The History of The Donner Laboratory

Session Two: John H. Lawrence and Dan Wilkes

DW: Let's go back for a moment to the initial experiment you did with Paul Aebersold in 1935 on the biological effects of neutrons. How did you prepare for it? I understand that you brought some mice out, that you drove a colony of mice out here. What are your impressions about the set-up at the Cyclotron, and your impressions of this entirely new kind of medical and biological work, and so on. Some of the things that you did; your procedures.

JL: I can remember coming out here when I was on the Faculty of the Yale School of Medicine, and I came out really to visit my brother. I must have come out the summer of 1935, really for a visit; I didn't bring any mice with me. Although I had been seeing him pretty often in his trips East -- he would always come and see me in Boston when I was a medical student, and then at Yale when I was at Yale Faculty.

DW: You did that experiment actually before you came out for a visit then?

JL: That's right. The real reason for that experiment on neutrons was obvious, I guess. Ernest and all the rest were concerned about neutron radiation but nobody had ever studied their effects. I remember that I was impressed when I saw the Wilson-Clougt Chamber of the radiation which had come from the beryllium target when it was bombarded in the Cyclotron with the deuterons. I cam remember Franz Kurie was the expert with the Wilson-Clougt Chamber which was invented by a Scotsman who was also a mountain climber and who got the Nobel Prize for it. It was a way of visualizing radiation effects — it had sort of a piston effect, this piston would pull down and rarify the hydrogen and another gas in there. Radiation (neutrons and gamma rays) would then make it possible to see the ionization produced; then you could photograph that and you could see the different kinds of ionization. There were just small fine tracks which were due to the beta rays liberated by the gamma

rays from the beryllium target, and the other were very long wide tracks which were caused by neutrons striking the hydrogen; those neutrons striking the hydrogen would cause very dense ionization. So even I, who was not a physicist, could say: "Gee whiz, when that hits the body that must do different things than x rays do." That's the way my interest started.

DW: In other words, the same kind of thing happens -- the ionization happens in the body and the body cells, and you would expect the neutrons would disrupt cells by this kind of dense radiation — or the possibility was there.

JL: Yes, of course, we knew that x rays would kill a person if one got a big dose like 500 r. or so.

DW: And that of course is ionization, too.

JL: Yes, by the process of ionization. Then, I got acquainted with Paul Aebersold who was a young graduate student in physics and working chiefly with Ernest. I think he was a graduate of Stanford and he came up here to get his Ph.D. Paul was a physicist. You remember him?

DW: Oh yes, I knew Paul.

JL: I went down to Cowell Hospital and talked to the head of the hospital and asked if I could use laboratory space downstairs which included a room, a microscope, and a laboratory bench. I went to Herbert Evans and got some animals; they were rats. So, with the microscope, a blood-counting set-up, and ordinary instruments that I borrowed, we proceeded to study the comparative effects of x rays and neutrons on the blood picture of these rats and also on the lethal effect, the killing effect. So, that's the way I started.

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DW: Then, you would take the rats to the Cyclotron, and I guess that you would put them in some kind of a contraption which the beam could be directed to, so that it would irradiate the rats.

JL: Right. With Paul and the help of Ernest's engineering people in the Lab (there weren't very many then, just a few), we rigged up a chamber with two inlets; one for air going in and one for air going out. We set that up next to the beryllium target where the deuteron beam was aimed and struck this target. When deuterons strike beryllium, they produce a mixture of gamma rays and neutrons. I think it is about 95% neutrons. I can remember one particular experiment: I think it was with the very first rat. Ernest was running the Cyclotron; I remember that because a lot of people couldn't run it. He could always make it run by just the touch he had; that Cyclotron just didn't run well in those days. So, he was running it, and Paul and I had done blood counts on this rat to see what the normal count was. We put this rat in the chamber and fastened the hoses that put air into it and another outlet, of course. We asked Ernest to turn off the Cyclotron so we could crawl back in there after about two minutes and see whether the rat was okay, and the rat was dead! I've told you this before. I think quite honestly we didn't know for sure what killed the rat. It scared everybody because there were only a few people, graduate students and faculty, 20 to 25 people around there in those days working. I'm not sure whether Luis Alvarez was here yet or Ed McMilla. I don't think they were but they may have been.

