THE DEPARTMENT OF ENERGY
ORAL HISTORY PRESENTATION PROGRAM

OAK RIDGE, TENNESSEE

AN INTERVIEW WITH LIANE B. "LEE" RUSSELL

FOR THE

OAK RIDGE NATIONAL LABORATORY
ORAL HISTORY PROJECT

INTERVIEWED BY STEPHEN H. STOW

AND

MARILYN Z. MCLAUGHLIN (ASSISTANT)

APRIL 23, 2003

TRANSCRIPT BY
ROGER A. SHINN

STOW: Today, we're talking with Lee Russell, a native of Vienna, Austria. Lee and her husband Bill came here to Clinton Laboratories in 1947 from Bar Harbor, Maine, and established themselves over the decades as really the cornerstone of the Oak Ridge National Laboratory biology program in studying mutagenic effects of radiation, chemicals, and other impacts on mice, which are related to humans genetically. So, we look forward to a good discussion today with Lee.

Lee, it's good to have you here today, and I look forward to talking with you for a while about your career and the career of Bill, your husband. Let's go back to your earliest days in the 1940s. What got you interested in science to begin with?

RUSSELL: Well, I probably got interested through my father, who was a chemist. So, I had always leaned towards science in my education.

STOW: And, this was in Vienna, right?

RUSSELL: No. I left Vienna when I was only 14.

STOW: Oh, I see.

RUSSELL: So, this was in 1938. I went to high school in England and then to college in New York City at Hunter College. Then I really got interested [in science] because, at that point, I was still thinking about going into medicine. But, I got strongly disabused of that [idea] when I met Bill. The way that happened was that I looked at the bulletin board in the Biology Department at Hunter College and saw an ad for a summer school at the Jackson Laboratory in Maine.

STOW: You were a sophomore at the time, I think.

RUSSELL: I was a sophomore when I first went up there. So, I applied for the summer school [and was accepted]. It's the thing that really changed my life because the summer school had been created by and was being run by Bill Russell, my future husband. His school worked on the principle of giving the students real experience -- hands-on experience -- in experimental work. It was a small group of about a dozen students. At that time, because of the war -- this was in 1943-- all the students happened to be female, but it hadn't been that way to start with. I got assigned to a staff member -- each student got assigned to a staff member -- and did a couple of projects. And, I remember first looking down a microscope at a fertilized egg. The total wonder was that this little thing is going to be a whole mouse! And, it was just -- it was just an incredible experience.

STOW: Turned you on, right?

RUSSELL: Turned me on right away to think that there in this little thing was everything for a whole mouse. I spent the summer and got a scholarship to come back for free the next summer. [So I was there in] the summers of 1943 and '44. In the meantime, Bill and I really got together, but it wasn't till '47, actually, that we came to Oak Ridge. In the meantime, I graduated from Hunter College. I went to graduate school at the University of Chicago, where Bill had gone thirteen years before me.

STOW: You had the same major professor there, too, didn't you?

RUSSELL: I had the same major professor. In fact, one reason I chose Chicago is that I applied to several places, and I was accepted at several places, but, because of [Bill's] experience with Dr. Sewell

Wright, I decided to go to Chicago and finish my course work there. Dr. Wright turned out to be far from an ideal major professor in many ways. Scientifically, he was unbeatable. But, from a personal point of view, he didn't really take care of his students. He had some junior professor who assigned desks and all this kind of stuff. Then because of personal circumstances, Bill left the Jackson Laboratory.

STOW: Well, there was a fire there, wasn't there?

RUSSELL: Well, it was before that. I mean he actually got a divorce.

STOW: I see. All right.

RUSSELL: And, since his wife was also working there, one of them essentially had to leave, and he chose to leave. And, then he applied to various places, but the stipulation was that anywhere he went would have to be able to offer me a job as well, because he wanted me to have a career in science, also. And, that ruled out quite a few places that had nepotism rulings.

STOW: I'm sure it did.

RUSSELL: But Oak Ridge National Lab did not. In fact, as it turned out, the Biology Division ended up with a whole lot of husband-wife teams. But that didn't happen till later; I think we may have been the first one.

STOW: What did you know about Clinton Labs then?

RUSSELL: I knew very little. Now, Bill knew something about it because he had been there while working at the Jackson Laboratory. He was also a consultant to Don Charles, who was working on the Manhattan Project at the University of Rochester. It was a mouse genetics project -- a small one -- and Bill was a consultant. He had no idea, you know, about what was going on here. He just knew that some people were working on genetic effects of radiation. So, that was essentially his background knowledge, and when Alex Hollaender recruited him and later interviewed him, Bill came down here for two or three visits, and, of course, learned a little more about it then.

STOW: What were your impressions of Oak Ridge as a place to live when you came here in '47? Did you have any idea you'd end up spending your entire life here?

RUSSELL: Ah, no, not really. I sure did get hooked fast, but, when we first arrived -- I remember coming in through Elza Gate – I felt totally depressed because all along the east end of the Turnpike, which is now pretty empty, were a bunch of hutments, very decrepit looking buildings. And, I thought, "Gee, that's where I'm gonna live." You know, it was pretty bad, to start with.

STOW: I'm sure it was.

RUSSELL: But, it soon became very different.

STOW: Tell us about Alexander Hollaender. You mentioned him a moment ago.

RUSSELL: Yes.

STOW: What are your recollections of him?

