

NIH Clinical Center Office of Communications & Media Relations

Reflections: Dr. James F. Holland

September 6, 2013

Dr. James F. Holland is a Distinguished Professor of Neoplastic Diseases in the Department of Medicine at the Icahn School of Medicine at Mount Sinai in New York. He was in the first group of research physicians to staff the NIH Clinical Center, as a senior surgeon at the National Cancer Institute. In 1972 Dr. Holland was awarded the Albert Lasker Basic Medical Research Award for his outstanding contribution to the concept and application of combination therapy in the treatment of acute leukemia in children. His present and future efforts are aimed at consolidating the evidence for an etiologic role for a major portion of breast cancer, so that new preventive and therapeutic endeavors can begin. Dr. Holland shared his memories of his early days at the NIH Clinical Center, as well as his perspective on developments in scientific research since then, in a phone interview conducted on September 6, 2013 with the CC News.

CC News: You have graciously agreed to share with us some of your memories of being at the CC back when it first opened in 1953. You joined NCI in 1953: what was the position you were hired for, and what were your main responsibilities in that role?

Holland: I was a medical officer, and perhaps the most senior clinician. My immediate superior was Leonard Fenninger, who I think was chief of the medical service, and at the time G. Burroughs Mider was the acting clinical director. I ran a research activity primarily in acute leukemia at the time, and some junior colleagues who had just finished their residency joined me. There was no formal fellowship in medical oncology at the time, but I had been for two years under the aegis and supervision of Alfred Gelhorn, who was my mentor at the Francis Delafield Hospital at Columbia University in New York.

I conducted rounds, and supervised the implementation of research programs and research concepts with individuals, and there were several members of the faculty—Roy Hertz was one—who was senior to me, and ran an endocrinologic division. Fenninger I think ran the medical division, he was most interested in metabolism and nutrition. There wasn't anybody, really, who was more senior than I in chemotherapy, which at the time was my primary interest. And there was a surgeon named Robert Smith, and the director when I came was Rod Heller. And the most senior scientist in the group, I think, at the Cancer Institute at the time was Harry Eagle. These men all made for the implementation of a scientific environment.

I was particularly influenced by Lloyd Law, who became a lifelong friend and mentor. He was a mouse biologist who first demonstrated combination chemotherapy for the treatment of leukemia in mice, and by Abraham Goldin, who was a senior biologist who demonstrated in the leukemia of mice that when you give a drug, it's not just the drug and the leukemia, it's the age of the mouse, it's the age of the leukemia, the dose of the drug, the frequency of the drug, the duration of the drug, many different aspects that lead to outcome in the role of treatment. It was a wonderfully heady atmosphere at the time, with the concept of discovery and this new governmental resource that made it possible.

CC News: It must have been. So, were you in the Public Health Service?

Holland: I was in the Public Health Service, and was a senior surgeon, which I think is the equivalent of a lieutenant commander. I had been a captain in the Army, having served in the Occupation in Europe. I came on the day I arrived as a civilian, but then joined the Public Health Service. And I had served in the Navy and the Army—so I missed the Air Force, but there was no Air Force at the time. (laughs)

I arrived the day before the institution was dedicated by Mrs. Hobby, who was Secretary of Health, Education and Welfare, which subsequently became the Department of Health and Human Services. She was committed to the NIH, and it was indeed a wonderful organization. James Shannon was the director of the NIH at the time, and I had certainly known of him, because he had headed the Malaria Project during WWII in New York on Welfare Island, trying to find treatments for malaria, because all of our soldiers in the Pacific were exposed to malaria, and it caused a great deal of morbidity.

CC News: Did you say that you arrived literally the day before the dedication of the Clinical Center took place?

Holland: I certainly didn't arrive on that day because I would not have been able to attend, it was held sometime in the morning. So I must have arrived the day before, or even before that, to get someplace to live, and accommodations, and so forth. But I was there at the opening ceremony, and the opening ceremony was very interesting, because there was a whole revolution in concept. Vitamin B-12 had just been recognized, and its structure understood, and it was active at the microgram level, whereas everything up to then had been grams and milligrams.

CC News: Can you tell me just a little bit more about what your impressions were, or anything you remember about that day? The spirit in the air, or what people were saying?

