INTERVIEWEE: Jane S. Richardson
INTERVIEWER: Jessica Roseberry
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RICHARDSON INTERVIEW NO. 1

JESSICA ROSEBERRY: This is Jessica Roseberry. And I'm here with Jane S. Richardson. She is James B. Duke Professor of Biochemistry. Today is November 9, 2007, and we're here in her lab in the Nanaline H. Duke Building. And I want to thank you so much for agreeing to be interviewed. It's a real pleasure to talk with you today.

JANE RICHARDSON: Well, thanks. This seems like a really interesting venture.

ROSEBERRY: Well, I wonder if we might start with a little bit of background of yours, just—just if it's all right just when you were born, if that's okay to start there.

RICHARDSON: January 25, 1941.

ROSEBERRY: Thank you. And did you have any influences that kind of led you into science or those kinds of—?

RICHARDSON: Well, I guess three things important early on. One was that my father was an electrical engineer with NBC and helped develop color TV and was an executive at NBC for quite a while. But unfortunately, he died fairly young, so I didn't have him around as long as I would have liked. And my mother, by the time I was growing up, was teaching English in high school and was a really excellent teacher of writing and literature. She taught me how to write. And my father taught me how to do math, both more than what I got in school even. And then I was an amateur astronomer all through elementary school and high school and beginning of college, and very much always liked

the natural history end of science particularly. I started off as a math, physics, and astronomy major in college, Swarthmore College.

And actually I grew up right outside of New York, in Teaneck, New Jersey. There were a lot of astronomy clubs, particularly in New York, but also we had a local one in our county that had a 12-inch telescope. So I was very much involved in a lot of those clubs and did a lot of things at the planetarium in New York. For instance there, I ground a six-inch telescope mirror to make a telescope for me, and that was a lot of fun. In eighth grade I guess I did that. And about that time I went on an expedition to see my first total eclipse of the sun, which I got hooked on, really. I'd go to visit them whenever possible; they're just truly spectacular.

But anyway I—so I started off in math, physics and astronomy but partway through Swarthmore, I got really intrigued with philosophy, had some really wonderful professors, particularly pre-Socratics and history of philosophy, Spinoza. And so my B.A. from Swarthmore is in philosophy. And I went off to Harvard for a year in philosophy but decided it really wasn't what I wanted to do for a living. It was fun to study, but I didn't really want a career in it. So I left and bounced around for quite a long time trying various other things.

And then what ended up working was going to work in the same lab where my husband was getting his PhD in inorganic chemistry. We had met at Swarthmore and got married about half a year after we went up to Boston. But he was at MIT in the chemistry department and took on as his project doing a protein structure. He was working in Al Cotton's lab, who did small—molecule, inorganic chemistry, and crystallography. And at that point, there had only been two protein structures done,

hemoglobin and myoglobin. And Dave had gotten very interested in them his senior year at Swarthmore and did a big project in a physiology course about hemoglobin. And so he had been looking around for a lab to join his first year and decided he was interested in the structures that Cotton was doing. But he said that he wanted to minor in biochemistry; he'd gotten very intrigued with protein structures. And so Al said, "Gee, well, how would you like to do the structure of the protein as your project?" And neither one of them had any conception of what they were getting into at that point. They thought maybe they could just do the active site and didn't realize that the whole structure is related to the data by a Fourier transform, so you get all or nothing. There is no such thing as just looking at the active site.

ROSEBERRY: So they were going to do a smaller piece maybe?

RICHARDSON: Well, just that they didn't know enough about it when they were getting into it. Actually Al should have known better since he did small molecule structures, and probably he did. But anyway, that's the story the way we remember telling it. (*laughs*) And that was started sort of by a rivalry between Cotton and Lipscomb, who had a lab at Harvard down the street and was working on carboxypeptidase at the time. And so Al thought it would be a good thing for him to do a crystal structure of a protein, too. But for a while, Dave and a postdoc protein chemist, Ted Hazen, were starting to set up this project and trying different proteins and thinking about them. And about that time, Chris Anfinsen was visiting from NIH, who really wanted to persuade someone to do the structure of staph nuclease, which was—he was convinced would be a really important model system for protein folding. He'd been using ribonuclease, but ribonuclease has disulfide bonds, which make the folding more confusing. The staph nuclease is about the