RUSSELL: He was, I think, a person like no one else. He was the true "go-getter" in the scientific world. He was essentially recruited, as I recall, by Dr. Eugene Wigner in 1946, simply to look at biological effects of radiation. I think that he chose the mouse project, which was a politically popular one, and one with potentially good sources of funding. He chose it to sort of piggyback a lot of other things onto [what] were not strictly program related. In fact, they were very far from program related. So, in this way he built up an incredible division that had young, energetic scientists in every area of genetics: maize, neurospora, yeast, *Drosophila* [fruit flies], various kinds of plants, microorganisms of various kinds. He also had a great talent for outreach. He organized symposia all over the world. He started scientific societies all over the world. He allowed his scientists to travel and give lectures everywhere. We even went to some of the little colleges around the Southeast on a traveling lecture program the first few years we were here. He had people coming in for summer "investigatorships." It was just an incredible scientific outreach.

STOW: Well, his legacy has lived on through the years. That's for certain.

RUSSELL: Oh, yes. Yes.

STOW: Let's switch gears and talk about your work here at Oak Ridge National Lab. You've mentioned mice. Why are mice such good subjects for mutagenesis studies, as opposed to fruit flies, for instance?

RUSSELL: Well, of course, practically the only work that had been done on the genetic effects of radiation had been done in a fruit fly or in corn -- maize. The reason mice are so important [for research] is that they are so much more closely related to human beings genetically [than are other organisms]. Of course, that's what the researchers were interested in then from a practical point of view. Now, we know how much more closely related they are in terms of the [mouse and human] genome, an incredibly close relationship. But, even in those days, you had to have a mammal to determine genetic risk to humans. The mouse, also, is a prolific producer. It can have five litters a year. You can build up a number of generations very quickly. Mice are very cheap to maintain. I know when we first had a big colony, we would tell people it costs us one cent a day to keep a mouse. (Chuckle) The most important criterion, though, was that of all the mammals, the mouse was by far the best known genetically. There had been a lot of mouse genetics [research], actually not just during the twentieth century, but, even the century before, because of the so-called "mouse fancy" -- that is, people who were breeding mice for fun. And, in that way they built up some preliminary mouse genetic information.

STOW: And, of course, Bill had been working on radiation damage to mice anyway, during the war years.

RUSSELL: No, not before he came here, except as a consultant.

STOW: As a consultant during the war years. So, he had at least a little bit of that experience, right?

RUSSELL: He'd had that. But, his greatest interest when he was at the Jackson Lab was really to find ways of gauging environmental and hereditary effects -- the relative effects of what they could do and how they added to genetic variability. And he developed some really neat methods for doing this. For example, he developed ovarian transplantation as a technique so that you could raise mice in a different maternal environment, and figure out the effects of maternal environment on variability. I mean that was just one of many things he did. He published wonderful sounding papers. One was called "Inbred Mice from Hybrid Mothers." (Laughter). And then, the other one was called "Offspring from Unborn Offspring from Unborn Mothers."

STOW: Those are fascinating titles.

RUSSELL: So, it was really an interesting area of work that he was leaving to come here and do something that originally looked pretty programmatic and not all that interesting at the beginning.

STOW: I understand, he didn't want to accept Hollaender's offer at first, thinking that because Monsanto ran this place, it would be an industrial research environment, as opposed to an academic environment.

RUSSELL: That's right.

STOW: But, fortunately for you and for all of us, he made the decision to come here, and here we are today.

RUSSELL: Here we are.

STOW: Sixty years later. One of the earliest projects you got started on was the impact of X-rays on embryonic development. I may not be saying that exactly right, but how did you get started in that?

RUSSELL: That [work] was actually my baby, rather than his. And, I got started on that project because I still had not finished my Ph.D. degree work when I got here. I had done my course work, but I still had my dissertation to do. And, the subject I chose was to look at somatic mutations -- that is, mutations that occur not in the reproductive cells but in the cells of the body.

STOW: Okay.

RUSSELL: I wanted to develop a scheme for comparing [mutability] of the same genes in the two types of cells. And, in order to do this in a preliminary way, I had to find out the best stage of embryos to irradiate. I wanted to have enough [precursor] cells there to make it worthwhile, but not so many that the resulting spot would be very small. So, I had to find just the right number of cells. I was irradiating embryos in different stages of development, just as a preliminary to this genetic experiment, and I ended up getting these strange abnormalities, such as [misshapen] legs, toes fused together, or kinky tails. And so, I got sidetracked and actually ended up doing my dissertation on radiation effects on embryos.

STOW: This was X-radiation, right?

RUSSELL: This was X-radiation at that time. The most important outcome of that work really was the strong effect of the embryo's stage [of development on the probability that X-rays would cause abnormalities]. The critical periods for different types of abnormalities were very strictly delineated. [During] the very [earliest] part of pregnancy, of embryonic development, effects were all-or-none -- either you kill the embryo, or it [remains] totally normal. [But, right after that, major malformations were induced.] And so, we ended up developing what turned out to be called the 14-day rule for humans. And, the rule was that, unless diagnostic radiation is required at a certain time, X-rays of women capable of having babies should be scheduled fourteen days after the menstrual period, to avoid the possibility of irradiating an embryo in an unknown pregnancy. And, that rule became pretty widely adopted.

STOW: Well, it became adopted on an international basis, didn't it?

RUSSELL: It did, yes, after some objections from radiologists. They were afraid that [violation of this rule] would lead to lawsuits, but it really did get adopted.

STOW: Does the same rule apply today, in the year 2003, as it did after you developed it back fifty years ago? I mean, we have much more sensitive, low-dose X-ray systems now and better methods of interpreting X-rays, so is a pregnant woman in as much danger today as she was in those early days of X-rays?

RUSSELL: Well, the thing is that the real danger was not to a known pregnancy but to an unsuspected, unknown pregnancy. So, although I think everybody agreed to try to keep pregnant women away, we were trying to avoid the really sensitive stages before pregnancies were known [to exist].

STOW: And, you published some research on this, I'm sure, throughout the years, but I think 1952 was the year when you published your most definitive paper.

