Remarks* by

Norman E. Sharpless, M.D.
Director, National Cancer Institute

"Patients I Will Never Forget"

The 2018 Hardesty Lecture
West Virginia University
Morgantown, WV

October 18, 2018

Good afternoon. First off, I would like to add my congratulations to David and Susan Hardesty. What a wonderful event. I can tell your fingerprints are all over it. A round of applause for them.

There is a palpable sense of momentum around cancer research and cancer care here, and this is a state that has a large burden of cancer. West Virginia University is bringing in great leadership with the goal of developing a world-class cancer institute. That's a wonderful vision that the NCI shares with this university.

Being here on campus reminds me of my last day of school, 25 years ago. If I close my eyes, I can recall the day I graduated from the University of North Carolina School of Medicine.

There were family members, hugs and tears, and buckets of dubious fried chicken. My peers and I recited the Physician's Oath. This is a modified version of the Hippocratic Oath, which is about 2,500 years old. The Physician's Oath includes solemn commitments to certain principles of being a good physician.

We committed to treat not just a disease, but the whole patient.

We committed to ask for help when we need it. That part has served me well in federal government.

We committed to the sharing of knowledge. We committed to teaching our peers and our patients.

And then there's the last line that I've always kept with me. It is: "May I long experience the joy of healing those who seek my help."

The *joy of healing.*

The joy of patient care is really what drove me to practice medical oncology. When a former patient comes back to see you and he or she is healthy and happy, the joy is profound.

But you also see patients at their sickest. Staring death in the eye. And they can astonish you with their sense of humor and dignity under the most terrible circumstances.

*This text is the basis of Dr. Sharpless's oral remarks. Use with the understanding that some material may have been added or omitted during final presentation.

I once took care of a patient with leukemia who was treated heavily with chemotherapy. She was eventually cured of her disease but, physically, she went through hell first. The treatment ruined the taste of all food, so she developed chemotherapy-induced anorexia. As a result, she lost weight, and became very weak and debilitated. We tried lots of stuff to help her regain her appetite and nothing really worked. She looked so frail and I was concerned about her. I said, "How are you doing?" She said, "Well, Dr. Sharpless, I would really like to thank you for this highly effective weight loss program you put me on." I was awe-struck that despite the circumstances, she was trying to make *other people* laugh.

But not every patient is healed. You take care of some patients for a very long time, you get to know them, and you get your hopes up that you can help them. You use the best research you can find. But, despite your best efforts, sometimes there are terrible outcomes. There are no answers why. There is no joy and no healing. There are some terribly dark and difficult days for both patients and physicians.

Eventually, I felt that the needs of my patients outpaced the information that was available. The pursuit of the joy of healing drew me back to the lab so I might get closer to finding the answers that my patients, my colleagues, and I so desperately needed.

So, as both a clinical oncologist and a cancer researcher, I've been able to see how these two worlds work together. Today, I'll honor my commitment to share information. I will tell you about three patients who changed the way I think about the field of cancer research.

The first patient I'd like to talk about is someone I met in 1997, when I was an oncology fellow at the Massachusetts General Hospital in Boston. I'd done my internal medicine training for three years, and now I was a would-be cancer specialist. And those of you who remember the late 1990s, that was the height of the AIDS epidemic.

It’s hard to explain to young doctors today what it was like back then. Half of an internal medicine service, in those days in a big city like Boston, would be patients dying of AIDS, in the most baroque, Gothic ways imaginable, with these terrible infections, with organisms we'd never heard of. And normally harmless microbes, like bread mold, could make them sick. It was an unbelievably difficult time because AIDS was so new.

Constantly, there were new clinical situations that we'd never encountered. We learned how important the immune system is to keep all these infections at bay, and there were a lot of young patients and a lot of patients from vulnerable populations. It was a dark time in American medicine.

I remember one young man, an artist, who had not thought of himself as sick. He'd never been ill, and he came to the hospital because he was having trouble breathing. He did not know he was HIV-positive at that time. He went from being someone who thought of himself as a well individual to being critically ill in just a moment. He was rapidly diagnosed with this disease called pneumocystis pneumonia. It's this weird organism that didn't really cause illness until the AIDS epidemic. He needed a breathing tube, so he couldn't even talk with us. We treated that disease, and he got a bit better, and he was extubated. He could finally tell us about the terrible headaches he was having.

He then had a lumbar puncture and turned out to have a disease called cryptococcal meningitis, which was another AIDS-defining illness nobody had ever really treated before. So, he had been diagnosed with two extremely rare conditions within two days of each other. We treated those, and he started feeling better.

Then, we noticed he had enlarged lymph nodes. One of these was biopsied, and it turns out he had non-Hodgkin lymphoma, an AIDS-defining illness as well—at least this subtype of it.

The oncology service was called in so that's how I became involved. I remember that I had never taken care of such a patient. There wasn't a lot of literature on how to treat lymphoma in patients with AIDS at that time, and I was a fellow-in-training.