DW: I think Ed was, but Luis came in about 1936.

JL: Of course, a lot of the others came many years later, like Glenn Seaborg.

DW: I think he was working for his Ph.D. at the time; he was only a graduate student then. He hadn't started working at the Cyclotron.

JL: Yes, and Bill Libby was working for his Ph.D. with G.N. Lewis, too.

Later on, after a couple of weeks when we got our sections through, and as we suspected, the animal died of suffocation, not radiation. Before that, the gossip got around that this animal really was killed in a hurry with neutrons.

DW: Do I remember correctly that you — in trying to identify the cause (it seemed pretty amazing that the rat would go just like that) -- investigated it and found that there was no air going into that chamber? Is that what happened?

JL: Right. The air inlet hose had pulled off. But still, we weren't really sure that the rat didn't die from radiation anyway. It was a pretty good-sized chamber; it had two holes at each end. We thought it might have been radiation. When the microscopic sections came through, we looked at the bone marrow and intestines. I knew quite a bit about radiation because I had done a lot of work at Yale on x rays. There was nothing wrong with the animal; it obviously didn't die of radiation. You could kill an animal in a couple of hours with a massive dose of x rays or a less massive dose of neutrons. Well, anyway, that's the way the experiment started.

DW: So, you would do some tests to determine the blood counts before and after exposure — that sort of thing.

JL: Yes, red counts, white counts, complete blood counts. I did all of those personally. We did that on quite a few rats. I had curves which showed the blood counts falling off; the white counts falling off. Then we started giving big doses and animals would die. So, we started comparing the dose that produced an equal fall in blood count from neutrons and an equal fall from x rays. I've got some lantern slides of that. I used those in the initial talks that I gave when I first talked in the East at Yale (Mr. Donner was in the audience). We also started doing

JL: (continued) lethal studies. We compared the dose using a condenser R meter put out by a company in Cleveland. Everybody was using that for measuring radiation. We would measure the ionization dose with this condenser R meter for x rays and neutrons. I think that neutrons were 5 to 10 times as killing on the blood counts and on the animals as I remember it on dozens of experiments with rats and mice, too. We warned everybody that the allowable safe dose had to be cut to about a tenth of that allowed for x rays. I can't remember now exactly what the daily dose was in those days but of course it was cut way down for laboratory workers. I also remember the relationship of this work to shielding. Just how much shielding they put around the Cyclotron when I first came there in '35, the 37" -- some of it was water, some was concrete; it was all over the place.

DW: Was there shielding there when you came?

JL: I can't remember how much but I think there was a lot more went in after that. Early in these experiments, people would go in and look at this beautiful purple deuteron beam to get a glance at it. It was a beautiful thing; I saw it.

DW: The ionization of the air caused that, I guess.

JL: I guess so. You've seen the picture of it. Well, I think that was very dangerous. They quit doing that after these animal experiments were started, and nobody went in there to watch that beam anymore. Many years later, we didn't discover this but others discovered that neutrons were very dangerous to the eye. Do you remember that?

DW: Yes, it caused cataracts.

JL: It's interesting that nobody in the Laboratory at Berkeley ever got a cataract.

DW: They instituted some strict measures as a result of this work, that is, safety measures.

JL: Oh, you mean after cataracts were known to be formed.

DW: I mean, after your work.

JL: Yes, I think we barred everyone from going in there near that target when the machine was on.

DW: Did they have some way at that time to determine how much radiation people were getting? Did they have a routine...

JL: Yes, people were wearing badges at that time, although I don't know when they started wearing them but it was early.

DW: Obviously, they knew that radiation, that x rays, were coming out all of that stuff. And they knew that was dangerous, so they had to wear badges.

JL: Sure. They had no federal or state regulations; they were just doing that on their own.

DW: Did you present papers on this. I know that you and Paul published one.