RUSSELL: I started in 1950 with a series, and I think that paper in '52 was a summary.

STOW: And, you went to the 1955 Geneva Conference.

RUSSELL: I did.

STOW: As the only woman in the U.S. delegation.

RUSSELL: That's right.

STOW: Tell us about that experience. That had to be a highlight in your early career.

RUSSELL: It really was. I was our first trip abroad together. It was a really big business with practically all of the nations of the world represented there. It was quite an experience.

STOW: You mentioned a "spot" a moment ago when you were talking about the impact of X-rays on mouse embryos. Were you referring to the spot test that you developed?

RUSSELL: Well, yes, the spot test eventually was developed for the early somatic mutation work that I was hoping to do for my thesis, and ended up not doing. I went back to it after I got through with the embryo work. I essentially, more-or-less, stopped the embryo work, in probably the mid-'50s, and I got back into genetics research. And, the spot test eventually grew out of that. What we were looking for were mutations in cells up and down [the embryonic] spine, or neural crest, which end up as pigment cells. So it was possible that if you incorporated the right genes in that embryo, you could diagnose a mutation as a spot of a different color [on the mouse after it was born.]

STOW: So, this mutation would be shown as a spot on -- in the -- the hair of the mouse?

RUSSELL: In the fur. If you were expecting an all-black mouse, the mouse might end up with a spot that's light gray or brown – depending on what gene you mutated.

STOW: Where did these mice originally come from? We're talking about mice, and before we get too far down the road, I'd like to know where the first mouse came from?

RUSSELL: Well, that is a very good question, because we came here without a single mouse. Bill had gotten a lot of mouse stocks ready at the Jackson Lab to bring with us or to have sent here to arrive with us. Then, just while we were still waiting for our security clearances, [one test] turned out to be so very successful -- it was called the "specific locus test." It essentially looked for mutations in genes that had mutated spontaneously in the past. We looked to see whether radiation could mutate those same genes again. Only one generation of mice was required to detect the mutations, in contrast with some of the other proposed tests, where you would have had to run a big breeding program and keep a lot of records. You could pick up the mutants in one generation. It didn't take a skilled person to find the mutations, just a person trained in visual observation. It could be done very, very quickly, so all the mice that didn't have limitations could be discarded, so that you didn't build up a huge mouse population—you picked up only the mutants. And, its biggest advantage was that it was perfectly suited for comparative studies. The comparisons we made included looking at different types of radiations, looking at the different ways the radiation was administered — whether it was given very quickly or spread out in time — and looking at a lot of biological factors, such as the effects of radiation on the mouse's germ cells, the reproductive cells — which turned out to be the most important variable of all in mutation rate.

STOW: Now, did you find different mutation rates in males versus females?

RUSSELL: Yes, absolutely. And, not only that, we found that in irradiated mice, the different stages of development of the reproductive cells in both sexes had very different mutation rates and qualitatively different types of mutations. These differences were probably the most important thing to determine, because they carried over later into other types of mutagenesis.

STOW: Well, now the basis for this, or the reason for doing this research, was so that the Atomic Energy Commission could understand more about the impact of probably low-level radiation on humans [because of the growing presence of radiation-emitting hydrogen bomb tests and later nuclear power plants]. And so, can you, in a simple fashion, tell us how your research results were then translated into radiation-exposure standards?

RUSSELL: There were all sorts of committees and bodies that were making extrapolations. There were committees of the National Academy of Sciences, called BEAR for Biological Effects of Atomic Radiations, and then BEIR for Biological Effects of Ionizing Radiations. And, there was an international group called UNSCEAR, for the United Nations Scientific Committee on Effects of Atomic Radiations. There were many ad hoc bodies because the problem was that mutation rates cannot be measured at the very low doses that people [receive]. It's just not possible, so you have to extrapolate. The extrapolation is based on the unproven hypothesis that mutation rates exist in a linear relation with the dose of radiation that would be given. [The higher the dose of radiation, the higher the mutation rate in cells was thought to be.] The so-called dose-rate effect that you mentioned was a big revolution in extrapolation in mammals because, in the fruit fly *Drosophila*, there was no effect of dose rate. No matter how you gave the radiation, [the effect] was always the same. It indicated that in mammals (at least in a mouse and presumably in other mammals) – repair [of mutated genes] was possible. At that time nobody had been talking about repair of mutagenic or pre-mutagenic damage. So, this was essentially a first, and it was heresy to start with -- it was really strongly attacked. It turned out that [the mouse] was not so different from *Drosophila* because [the mouse dose-rate effect] happened only in the stem cells -- the cells that constantly produce germ cells -- and in those cells, you get repair. But, once the cells get mature, repair is no longer possible. And, in *Drosophila*, the stem cells had not been studied, only the mature germ cells. So, there was really no difference between the mouse and *Drosophila*, because the comparison was not based on the [comparable] cell type.

STOW: Somewhere I've read that the famous geneticist Herman Mueller didn't want to believe all this at first. Is that right?

RUSSELL: He didn't, but he was a wonderful friend. He was the one who got the Nobel Prize for demonstrating genetic radiation effects in *Drosophila*. He didn't want to believe [the dose-rate effect], but he became totally convinced, especially when he realized, after Bill pointed it out -- that the *Drosophila* work had not been done on the stem cells. So, the stem cells have the capacity to repair [damage to genes], and the mature cells do not. And, from the point of view of human hazards, that's the most important. The stems cells are [present] for the rest of your life; the mature cells will be gone in a matter of a few weeks.

STOW: Where physically were the mice irradiated? Did you do this in the building there at the Y-12 Plant?

RUSSELL: Most of them I should say were. We had an X-ray machine to which mice were exposed in lucite containers. We had a couple of gamma-ray sources that gave the mice very low dose rates.

