment for Waldenström's disease "has improved the survival of those patients from an average of five years to an average of about nine years. Many of these patients . . . live so long that they die of something else before they show recurrence of the Waldenström's disease," he says.

"Unfortunately the same can't be said yet about myeloma," Alexanian adds. Although the disease may go into remission, it will recur after a few years. The best physicians can do is to achieve a complete remission—where all signs of the disease disappear—and then "to try to sustain that remission for as long as possible."

**W**hen Alexanian is not exploring new treatments for myeloma, he sees patients, publishes papers, teaches students and residents, participates on hospital committees, and gives presentations at national and international meetings. He also enjoys traveling with his wife, Lois, including to Tokyo, where their daughter and her family live.

As for the future of the field to which he has devoted his career, Alexanian says, "There are so many things going on with all cancers now—it's almost a revolution with new molecular treatments and other techniques that we never imagined becoming available. I think we're going to see a real revolution in treating all cancers."

He is modest about his own contributions but admits that "I'd like to know that when people look back on the history of myeloma . . . somewhere, buried in the fine print or a footnote, there might be some reference to our work." Perhaps a century and a half from now, one of Sarah Newbury's descendants will come across such a reference and wish Alexanian had been around in the 1840s. ■