JL: We continued those experiments during that period of time, and then I went back to New Haven. Paul, Ernest and I wrote a paper -- we were sending the manuscript back and forth on the biological effects of neutrons. But I don't think any of us gave any talks on it. I kept coming back every two or three months, and that's when I got that first grant from the Macy Foundation (on the second trip, I think it was). Of course, I had a laboratory at Yale which included a technician and a large colony of mice and rats, and lots of mice with tumors because I was working with them for several years before I came out here; not in preparation for this, but I was interested in cancer. Soon after I came out here, I brought out my own animals and those with tumors, too. I'd come out third class on the train with these Macy funds, and in

JL: (continued) the baggage car, I'd have the mice; maybe I would have 500 to 1,000 mice. Then, we'd do these experiments. We'd go over to the X-ray Department at the Medical School in San Francisco at night to get our x ray exposures. We finally began working with tumors. We wouldn't radiate the tumor in the animal — we'd take the tumor out and pack them in little packages, and radiate these packages with x rays and neutrons, and then implant them back into the mouse. These mice were 100% susceptible; they would all die of a tumor they were injected with. So, we would simply plot the percentage of animals that would not take the tumor because it had been killed by the radiation, and we would draw curves, survival curves, and get ratios of the effects of neutrons versus x rays on the tumors and on the normal animal. We got a differential effect which showed that neutrons were about 20% more lethal to tumor cells than were the normal cells. I can remember that Ernest and I talked about that. We and others said that maybe we had a radiation here that is selective against cancer. So, that's really what started the program of treating patients.

DW: That's what started the whole field, I guess, of the use of nuclear particles, and the particles in the treatment of cancer. That was probably the precipitating event when you found the differential effect of cancer on normal cells.

JL: I think you're right. It was proven later by L.H. Gray whom I became acquainted with. He visited the Laboratory many times; he was a great physicist. I also saw him in his laboratory out at Northwood in London where he was the chief physicist. He built the cyclotron at Hammersmith Hospital where I've been many times. It must be 25 years since they built it. He died about five years ago. He's not entirely responsible for it; he's given the credit for discovering the so-called oxygen effect; that is, when x rays radiate a tissue culture, or an animal or plant in oxygen, and then radiate the same object in air or nitrogen, it could kill the plant or the bacteria or the animal with about a third of the dose if it had 100% oxygen compared to nitrogen.

JL: (continued) So, I think in looking back in those days, Paul and I had these packages of tumor cells; they were really hypoxic. They were low in oxygen because they didn't have any circulation, so they were hypoxic. Also later, it was shown that the dense ionization of neutron ionization kills cells regardless of oxygen presence or oxygen absence. So it made it look like this kind of radiation was sort of selective because the normal animals were not getting the normal amount of oxygen — these cells were low in oxygen. The dense ionization was not having an effect on the normal animal but it was having more of an effect, relatively speaking, on these cells that were low in oxygen.

DW: The effect was not what you thought it was at first? Is that what you mean that the differential didn't really exist?

JL: Well, the differential existed but the mechanism of it was that we were dealing with dense ionization, and dense ionization is relatively insensitive to the amount of oxygen that is present in what you radiate. Thus, these cells being radiated with neutrons were relatively killed with a 20% lower dose.

DW: They were low in oxygen.

JL: They were low in oxygen because they were out of the body and had no circulation; they were out for about one-half of an hour.

DW: They were on their way to being dead already, I suppose then.

JL: They weren't dead but these cells were low in oxygen, and you could inject them and they would grow. But they were low in oxygen.

DW: So, they would be killed at a relatively higher rate conpared to x rays?

JL: Right. We spent a couple of years radiating mice and rats; normal ones and with various kinds of tumors. We finally developed a laboratory in the old radiation laboratory where I had a fulltime technician and a large animal colony that kept going while, for two years, I kept going back and forth; I had two laboratories. I would take my mice back to New Haven and follow them. I did all of my drawings then myself, and all my charts. I had all my lantern slides made in New Haven. I would finish one experiment, and then I would come back and we'd start another one. So, we did a lot of experiments and plotted curves. Of course, at the same time, there were other people here who began coming to work with neutrons. Among them was Raymond Zirkle — I think he came the second summer; I'm not sure. He later went to Chicago. There was another Englishman who came over by the name of Spear from the British Empire Cancer Campaign, and he did some work too. Well, those were the main two, I think. Again, we found the comparing of the animal results with the results on the plants and fern spores a great variation in sensitivity all the way from 5 times up to 20 to 30 times. But neutrons were definitely more destructive than x rays. Then, of course, as you earlier mentioned therapy, we got patients from the Medical School in San Francisco and got Dr. Stone to come over. We started radiating with neutrons those patients with hopeless cancer. That must have been started about 1938. I don't know how many patients were treated. I became discouraged with that work (I worked with Dr. Stone on that for about a year), and in the meantime, I started using radioactive isotopes, particularly P32, in studying metabolism in normal animals and in cancer animals. And at that time, too, Joe Hamilton who was a young graduate in chemistry (but I think he was an intern at San Francisco) began working with radioactive sodium in normal people and then radioactive iodine, too. The dates I can't remember, but it was about that time — I'd say '36 or '37. I don't think he was working when Paul and I were there that first summer.