STOW: What were the gamma sources? Cobalt, or what...?

RUSSELL: The gamma sources were cesium. The one we had on the top floor of the building was fixed up in a way so that the radiation would go up and out through the walls into space. Above the top floor of the building was not an area where anybody would get [exposed] -- of course, by that time, the radiation was very attenuated, anyway. We could place the mice on racks around the periphery of the room. Because of the great distance from the cesium source, the mice got their dose of radiation at a very low rate. So, it might take almost a year for them to accumulate a certain dose. They were just living there.

STOW: Does any of that work still go on today? In a research capacity?

RUSSELL: No, I hate to say that the source has been dismantled. It's in a storage room now -- where it used to be. We had another source in the ground. But not all [radiation] was given in the building. We used the Oak Ridge Isochronous Cyclotron [at X-10] for neutrons. We used the Health Physics Research Reactor for neutrons. And, most exciting of all, some mice were exposed to the bomb tests in Nevada, where they received very high, high bursts of neutrons ...

STOW: You mean you took those little mice to an atomic bomb test site? Shame on you.

RUSSELL: Bill and Gene Oakberg, one of our first staff members, went to the bomb test. I didn't go out, because I had just had our second child. The mice were exposed in what they call lead hemispheres, which sat on the desert floor. The hemisphere walls, which were made of about a seven-inch thickness of lead, looked like little igloos. The mice and other biological test materials were [encapsulated] in a little air-conditioned space inside. The hemispheres were placed at different distances from [ground zero], where the bomb was going to be set off. This was still in the days of above-ground testing. The lead in the hemispheres stopped the gamma radiation from the exploding bomb but it didn't stop the neutrons.

STOW: Well now, mice experimentation had started here at Clinton Laboratories as early as 1943, I believe. Howard Curtis, does that name ring a bell with you?

RUSSELL: That's right. It rings a bell.

STOW: I believe he got involved with some of those studies using the Graphite Reactor and using mice and rabbits, I believe, for exposure studies.

RUSSELL: But those were not genetic effects.

STOW: They weren't doing anything with the sophistication you had there.

RUSSELL: I think they were looking at different physiological effects.

STOW: Does any of that work go on today, and is there a need for that sort of research today? Or have we pretty much gotten to the point where we understand the genetic effects of radiation on mammals, like mice and humans?

RUSSELL: I think we understand what we need to, from a practical point of view. I think there are still things that need to be found out, but they don't require the large-scale experiments we used to do.

STOW: So that work doesn't go on anywhere, does it?

RUSSELL: I'm not aware of it, no. Of course, the radiation work merged into chemical work.

STOW: Before we get to that, tell us a little about the work you did on the Y sex chromosome. That was pretty exclusively your research, was it not?

RUSSELL: That [research was done] in the one or two percent of space that wasn't [devoted to a radiation] genetic experiment. I think one of the best decisions that we had made early on was to maintain the mutants as stocks. Because if you don't get many [mutations] even with a good mutagen like radiation, the number of offspring that have a mutation is just miniscule compared with the number that don't. And so, the mice that had mutations and were propagated as breeding stocks provided us with mouse mutants in a biological bank for years to come. We could [study] the various properties of each mutation in every mouse we bred. Among the stocks we kept were not just the types with mutations that we picked up in the main test but also mice with mutations that occurred spontaneously. And, one of those was the first sex-linked mutation ever to occur -- ever to be recorded -- in the mouse. It was, unfortunately, not the first one published because Bill was a very slow publisher. (Chuckle) So, somebody else first published a paper on another spontaneous sex-linked mutation, but our mutation was the first one to occur. And, in that stock we found some exceptional mice that didn't breed according to type. I won't go into the genetic details, but it turned out that they were females that had lost one of their two X sex chromosomes. [Normal female mammals have two X sex chromosomes, and normal male mammals have an X sex chromosome and a Y sex chromosome.] So, we called them XO females. And then, in other stocks, we found some male mice that had the color markings only females in that stock should have. They turned out to be males that carried two X chromosomes and a Y. We called them XXY males. So, we had two new types: the XO females and the XXY males. In conjunction with what was known about normal X and Y sex chromosomes, it became clear to us that what made a mouse a male was the fact that it had a Y chromosome, which was different from *Drosophila*, in which the ratio of sex chromosomes to non-sex chromosomes determined the gender. In *Drosophila*, XO would be a male, whereas an XO mouse is a female. An XXY fruit fly is a female, but an XXY mouse is a male.

STOW: Is what you found for the mouse unique to mammals, or just to mice, now? Does this finding have applicability to humans?

RUSSELL: It applies to all mammals.

STOW: Pretty important discovery, wasn't it?

RUSSELL: It was interesting, yes.

STOW: Did you understand the importance of this discovery at the time?

RUSSELL: Yes, I think we did. But, what really helped, along with [these observations], was cytogenetics – the ability to look at the sex chromosomes in cells on a slide, essentially. We only slowly acquired that expertise. In humans, geneticists had the cytogenetics capability, but the breeding could not be done, so they didn't have the genetic evidence. Otherwise, they would have found it out -- in fact, they did find it out in humans, too, but only based on the cytogenetics and slightly after our discovery. But the mouse evidence we got was much more solid, because [it was both] genetic and cytogenetic. And, in humans, it was just cytogenetic.

STOW: Tell me, since you're dealing with thousands of mice, how do you keep one mouse separate from another?