Holland: Oh, it was a great celebration, because here was this giant new federal hospital for research, and the people who were there were all interested in doing research. There had been cancer institute hospitals in California, I think in Loma Linda, and in Baltimore, and maybe one in Boston. But they had been closed down, and they were now going to be located in a central location, next to the basic scientists. Abraham Goldin and Lloyd Law and others were already working in Bethesda, but there hadn't been a clinical correlation, and all good basic scientists are interested in seeing their science applied to humans. You know, they're not primarily interested in test tubes or in mice, they're primarily interested in something that will affect and benefit the human race. So the concept that "Now, by gum, we're going to be totally integrated." That was a huge asset.

CC News: So it was something really new, right?

Holland: It was very new. It was very new! This was a hospital that was given over specifically to research, not just limited to cancer. There were certain beds allotted to cancer, and to heart disease, and to psychiatry, and other kinds of specialties. To have that kind of a multi-institutional, multi-factorial basis specifically for research, to carry on research programs, not just for the benefit of people who were sick, but to understand the causes and the cures, potentially, of their diseases, was certainly a big concept. There's no place in the world that's even comparable to it, no place that's been as productive, no place that's had as many great discoveries, and trained as many fine, young scientists and physicians, men and women, who have populated the medical schools and research institutes of the world, not just the United States, because international students can go there too. It has had a tremendous and dramatic influence on medical evolution and science evolution in the biological sciences ever since its implementation. There's nothing in the same league with it.

CC News: What are some of the most memorable things that you remember about your time at the Clinical Center in its early days?

Holland: James Wyngaarden was one of the young men in my group. He subsequently became the director of the NIH. He was brighter than I was by far, but he taught me how, and helped me conceptually, to isolate an enzyme from the liver. I went to an abattoir with my technician, got a pig liver, came back and processed it in the proper way to get the enzymatic activity, which was to isolate uricase. Uricase is an enzyme from pig liver, and that was used to measure uric acid, which is the byproduct of a great portion of the DNA in leukemic cells. Then I was able, treating children with leukemia, to see how much DNA was being degraded, which was a marker for how many cells were being killed, by isolating the uric acid in their urine, and we could show a major impact of chemotherapy. That kind of correlation of a treatment—I put together the two drugs that Lloyd Law had pioneered in mice, I put the human equivalents of those two drugs together, and treated a group of patients with acute leukemia. And then to be able to see that we were destroying leukemic cells not only by counting their blood and looking in their bone marrow, but by measuring a chemical product of the DNA that was being destroyed by the chemotherapy was very exciting, and novel at the time. There were no comparable studies. Subsequently I went on to other kinds of things, but to learn how to isolate an enzyme from the liver and to be taught by a peer who himself was really an exceptionally fine clinical scientist, and to convert that into an understanding of what we were doing when we gave the chemotherapy was pretty exciting stuff. Very exciting stuff—not pretty exciting—very exciting!

CC News: How long were you there?

Holland: I was there from July of 1953 to November of 1954, and my salary was \$7,200 a year, which was tremendous. But I got an offer of a job at Roswell Park, in New York State's cancer institute, for \$11,000, and that was real money in those days.

CC News: I read somewhere that at the time the Clinical Center opened, the idea of the federal government being involved in this kind of work was somewhat controversial. Not everybody thought it was a good idea. Do you remember anything about that?

Holland: Well, I wasn't involved in the politics then in the same way that I am now. I would guess that in fact there had been public health concepts for at least half a century. Keep in mind it was United States Army doctors who recognized the cause of yellow fever during the building of the Panama Canal by doing experiments on live people, to see who and how they got bitten by mosquitoes and had yellow fever transferred. There certainly was a general understanding that health is important for a nation. And one of the characteristics of a nation that's strong is that it takes care of its own people. There's always been a controversy about individualism and governmental activism, but there's a fine balance between the two, and I don't think there's any better place to see it than in the NIH, where in fact it is the federal government, and it is nurturing independent thought, creative, new thought, that's one of the rarest commodities there is.

It's very easy to see a whole army of sheep follow the leader, but to be able to pick a new path, to understand a new concept, to pursue an idea that eventually creates a whole new concept, that's very difficult. And the federal government, I think very smartly, has said, "This is an important part of our civilization, is to do things that are going to be of use to the people of the United States." And of course, it spills over into the people of the world. There's no question that the NIH is the dominant embryonic incubator for health concepts the world over. And many of the scientists from institutions in Europe and Asia and South America have gotten their stimulus and their education at the NIH, and have gone home to lead similar activities in their own countries.

CC News: I came across a quote by Lewis Thomas, I don't remember it verbatim, but he was talking about how really this is one of the things the government has done the best...