DW: The sodium work was done in '36. I think Joe started out with normal patients. Over at the Medical Center, he and Stone did an experiment, a tracer experiment, in a patient. I don't recall what the patient had.

JL: Don't you think prior to that Joe had done experiments on normal people, or not?

DW: I think it was '36 in humans, but '35 in animals. Sodium was one of the early ones that they could make in some quantity. It was kind of easy to make and easy to use widely in a lot of biological systems, and you could trace it pretty easily. It was a good one to start out with. I think the first tracer study in humans was that one with sodium at the Medical Center with Hamilton and Bob Stone.

JL: That was the first patient, yes. But I remember they were misguided because that was a patient with leukemia...

DW: Yes, they discovered that it wasn't going to go, but they took some samples and did some observations on where the sodium went, I think.

JL: Yes, it was a sort of stunt. I remember talking to them about it -- all you can do with sodium is to give them whole-body radiation. I had started working with P32. Martin Kamen (whom I haven't seen for sometime, but he's now at San Diego anymore) prepared the phosphorous, the target, and the solutions for me to use; he was a wonderful and generous guy. To get back to Joe and his patients, I realized that on the basis of experiments with normal mice and in experiments with leukemic mice (I had very nice colonies of all kinds of leukemia and cancers and all kinds of normal mice who would take 100% when a tumor was implanted, and you could produce leukemia very simply), we could study the distribution of radioactive phosphorous and found that it went where we wanted it -- it went to the bone marrow, to the lymph nodes which were filled with leukemic cells, and to the spleen. It had ~~a beta ray~~ instead of a gamma ray. The gamma ray from sodium would radiate the whole body whereas P32 would

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JL: (continued) have a maximum penetration of say 8 millimeters and an average penetration of one millimeter or so.

DW: But a gamma ray, of course, is much more penetrative of a lot more tissue than...

JL: Which you wouldn't want. You only want to hit the part that is bad. To get back to the neutron work. Again, I can remember the first paper — I think that Ernest mentioned in talks about making large quantities of radioactive isotopes. However, the first talk on neutrons I gave in New Haven, Connecticut; I think in the fall of '37. Harvey Cushing gave a paper on that same program on Cushing's disease which I learned a lot about for many years in the East before I came out here. In recent years, we've seen a lot of patients here with Cushing's disease and treated them successfully. But anyway, I gave the first paper there and I think the title of it was: "Artificial Radioactivity and Neutron Rays in Biology and Medicine." It was before the Interurban Surgical Clinical Club; they had a lot of famous surgeons up and down the East Coast. (I talked to the group called the Interurban Medical Club in Vancouver about two months ago; we have that club that I belong to where all of them are professors of medicine.) That was the first paper. Then, I gave a seminar, I think, that same Fall over in the Department of Anatomy where I got my mice from Bill Gardner and Dr. Strong. Dr. Strong was a great pioneer in developing inbred strains of mice. I had that colony of my own which I brought with me but if I wanted new tumors, I would get them from Bill Gardner because he was inducing tumors; he was a young instructor then. Later, he was a professor of anatomy and he's retired now; he's a fellow about my age. In the audience at that seminar was Mr. Donner and his daughter. This is several years after he lost his son, his oldest son, J[redacted] from cancer of the lung. So, Mr. Donner (this was '29 or '30), who was a very wealthy man, pulled out of the stock market and started the Donner Foundation. After I gave my paper on neutrons and their possible differential effect on cancer, he and I talked about it. The widow of his son was living out on the

JL: (continued) Peninsula, and he said that he was going to go out and visit her. I asked him if he could come over and visit the laboratory. And that's how he visited the radiation laboratory for the first time. That's were we first got him interested in building us a building.