RUSSELL: A very simple but foolproof method of recordkeeping allows us to pick up any mouse and trace it back decades. The mice themselves are earmarked -- they have little notches taken out of their ears. You can get numbers from one to ninety-nine that way. Of course, you could run higher than ninety-nine, in any given stock, but it's unlikely that two mice with the same number would be alive at the same time. The first ninety-nine would probably be dead by the time you get to the next. We also have cards [that record information on the mice in each] cage. For each breeding female, we had on file a card for recording all the successive litters. We also had a ledger record [for each stock], and all the litters were entered in the ledgers. All the breeding and litter information was cross-referenced, so we could get from a breeding card to the ledger and back very quickly and very easily. And [that] was quite foolproof.

STOW: Let's jump to what you mentioned a moment ago on the mutagenic effects on mice of chemicals and other environmental hazards. You got started on that in what, the 1960s?

RUSSELL: It was in the early '60s, I think. Actually, we were not the first to discover that chemicals could cause mutations. A woman in Great Britain named Charlotte Auerbach worked with two men on mustard gas during World War II. [She discovered in 1942 that mustard gas can cause mutations in fruit flies.] That was secret work, I guess, but their findings became pretty widely known. However, nobody had much of an interest in working with chemicals [to learn their mutagenic effects]. But then in the 1960s at ORNL -- actually through a student of hers who was a postdoctoral scientist at our lab -- he did some chemical [mutagenesis] experiments. Then we sort of blossomed from there.

STOW: Was this something that the Atomic Energy Commission wanted you to get into?

RUSSELL: No, it wasn't at that point, but much of our work was supported by other agencies. I know, for instance, that we had some FDA [Food and Drug Administration] funding and some money from what became EPA [Environmental Protection Agency]. We had support, of course, during the Carter presidency in the 1970s because there was much interest in [developing] synthetic fuels and [studying their health effects].

STOW: That would be after the Arab oil embargo in 1973, when there was interest in the U.S. in extracting shale oil and building coal gasification and liquefaction plants.

RUSSELL: Yes, I've forgotten all the chemicals we studied, but I know we did a big experiment [on the mutagenic effects of diesel fumes on mice]. We had to send our mice to Cincinnati to be exposed to diesel fumes. (Laughter) Not in the street. (Laughs) But that was a real problem because the mice came back from there with three new viruses they didn't have [before], so we couldn't take them back into the building. So, we had to use a special wing of another building to test those mice.

STOW: The World Health Organization, I think, asked for your help in studying schistosomiasis, [an infection by a parasite that has afflicted many people in Third World countries]. What was the chemical used for treatment of this disease that you studied?

RUSSELL: Hycanthone. It was already [being] used [for treating schistosomiasis] in countries like Egypt in Africa, and in South America. The WHO was concerned because hycanthone had tested positive in genetic tests of some lower organisms, so WHO officials thought it ought to be tested in mice. And, Bill did a pretty large genetic experiment. He actually found negative results for gene mutations in mice, but hycanthone did turn out to be eventually positive for causing breakage in chromosomes. But in the meantime, people were so encouraged by his negative results, [especially] the countries that wanted to use it because they had a bad problem with [schistosomiasis]. Bill got invited all over the place to talk about this. You know, he went to Egypt a couple of times.

STOW: I understand that the wife of Anwar Sadat, the president of Egypt, contacted you at some point? Is that right?

RUSSELL: Not me. That must have been Bill. He had contacts with quite a few of the government people in these countries.

STOW: Talking about the mutagenic effect of chemicals, both you and Bill had a lot of experience on the mutagenic effects of radiation on mice, but then you moved to chemicals. Was that more complicated than dealing with radiation? I would think it would be.

RUSSELL: Yes, but the fortunate thing was that we could use all the tests that had been developed for radiation.

STOW: Your spot test came back, didn't it?

RUSSELL: It came back, right. So, we didn't have to spend any effort on test development. The main problem with chemicals is that you have to decide how best to administer them. Are you going to inject them into the mice? Are you going to use inhalation? Or feed them to the animals? Accuracy of results depended very much on the administration technique selected. And the dosimetry became so complicated. One of our staff members, Gary Sega, did molecular dosimetry, trying to measure the portion of the chemical [dose] that actually was retained in the germ cells. You don't know how much of the chemical that [enters the body] actually gets into the germ cells.

STOW: You don't know what the chemical breakdown is, do you?

RUSSELL: And, that's the complicated part, because with radiation, you know that whatever you [administer] gets there. The other problem with chemicals is that there are so doggone many of them.

STOW: Well, yes, all these organic chemicals and everything else. Is it a safe or fair question for me to ask you what are some of the most dangerous chemicals, with regard to mutagenic effects?

RUSSELL: Well, of course, some of the hydrocarbons and similar fuel products that we tested are pretty bad. But, I think there are many [chemicals] that are dangerous.

STOW: Where did I read about a chemical called ENU?

RUSSELL: Ah, ENU! It's a wonderful one ...

STOW: A wonderful one?

RUSSELL: ... from a genetic point of view. Normally, people would not encounter it in real life. But, Bill got to testing [it] because he was looking for a really mutagenic chemical. For a long time he'd been testing quite a bunch, but none of them was as good as radiation in causing mutations. [There was a] chemical that was very hot [as a mutagen] in *Drosophila*. It was called diethyl nitrosamine. He tested this chemical, but it was either totally negative or just very weakly positive as a mutagen in the mouse. So, he scrounged around among related chemicals and decided to test ethylnitrosourea, or ENU. It had been used in cancer therapy, particularly in the Soviet Union. And ENU turned out to be a miracle! It is beautifully mutagenic in the mouse ... (Laughter)

STOW: A terrible chemical, huh?