Holland: I think that's true. Absolutely. I knew Lew Thomas, he was the Dean at the New York University School of Medicine and then became President at the Sloan Kettering Cancer Center. We were friends and had quite a lot of activity together in a group that was called the New York Consortium Against Cancer. I was trying to amalgamate the efforts of many of the different medical schools and activities, to bring a public health impact on New York City with respect to breast cancer and chemotherapy for women in the immediate period after surgery, and he was very helpful and very strong. I agree with him! I think that perhaps the best diplomacy that the United States can offer is through its health services. Because every country really wants its people to be healthy, every sensible citizen deplores the fact that people die from preventable causes, and so I think doctors turn out to be very good diplomats. Later in life I had the opportunity to go to the Soviet Union. Premier and Communist Party Secretary Brezhnev had met with President Nixon and the two of them, trying to cool down the Cold War looked for things that were non-controversial, and cancer research is non-controversial. Everybody in the world is against cancer, nobody wants to have a disease that kills people when it's untreated, and so cancer research became an area of collaboration. And the Russians were going to send a family to the United

States, and we'd send a family to the Soviet Union. Dr. Gordon Zubrod, who'd become the Clinical Director of NCI was really a patron saint of cancer research, a wonderful human being, and he used to call me and say, "Have you got somebody to send to the Soviet Union? The President promised we would..." and I'd say "Well, no, I don't have anybody to send." After two or three such phone calls, because it seemed like it was part of the American responsibility to do so, and because things had changed at Roswell Park and I had decided I was going to leave, the night of the third phone call, I said to my wife, "How about us?" And she said "Okay!" And so we went to Russia with six children, and spent I guess seven or eight months in Moscow. And I lectured all over the Soviet Union, and was welcomed, even though I came from a contrary political system. I've never had better audiences than I had in the Soviet Union—standing room only.

CC News: That must have been quite an experience for your whole family.

Holland: Oh, it was an extraordinary experience. An extraordinary experience! In essence I was a doctor taking health information, which was welcome to all other people, and it was a wonderful experience, I could expand on that in great detail. The three boys had to sleep in one room, and three girls in another, and it added to the community and bonding between them.

CC News: How old were they?

Holland: This was 1973, forty years ago, so I guess the youngest one was about eight or nine. And the oldest one at the time was 18 or 19, something like that...It was a wonderful change. Nothing brings community better than a hostile environment. It wasn't hostile, but initially it was scary, because it was totally, totally different.

CC News: And relations were not so good...

Holland: Oh, relations were bad at the time, but this was an opening. And I still have many friends in the Soviet Union. We went back on the 20th anniversary, and we've been invited back on the 40th anniversary of our having been there. There are still people who have benefited by it, and who remember it. We went to the school where our children went, there was a school that taught English as its primary mission, we went there 40 years later, and there was one teacher who was still there, and she remembered my daughter. My daughter is a brilliant girl, and she couldn't speak Russian, but she got a 5 on the chemistry exam, because the chemical symbols were all the same. And this woman, who had taught chemistry and mathematics, remembered that.

CC News: I also wanted to ask you about changes. You've got the advantage of perspective, sixty years since the Clinical Center first started. You remember how it was this very, very new thing, all this exciting work going on. And you were just back there this summer, to deliver the lecture at the 60th Anniversary Grand Rounds. So you've seen 60 years of clinical research. What are some of the things that are different now than they were then, and maybe also what's the same?

Holland: What's different is the whole development and understanding of DNA and the organization of how a cell works. DNA had been discovered, and it was recognized as the hereditary substance before then, that happened while I was in medical school. But nobody could make use of that information except in experimental circumstances until Watson and Crick discovered the structure of DNA. And then from the NIH—in an accident, I think—it was recognized that if you put in a particular string of nucleic acids all the same, out came a string of amino acids all the same, which was insoluble. I don't think that Marshall Nirenberg, subsequently awarded the Nobel Prize for having discovered how DNA gets transferred in its information to make a protein, predicted it was going to happen that way. A lot of good science happens because accidents happen, and people are smart, and alert, and pay attention. They're alive at the switch, instead of asleep at the switch.

The understanding of how a cell works—and our information is still imperfect, but it's much advanced from what it was at that time—allows us now to go into the mechanisms that cause disease, and that is a dramatic, revolutionary change. I think that's the biggest change, that we understand how a cell, what a cell is made of, and how it works. We still are groping to understand the complexity of it, because it's much more complex than any other thing except possibly the universe. Nobody really knows what happened at the Big Bang, what happened before the Big Bang, why there was a Big Bang, what existed then, why is space expanding, where are all these billions and billions of planets, and stars, and its infinite number. And a cell is just as complicated as that. How cells interact with one another, and why the tissues in your eye, where there are many different kinds of tissues, or in your finger, where there are many kinds of tissues, why they misbehave and become a cancer, and why one tissue doesn't respect the confines of its own designated place, and invades another space, that's still a mystery of cancer and we still don't have all the answers by far.