So, let's see where we stand here, now. Please briefly outline what you have to say...

DW: I would just like to suggest, John, that we probably could get a more coherent understanding of the history of this field if we take each thread and follow it through from the beginning until recent times. For example: you've just been talking about neutrons and the use of neutrons in therapy — the background of how neutrons looked promising in therapy and, of course, that led to the promise of other particle beams in therapy. If we could take this whole thread of particle beam therapy and follow it from the beginning to the end, I think a reader would have a better understanding of what happened there, and then some of the other areas would include therapy with radioisotpes, another thread is the evolution of instrumentation for use with radioisotopes including basic research, and diagnosis of disease which has become an extremely important medicine. As we have started now to talk about how particle beam therapy began, your experiment with neutrons, for example, could be followed through that whole area to the present time; then, I think that is one phase of atomic medicine that a reader could follow and see that this was how it started and what happened.

JL: So, you would take one thread, we'll say particle therapy, and carry it right on through the present time.

DW: I think it might be a good way to go.

JL: It's a good thought.

DW: And then the identifiable threads also. It would be certainly more coherent.

JL: There are certainly so many things to talk about. Yes, it might be more coherent for the reader, and for you and me to work that way. I think that's a good idea, and I agree with you. Particle therapy...

DW: Yes, you would go on to talk about the neutron work in '38 to '41 or thereabouts with the 37" first, and then the 60" was used in that, too. Describe that a bit and indicate what was learned about it. Actually, I think that would help you start in another direction, that is, the use of positive particle beams.

JL: Then, you'd carry it right on through to the positive particle beams, the pituitary work, then pretty soon you'd get into the very heavy particles, and go right up to date.

DW: To the Bevalac.

JL: That would be one story. Then, you would go on to the therapy with radioactive isotopes, that would be another story, then on to tracer research, to diagnostic instrumentation with radioisotopes, etc. I think that would make it a lot better, I really do. An excellent idea.

DW: I think, John, at some point we ought to get you to talk about what the Laboratory was like in the first two or three years that you were there. What your impressions were. What you saw and what you did. And what was going on there, not only what you were doing but what other people were doing. Maybe that will come out in some of these threads that we're going to talk about if we remember to bring them in.

JL: Yes, I think it's hard for me to recollect my impressions. Having had a long training in medicine, although I had had a laboratory and was doing animal research, it was such a different atmosphere in coming and working here. It wasn't entirely a

JL: (continued) surprise to me because Ernest and I talked about the tremendous potential that there would be in getting more into medicine more of the basic science. We talked about that a lot. We never figured how we could do it. That was before the discovery of radioactivity, too. Hospitals and medical schools in those days (and it's still true now), are getting people in x ray departments and medical departments who are chemists, physicists and mathematicians. It was really very exciting for me to come to a place where you were surrounded by all these basic scientists; all these bright young guys who could help you do things that you couldn't do. The medical men were trained primarily in patient care, so I was very excited to see the potential of getting medical men in a laboratory like this where they had all these bright young chemists, physicists and engineers. And, of course, Harvey Cushing saw the excitement of it, too. He developed a bibliography of Bohr and Rutherford and all of those; it's now in the Yale Library -- he gave it to them. He saw the excitement of this field where isotopes were discovered and these new radiations. He said that this was something like bacteriology when he was a young fellow; he said that this was going to be a terrific field. He was a remarkable man. So, I absorbed some of that from Harvey Cushing. I did get that feeling of excitement that was different from the feeling of medicine. I liked medicine; I could have stayed at Yale as a Professor and if I had stayed, there I would have been teaching and taking care of patients and doing research.

(Side One finished)

(Side Two — Beginning in car traveling)

DW: One thing that we maybe need to do is to have some kind of outline; some kind of event, dates of things happening, in some kind of sequence to keep us on the track. I was looking through some of the files that I have at home (and I haven't searched enough yet), and I pulled out something. I was doing a list in the early Sixties, for some reason or another, on the things in nuclear medicine that were done first by Donner Lab and before that by the Rad Lab (before there was a Donner Lab). In other

DW: (continued) words, it was in a kind of sequence; I think I called it "The Firsts." ... (recorded was turned off due to windshield wiper malfunction)