RUSSELL: It was lovely. (Laughs) Not only that, but you could give it in high doses. It didn't really cause much [organismic] damage, so you could administer pretty high doses without hurting the animal. With some of the other chemicals that were quite mutagenic, you were so limited as to dose because they were so harmful to the organism. But ENU was tolerated. You could up the dose and make zillions of mutations. (Laughter) And, of course, you can't directly compare a rad of radiation with milligrams of a chemical – it's too hard to do. But for doses that are equally harmful to the organism, you can make many more mutations with ENU than you can with radiation. Not only that, but they were all what we call point mutations: ENU makes changes in single base pairs in [the DNA of] genes. On the other hand, radiation knocks out parts of genes, or even more DNA than that in a whole gene. So, ENU was a different type of chemical, a different kind of mutagen. It's become the world's most used mutagen now. Every lab in the world is using ENU to make mutations.

STOW: It's the world greatest monster producer, huh?

RUSSELL: Yes, that's right...

STOW: I say that because in reading up on your background, I came across a word I wasn't familiar with: "Teratologic." Am I pronouncing that right?

RUSSELL: Yes.

STOW: So I looked it up, and it comes from the Greek word that means "to produce a monster."

RUSSELL: That's exactly right. That's the stuff I did earlier, you know, by administering radiation [to embryos]. Teratology is a branch of the biological sciences.

STOW: Teratology is a new word to me. Let's talk a little about your career in general. Both you and Bill have received a tremendous number of awards and honors. You've both gotten the Enrico Fermi award. You've received an International Roentgen Medal. You're both members of the National Academy of

Sciences. You are both ORNL corporate fellows. Is there any one of these awards or honors that stands out in your mind as the most pleasing -- the one you're most proud of?

RUSSELL: I really enjoyed getting the Fermi Award a lot. And, I had a very different experience from what Bill had when he got his. He received his many years before I did, but he got his on a cold winter day in an armory in Washington, where they were giving awards for everything that anybody was doing in DOE. I got mine at the State Department -- in a beautiful room, and with all sorts of ceremony. I got to give a lecture at the Smithsonian Institution. I was going to meet President Bill Clinton, but he was busy right after giving his "State of the Union" address, so I got to meet Vice President Al Gore, whom I knew very well from when he was a senator from Tennessee. And, the best thing about it was that every one of my friends, practically, showed up for the award, so it was a big thing.

STOW: A real honor. I can imagine that award would stand out, then.

RUSSELL: Yes, that was great.

STOW: As you look back over your career -- with the exception of your husband Bill -- who would have influenced you the most from a scientific standpoint?

RUSSELL: Oh, gosh, that's a question I should have thought about before. Just an awful lot of people whose work I read, and ...

STOW: If we were to ask that question of Bill, what do you think his answer would be?

RUSSELL: I think he would say that his early career was most influenced by Sewell Wright. And then, I think, he had some very fruitful contacts with Herman Muller after that.

STOW: As you look back over your career, Lee, what are you most proud of, as far as your accomplishments go?

RUSSELL: I am very proud of [the] sex chromosome discovery. One thing we had not mentioned was the "single active X chromosome" hypothesis, which I thought was very important. It came out of some pretty intricate genetic work that I did.

STOW: Well, go on and expand on that a little bit.

RUSSELL: Among the various types of mice that we had saved were males and females that turned out to have translocations, in which a piece of an X sex chromosome had gotten attached to a piece of an autosome, which is a non-sex chromosome. And, it turned out that the females that [carried the translocation] were mottled – had spots of different colors. The males were not mottled. And, by having several of those mice [in which] the X sex chromosome was broken in different places, we were able to infer that something in the X chromosome inactivated [genes located] in the stuck-on piece of autosome – the genes got inactivated by [the attached] piece of the X chromosome. And, with that inference as a basis, plus the fact that when only one X sex chromosome was present, as in the males and as in the XO females, [the animals] were not mottled -- we were able to generate the hypothesis that only one X sex chromosome needed to be active in a cell. You have to have two each of all the other chromosomes, but only one X sex chromosome was needed, and the other X sex chromosome wasn't doing anything. This [inactivity] was random -- it could be one or the other X that is active, or inactive. And, there was a center in the X sex chromosome from which this inactivation came, because it depended on which part of

the X chromosome was attached to an autosome to cause this effect. It became known as the single active X chromosome. It's similar to the hypothesis enunciated about the same time in England by Mary Lyon. She called it "the inactive X chromosome," which was slightly different because she was not aware of the concept that this sex chromosome had been only partially inactivated.

STOW: And, what's the practical application of this work in today's world?

RUSSELL: Well, I don't know how practical it is. It simply means that maybe women aren't that different from men because both of them have only one X chromosome that's working. (Laughter)

STOW: Well, let's not go down that road, okay?

RUSSELL: But, I think, other than that early work, I think I'm proudest of the fact that we were able to use knowledge that came from the [accumulated] mutations we had maintained in the mouse stocks and studied qualitatively. We were able to discover a series of [chromosomal] deletions that had been caused by radiation. And, by combining overlapping deletions, we were able to do some pretty good fine-structure mapping of parts of the chromosomes. And this work led, with the [subsequent] molecular know-how, to the precursors of genome analysis.

STOW: You anticipated my next question...

RUSSELL: I think I'm very happy that I was able to attract some really good young molecular scientists at the time when I was section head. I was able to do some hiring, and so we got a good molecular genetics staff, and we were able to build on this genetic fine-structure work we had done. [We used these deletion complexes] as tools for identifying and cloning quite a few of those genes.

STOW: Well, in this year, scientists have mapped the human genome, supposedly. Can you in layman's language explain how the knowledge you and Bill acquired in those early years has supported or fit into the mapping of the human genome today?

RUSSELL: Well, it has fit more into the mapping of the mouse genome, not so much the human genome. I think that the deletion work [I tried] to describe – it's kind of complex and it's hard to really tell you what it is – evolved into a method for what is called positional cloning, which then can be followed up by molecular techniques. And, of course, Bill's ENU turned out to be a fabulous tool for all the molecular genetics that's going on now -- all the mutagenesis that's carried out in order to make mutations and further study them.