From an academic perspective, this was a fascinating educational challenge. I read up on HIV lymphoma. I talked to one of the greatest lymphoma doctors I've ever worked with—Mike Grossbard, who was, at that time, my attending.

We discussed it a lot, and we decided that this patient was way too sick for standard cancer therapy. We couldn't give him the heavy doses of drug we normally would in this situation, so we found this unusual regimen. We cut the dose in half, and we gave him this therapy.

As a result, his cancer melted away. It was marvelous. Mike and I felt so self-congratulatory. We were already figuring out how we were going to write this guy up as a case report. We thought we were really clever.

Well, there was a lot we didn't know back then. About retrovirology, immunology and biomedical research. The AIDS epidemic was a tremendous teacher, but we learned those lessons in the worst way.

After about a month of therapy, our patient's immune system was shot. He developed sepsis and shortly after that, he died.

It doesn't really benefit someone if we make his cancer go away and we don't make him better. Sometimes the treatment is worse than the disease.

I learned another lesson from this patient that only becomes obvious in the context of time. When I think about this patient I took care of 21 years ago, and what would happen with him today, I realize how much times have changed. We have drugs like rituximab that are much better. We have a regimen called EPOCH, which was developed by Wyndham Wilson at NCI , and that's better. We would sequence his tumor and molecularly characterize it. We know now that these tumors are largely caused by the Epstein-Barr virus.

We know a lot more about the cancer, but most importantly, this patient would probably *never get lymphoma in the first place* because we have highly active antiretroviral therapy. So, we have all these treatment options which didn't exist back then that have made HIV lymphoma really rare in the United States now. We have made an unbelievable amount of progress in that area in just 21 years. We've totally transformed that disease, its therapy, and its prognosis. It shows how fast cancer research can go. We can make great progress in short bits of time.

The next patient I'd like to talk about is someone I took care of at the University of North Carolina Medical Center in Chapel Hill in 2010. She was an Hispanic woman who didn't speak much English. She was about 24 years old and she had a few young children. She came to our emergency room for chest pain and trouble breathing. She had a scary looking chest x-ray. She had a biopsy and it turned out that she had lung cancer.

This was very odd, because this was a young woman—24 years old—and she never smoked cigarettes. It was a strange presentation for lung cancer. She was stabilized on the inpatient service and then started on carboplatin/Taxol, routine chemotherapy for lung cancer. She was sent back home, where she was going to get cyclic chemotherapy. Every 3 weeks, she'd come in and get another round of treatment.

I met her a couple of months into her therapy, when she came in for her fifth cycle of this regimen. I was doing what we called the “Doc of the Day,” which meant that I would see the patients who were getting established therapy and make sure they were doing okay, and then give them their next round of therapy.

A young oncologist-in-training came to me and said, "Yeah, here's this patient who is getting treated for lung cancer, and she's 24, and she’s never smoked, and sign here." He handed me the chemotherapy orders and I said, “Wait, wait. Did you say 24 years old?” He said, "Yes." And I said, "Did you say, ‘Never smoked?’" And he said, "Yes." And I said, "Well, that's really unusual. What do you think is going on? Did you sequence her for this gene called EGFR?" And he said, "Yeah, we did that. She didn't have that, so, you know, she's getting this regimen." Also, it was also clear the chemotherapy that had worked for a while and helped her, was not working anymore. So, it was time to start thinking about what to do next. I asked, "Well, did you sequence the other genes, like ALK and ROS-1?" And the fellow looked at me and said, "What's ALK?" I said, "Oh, well, let me tell you, because I'm a scientist. I'm in the lab a lot." I had just been in a meeting a week before and heard a talk by Jeff Engelman, a prominent lung cancer researcher and doctor at the time.

Jeff was one of the people who was starting to use ALK inhibitors for a rare lung cancer called ALK-translocated lung cancer. It's only a couple of percent of patients, but they tend to be young women who have never smoked. This patient had the demographics for ALK-translocated lung cancer, but we would need to sequence her tumor again to find out for sure.

This kind of sequencing was not routinely available at the time, but we did it. We sent a tumor specimen to a special lab, and we were told that it would take 5 or 6 weeks to get the results back.

In the meantime, our patient’s treatment stopped working. She got sicker and sicker and, finally, she decided to stop treatment and enroll in hospice care.

Coincidentally, that very same day, we got the lab results back. She had a classic defining mutation that showed what I suspected: she had ALK-translocated lung cancer.

At the same time, a clinical trial for an ALK-inhibitor drug was taking place just a few hundred feet from the emergency room door where this patient first entered. We did not

know then, but we know this now: an ALK-inhibiting drug can give patients with ALK translocated lung cancer about 4 more years of good quality life as opposed to a few weeks. She's exactly the kind of patient they were looking for.

The molecular diagnostics would have helped her, but we got this information about 5 weeks too late.

This was not even a result of malpractice. She didn't get bad care. She got standard care. She got what she would've gotten at most any other institution in the country at that time. But the point is that sometimes the standard of care is not very good.