But what's the same is that it takes hard work, it takes intelligent people who are willing to listen to new ideas. Science changes things. Understanding changes. And I think that the NIH has kept its high standard of people and recruits, which is the most critical thing. You've got to have talent to develop new ideas. There are characteristics of science that demand a reverential approach to the problem, and making sure that what you say is true, and that what you say is still true when applied correctly. In that I think the NIH is outstanding, and the Clinical Center is a critical component of it—to apply new scientific knowledge to humans.

And so the talent and the hard work are still the same. What's different about the NIH from the ordinary university is that there is a stable understanding that these are good people, and they need to be funded every year. Every year there isn't going to be a new discovery. Every year they have to show that they are still talented, but they don't have to produce something this particular year, providing they're working well on some long-term goal. Everybody makes mistakes. Scientists make mistakes. Politicians make mistakes. You don't get penalized for that in the NIH in the same you do in a university, because universities don't have budgets to give to people, so they don't have sustained support. Scientists apply

for support and if the research one year is good, they get funded, if next year their research doesn't look good they may not get funded, and their career may be over. That's a very desperate, difficult situation and I can tell you, that's not perhaps the best way to have things function in the long run. But it is the way we do it, and so there is a security factor for new, exceptional science at the NIH which is very, very good, and very healthy, because the recruitment process there is very restrictive. You don't take duds, you take the people who are really achievers, who are in the super A class, and then you turn them loose to do what they can do.

CC News: I guess that's part of what makes room for those happy accidents...

Holland: Everybody has accidents, it's whether or not...It's sort of like a seed, if a seed falls into a well-fertilized field, it can grow. If it falls onto a sidewalk, it's dead on arrival.

CC News: I'm thinking about what you said before, that some of the most important discoveries have come about sort of as a result of some sort of accident, but it's providing that environment in which the accidents can be understood...

Holland: Absolutely. Absolutely. There are very few Einsteins in this world, but there's a lot of good science, and a lot of good science is because people were awake at the switch instead of asleep at the switch. They saw something they didn't anticipate, but then pursued it and found out why it happened, and what happened, what was going on. You have to have a goal, but part of the trip is to see what you find along the way. I presented a dissertation of 20 years of work of my colleagues and myself, trying to demonstrate absolutely that a good portion of human breast cancer is caused by a virus that is derivative of the virus that causes breast cancer in mice. And of course there's a lot of skepticism. A lot of people say, "Well, you've got contamination." We know we don't have contamination. And we've got many ways of proving that. But that's still a widespread belief. And there are many epidemiological factors that make this the logical explanation for differences in breast cancer, incidences in different parts of the world, and in different circumstances. It is hard to change a well-grounded belief, but we keep at it. Perseverance is another part of science that is absolutely essential. You don't give up just because somebody else doesn't believe you the first time around.

CC News: Is there anything else you'd like to add? Particularly in terms of what it's important for Americans to understand, especially in times like this when the funding is a bit insecure, what it's important to understand about the work that is going on here...

Holland: Funding is the green blood of science. If everybody were content with the information that we know now, and with the state of health, then, good, fine, not another dollar for research. But we'll be absolutely fixed exactly where we are. And it's unsatisfactory. People still die in great numbers from

cancer, from heart disease, people still suffer a lot from arthritis and psychological abnormalities, autism, we don't understand the causes of many of these things. If you want to solve the problems in the same way as we've solved the problems for certain cancers, where you can take a pill and get cured, or take some injections and get cured, or prevent them from happening altogether, or certain kinds of heart disease where in fact the mortality is going down, then you have to fund research. Research is the answer to the unsolved problems.

I'm much in favor of having a government organization comparable to the NIH for the study of peace. We've got a Naval Academy, an Army Academy, an Air Force Academy, on how to fight war. Where's the academy on how to establish and maintain peace? I think we need that kind of activity, that's what governments are for. And I believe that the American people do recognize, we're not there when it comes to curing everybody, or preventing disease in everybody, and could we get there? We certainly could do a lot better than we're doing. And that takes research. So it ought to be a very, very important goal of government.

CC News: Anything else you'd like to add?

Holland: The NCI and the NIH are great institutions, jewels in the American crown. We all are their beneficiaries.