STOW: Something to be proud of, to be sure. If you had the opportunity to go back and do something different in your career, would you change anything?

RUSSELL: I would have kept away from administrative work. I would have turned down the offer to become a section head. Once I took that on, my work [in research] really sadly languished. I could have done probably ten times as much during those years.

STOW: My goodness.

RUSSELL: And, I find that out very sadly now when I'm cleaning out my office. I have file drawers full of stuff that wasn't worth anything, really. That was just work that I had done that didn't really lead to any good scientific results.

STOW: You've been very active outside of the scientific world, also. One example is the Obed River community. Tell us a little bit about your activities there.

RUSSELL: Well, it really started in the mid-'60s. Before that we had been sadly negligent of our wonderful Tennessee environment. Ah, we awoke to it because a river that we had just discovered, the Obed River, which is only about a half hour's drive from Oak Ridge, turned out to be threatened by a dam that was about to be built on it by the Tennessee Valley Authority. And so, we devoted quite a bit of time to fighting TVA on that issue. And, having beaten back the dam, we then worked toward some positive legislative protection [of the river we saved]. And, we ended up with something called the Obed Wild and Scenic River. There was another river -- the Big South Fork of the Cumberland Plateau -- where we managed to get a park. And, we were very much involved in a lot of other, mostly Tennessee, but also other, environmental issues involving the Smokies and the Cumberland mountains. We formed a group called the Tennessee Citizens for Wilderness Planning in 1966. It's 37 years old now and has become a very respected group in the state -- very effective because it relies very much on good research and good factual background information before we get into any issues -- and then on really effective administrative and political contacts.

STOW: While we're talking about your work in the Tennessee river systems, and conservation and so on, I notice that you had gotten a fairly prestigious award: The Marjorie Stoneman Douglas Award from the National Parks and Conservation Association. Tell us what that was for.

RUSSELL: I think it was more or less for the totality of the [conservation work] that we had done. It is a very nice, wonderful award to have because it's given to only one person, but not every year. And so, that was a fine one to get. And, we also got a Lifetime Environmental Achievement Award from the State of Tennessee.

STOW: Well, you and Bill have been very active in the outdoors community -- hiking in parts of East Tennessee and other places, right?

RUSSELL: We had lots of fun trips elsewhere in the country too, you know. We took our kids down the Green River [in Utah] in canoes -- that was a two-week trip where we never saw anybody. We did a fair amount of white-water canoeing and rafting and a fair amount of hiking. And, more in our later years, in the '80s and '90s, we got to take some interesting trips like trekking in Nepal and going to Indonesia for snorkeling and going all the way up and down the coast of South America from Cape Horn all the way up to the Panama Canal. Bill and I had some very, very wonderful trips.

STOW: You never would have anticipated that in 1947, would you?

RUSSELL: No. (Laughs) No.

STOW: Ah, the necklace that you have on -- is that a piece of native wood?

RUSSELL: That is sumac. And it was made by Bill. He has made probably sixty or seventy different wooden pendants like that – they're all different woods -- all different configurations. They're simply cut the right way, and polished, and oiled -- he made a fantastic series of those. He was also a great photographer. He used to be very active in the Carbide Camera Club -- and there were a series of camera clubs that were run out of the Lab. He exhibited almost every year -- mostly black and white photos. He's done quite a lot of movie work, too. Filmmaking was one of his very big hobbies.

STOW: Well, it's a lovely necklace, there ...

RUSSELL: And, I didn't have any such great hobbies because I was so busy taking care of kids and things like that... (Laughs)

STOW: And, you were also a section head ... (Laughter). The west end of Oak Ridge National Lab now has the new Mouse House facilities going up, and, of course, those are dedicated to you and Bill in name. And, we're very pleased to have that dedication. Do you have any feelings of sadness as you move out of Y-12 and those lovely facilities that have been your home for all these years?

RUSSELL: They don't look very lovely from the outside, but they have been really great, and they have been very successful. And, though they're now looked upon as a horrible mouse place, they were [excellent facilities] for rearing so many mice in perfectly healthy conditions. We did not experience a single epidemic. We didn't have any serious diseases. And, our mice were such consistent breeders in different stocks, capable of repeated breeding year after year. Unlike [the same stocks] in other labs (when I compared results), ours were so constant. And Bill's philosophy was to have a conventional healthy colony, but not a pathogen-free one. And that way, if some pathogen should come in, [the mice] would develop a resistance to it and beat it down. And, it seemed to work out – the mice just did incredibly well. And, Bill designed designed every bit of the facility. We had, for example, pipe shelves. The cages were kept on pipes that were just resting on racks. That way dirt did not accumulate -- it all fell through. He designed the cages, the tops, and the bottle system. Everything he designed worked beautifully. So I am sad to leave that. Everything is going to be much cleaner in the other place, I guess. It's pathogen-free. It's going to be much more cumbersome to work with. It will be ten times more expensive to take care of the animals. And, it will be much harder for people to work with the animals, because they can't get to them as [easily]. It will be a big trade-off.

STOW: Of course, the mouse population will be much smaller, won't it now?

RUSSELL: It'll be much smaller, yes. But the kind of personal contact we had with the animals, which enabled us to observe an awful lot of things, I think was very important. And, you know, we could go from our office into the mouse room right across the hall, if we thought of something we needed to look up. You won't be able to do that in the new facility at ORNL. You'll have to shower and do various things. And, we just had a lot more space there. I'm now faced with having to move into an office over here that's less than half the size of the one I had at [in the old Biology Division building at Y-12].

STOW: What do you think the greatest challenge today is for the mouse program? Is it a financial challenge?