That was one of the worst days of my career. I was frustrated and upset. I remember thinking that this was going to happen again. These patients are going to come here. They're going to have mutations that we can treat, but we're not going to identify them in time. We're going to give them the standard of care, which may not be good. How are we going to prevent that from happening?

At that time, I also had a leadership role at the UNC Cancer Center, and I was in a position to make some changes. I went straight to one of the cancer geneticists at my cancer center—Dr. Neil Hayes. We hatched a plan to implement some changes.

Almost immediately, we made this kind of sequencing a reflex. If a patient had a new diagnosis of lung cancer, the pathologist wouldn't have to think about it. They would just test for EGFR and ALK, along with some other genes that indicate a cancer subtype.

Also, over the course of a few years, Neil and I developed a protocol called UNCSEQ. This is a panel of about 300 genes we would sequence in cancer patients. We went on to sequence 3,000 patients, and we followed them to find out what happened to them. In addition, we did something that was considered really innovative at the time- we shared the results with the patients and their doctors, so if there was a meaningful event, the therapy could be changed.

This allowed us to learn a lot, scientifically, and publish a lot of papers. We created new resources that helped patients with cancer, but it was all instigated by a bad outcome in a patient.

So, what did this patient teach me? If you think about our options in 2010 versus 2018, again, you will realize how fast cancer progress can be. If this patient came in today, to virtually any hospital in the United States, she'd get sequenced automatically for, not three genes but, hundreds of genes, for 10 or more driving events that all have therapeutic implications in lung cancer.

What's more -- the government will now *pay for* this testing. CMS has decided they cover next-generation sequencing for this for all Medicare patients. Some of these mutations and tests were *unheard of* in 2010. In 2018, they are standard of care. That was only 8 years ago.

Plus, the results of these new tests will come back in 3 days, not 2 months. The treatments that are done after identifying these genes are so much better now. In some types of lung

cancer, we believe we are curing some of these patients in the metastatic setting with immunotherapies. So, our ability to treat non-small cell lung cancer has improved markedly in the last 8 years.

I don't think we would've been able to cure that woman, had she come in today. But, we certainly would've been able to do much better than we did.

Another thing I learned from her is that we can't accept the status quo. When patients like this present to us, we have to fight for them. We have to advocate for them. We have to continuously work for them, to provide the best care possible, and not be satisfied with the standard of care if it's not good care. And we have to do this for all our patients. We have to do this for our rich VIP donors, but we also have to do this for patients who are poor and don't speak English.

The third patient I'd like to talk about is someone I took care of just a few years ago, in 2016, at the University of North Carolina. As Richard mentioned, I used to treat acute leukemia on the inpatient service, and this was a very charming 60-year-old African-American man who lived in Durham. He was a father, a husband, and a journalist, and he was diagnosed with acute myelogenous leukemia—AML. AML in a 60-year-old is generally a pretty bad disease. I had not seen his bone marrow biopsy results yet, but I assumed he was going to have an incurable cancer. I was preparing to tell him and his wife about how this was a really tough disease. He was going to need very aggressive therapy. If he was lucky, we might be able to get him into a bone marrow transplant, which was the only chance at a cure, and that was a very slim chance.

The bone marrow is tested for the cytogenetic abnormalities that drive the cancer and, in someone who's 60, most of the news you get from cytogenetics is bad—adverse cytogenetics. A few patients will have intermediate cytogenetics, and rarely, very rarely, will someone have good cytogenetics.

We got the results of the bone marrow biopsy, and to all our surprise, he came back with what's called “good cytogenetics.” This meant the disease is actually very curable, and he would need much less therapy. I remember the day I told his family that the results were surprisingly good. His two adult daughters were crying and happy, and his wife was crying and happy, and the patient was a little overwhelmed. It was a moment of joy for all of us.

We treated this patient with standard chemotherapy, and it wasn't terribly difficult. And then he promptly went into remission. Most of his treatment was out of the hospital, and he's in remission now. I had coffee with him a few weeks ago when he came to visit me at NIH and he’s doing well.

This story makes a point about molecularly-precise therapy. Our clinical decision making can be informed by having the diagnostic molecular information. That is a real movement in cancer. We need to understand the molecular biology of everybody's cancer to treat them right. No two patients are alike.

But the other thing it taught me is that sometimes things turn out much better than you expect in cancer. This was a patient where I expected the worst and he's doing great.

And that surprised me and motivated me and continues to motivate me now.

I have shared stories of three patients who have had an impact on my career and my life. Every one of these patients would have had a better outcome if they needed care today instead of 1997, or 2010, or even 2016. Options and outcomes continue to improve with every passing day. Every patient benefits from the discoveries that came before.

And tomorrow will be better than today in the fight against cancer.

So, I'll sum up what I learned from them:

I've learned that cancer progress happens really fast.

I've learned not to accept the status quo.

I've learned that the standard of care might not be good care.

I've learned that we have to keep pressing and fighting.

And I've learned that sometimes, we'll be pleasantly surprised and that we should always keep hope.

I will close today with that special line from the physician's oath again.

"May you long experience the joy of healing those who seek your help."

Thank you.