RUSSELL: Yes.

STOW: Is it a technological challenge?

RUSSELL: I think it's a financial one -- it really is. Fortunately, I'm no longer involved in having to get funding, because I don't do any more research. But my colleagues are constantly struggling. And work with mice -- even though it's greatly reduced – is still very consumptive of the funding that you can get. At the same time you have to have something that other people cannot compete with.

STOW: Where does our mouse program and ORNL's new Mouse House rank with regard to other mouse programs in this country or throughout the world?

RUSSELL: Well, there are some really good mouse programs in the world now. There's a good one at Harwell in England. And, I think, they have a good one in Nuremberg, Germany. There is a good one at Baylor University in Texas. Some other states now have very good mouse facilities. The ORNL Mouse House certainly is not going to be the only one, nor will it be the biggest one.

STOW: What is unique about ours?

RUSSELL: What was unique, and, hopefully, will continue to be so, is to have the availability of all sorts of genetic [stocks] that we have preserved. Unfortunately, we're not going to be able to move any [of our] mice in there. Did you realize that?

STOW: I knew you're not moving any mice from Y-12 to ORNL. You're moving mouse sperm, right?

RUSSELL: We have frozen embryos and sperm. We have to re-derive [the stocks], so they'll come in pathogen-free. And, that will be an enormous undertaking. There will be a lag of quite some time before we'll really have a mouse colony established there. So our investigators have already been planning for the past couple of years how they can occupy themselves during the two or three years they will must work without any mice. A major undertaking.

STOW: I asked you awhile ago if there was anybody that really influenced you the most. You certainly worked with dozens of others who you must hold in high regard. Anybody you want to mention there?

RUSSELL: Well, one person who was really incredibly important to our program was Gene Oakberg, because he was the first person to study the kinetics of germ-cell growth and replacement, to working out the timing, and also -- in a normal animal – [determine the same thing for mice exposed to radiation]. And, without his work, which was really quite complex, it would have been quite impossible to figure out the types of germ cells that we were actually irradiating, and what the different cell effects were. So, it was an intricate piece of work and a very close relationship between his work and the genetic experiments. I think he was one of the most important people to the program.

STOW: Gene Oakberg...

RUSSELL: Gene Oakberg, yes. And he was important later on during the chemical mutagenesis work. Well, I should mention some people who did the cytogenetics work. We had Ernie Chu way back then, and later on Nestor Cacheiro, who only recently retired. During the chemical mutagenesis work, Waldo Generoso was a very imaginative, active, and productive person. And, there were many others. I hate to slight anybody, but those are the ones that really stand out.

STOW: I understand. Those are names that are widely known, yes.

RUSSELL: And then, of course, the recent scientists that we've had since the late '80s that will be carrying on mammalian genetics research include Gene Rinchik. We had Rick Woychik for awhile, but he left to head the Jackson Laboratory.

STOW: I didn't realize that.

RUSSELL: Yes, that's where he ended up. And, Dabney Johnson, who was actually a student of Gene Rinchik's, has been our section head since the late '90s. You know that without her, we would have disappeared. So, we've had some really terrific people.

STOW: Well, I'm glad you had the opportunity to name and acknowledge them. One thing that I neglected to ask you about earlier has to do with risk analysis and risk projections. How has the work that you and Bill have done on chemical mutagenesis and radiological mutagenesis been translated into risk projections?

RUSSELL: Well, starting from the mid-'50s, it's been used in several ways. Many of the committees that I mentioned ended up setting maximum tolerated doses. So, a lot of the maximum tolerated doses that are now in effect were based originally on the work that [we] contributed on the genetic effects of radiation. It was interesting to see the genesis of this guideline because, depending on what we had just found at the time, we were praised either by the people who wanted to minimize the risk, or by the people who wanted to maximize the risk. For instance, early on, we found that the mouse was more sensitive to radiation and had a higher mutation rate than *Drosophila*.

STOW: Oh, yes, I read fifteen times higher …

RUSSELL: Fifteen times. So, everybody who wanted to say the risk was really bad talked about that work. And then, when the dose-rate effect came to be known, it went the other way, because it meant that at the low dose rates that people were getting, the risk of mutations from exposure to radiation really decreased. So, the people who wanted to minimize the risk thought that was great.

STOW: Kind of like the glass is half full or half-empty approach ...

RUSSELL: That's right. (Laughs) And so, depending on who invited you to give a talk, you could always tell whether you were in favor with one group or the other.

STOW: In looking over your resume, I saw that in 1955 you received a Mademoiselle Award. Can you tell us what that was?

RUSSELL: Well, *Mademoiselle* was the name of a magazine. [It ceased publication in November 2001.]

STOW: I think I've seen it at some point.

RUSSELL: And, the magazine honored ten women of the year, or something like that. Another interesting magazine experience was when Margaret Burke-White, the famous photographer, came down here to shoot photos for *Life* magazine. She set up a camera in our gamma source room, on the third floor, and photographed us in there many times. But, she also wanted to take photos of us outdoors, so we had to pitch a tent in the greenbelt, up above Delaware Avenue. It was supposed to come out in the magazine that we were out in the wild somewhere. And, I was supposed to jump on a pogo stick. We have all sorts of wonderful pictures that she took here.

STOW: Anything else that we need to cover while we're here?

RUSSELL: No, I don't think so

STOW: You know, we've touched on a lot of things ...

RUSSELL: Yes...

STOW: Okay, thanks very much.

RUSSELL: Thank you!

STOW: We've enjoyed it.

RUSSELL: It was a great interview.

STOW: Our pleasure to have you out today!

RUSSELL: A great way to get things out of me, huh?

STOW: Good.

---------- ----------END OF INTERVIEW---------- ----------