same size but with no disulfides and should be a cleaner example. And indeed, it has turned out to be a really good model system for protein folding: particularly the people at Johns Hopkins have done an enormous amount of work on it. So he came to try and persuade Alex Rich to do this structure. But Alex was very busy with some very interesting small molecule nucleic acid structures and really didn't want to do a protein. But he said, "Oh, well, Al Cotton's been talking about this down the hall so you should go see him." So we decided to do the staph nuclease structure. And it's one that would be considered extremely easy these days. But of course, we had never done one before, and not very many other people in the world had done one before. So it took us seven years, and we had a very good time doing it. We were off in a corner where it was sort of a long-shot gamble for Al Cotton whether this was going to work, and we didn't really know how long it would take or what it would do, but it was very interesting. And we kind of reverse engineered the methods from reading the papers, but they never have all the details in them. And so there's some things that we did a bit differently than other people. But we eventually got there and got a two-Ängstrom structure of staph nuclease in 1969. At that point, we tied with David Eisenberg and cytochrome C for tenth place—tenth protein structure, ones that were really different. And at that point, we were approached about this job at Duke, or I should say Dave was approached. I used to be invisible, which I really miss. It was very (*laughing*) nice being invisible.

ROSEBERRY: So you were—?

RICHARDSON: And so I was a technician; I never did get a Ph.D. I have a bachelor's, and I have a sort of booby-prize-for-going-away Master's in philosophy from Harvard and a Master of Arts in teaching, but although my mother's a really good teacher, I'm not

really, and that somehow didn't work. I think the real problem is that I can only think about one thing at once; I'm no good at multiprocessing. And that doesn't work in the classroom. (*laughs*) So I can concentrate. I'm better on research.

ROSEBERRY: So you were a technician?

RICHARDSON: Yeah. So I came in as a technician and the three of us—Dave as the graduate student and Ted Hazen the post doc and me as the technician—for most of that seven years, were the people working together on it. So for instance, Dave learned how to program by writing the programs to analyze the data and control the diffractometer.

ROSEBERRY: So tell me a little bit about— I don't have a science background, so what does the structure tell us about these proteins?

RICHARDSON: Well, you never know for sure until you get it. But one of the nice things—it's a little bit like getting a picture through a microscope. It really is a picture in three dimensions. You have to do some interpretation to build the atomic model into that picture, because what you actually see from the data is a three-dimensional density of the electrons around the atoms. And so at a high enough resolution if you can get data that goes far enough out, you can actually see a little peak for each atom. That's very unusual for proteins. You get that for small molecules. And nowadays we have it for some proteins. It's really fun to look at. And even some nucleic acids. But typically, the resolution isn't quite that good, but you still see the shapes and often at typical resolution you can see an oxygen sticking out to the side. You can actually see the picture of this individual atom. Now, you're not looking at one molecule, you're looking at a crystal. So it's the fact that you have lots of them lined up in the same orientation that lets you see it. And so if they're not all at exactly the same orientation, it blurs things a little bit. But

that initial picture, there isn't much of any way of fudging it, (*laughs*) because of this complicated Fourier transform relationship. A person looking at the individual data measurements, which are X rays diffracted off the crystal, you wouldn't know what to do with it to change it in order to make the final result look like something in particular. And so when you get this picture out, it can very often and very easily tell you really surprising things that you wouldn't have guessed in advance. And so you don't have to ask it specific questions in order to get certain answers.

And so for instance, one of the surprises on the first structure that we did here at Duke, which was copper/zinc superoxide dismutase. It's sort of a departmental enzyme. Its function was discovered by Irwin Fridovich, and the sequence was done in Bob Hill's lab, and a number of other people in the department have worked on it. And it's turned out to be quite medically important, because it's a protection against free radical damage that's involved with aging and radiation damage and also in surgery when you take away oxygen from a region and then it comes back, you get damage. But on that one—of course, there were very few proteins known at that point. It turned out to have a structure that looked very much like an immunoglobulin domain. And at first we thought that meant they must be related, which would have been interesting. It turns out what it means is that it's a good way to fold up proteins. And so that particular thing was more about protein folding and protein structure than about the particular SOD [superoxide dismutase], but it was something new that we hadn't known before. And we learned a great deal about the geometry at the active site of this SOD enzyme. It has a copper and a zinc right next to each other at the active site. And it's actually been—the mechanism has been pretty controversial over the years, but just recently it's now gotten back to pretty

well confirming what we thought originally the mechanism must have been when we first looked at the structure. But usually it's the structure along with other information. It's only rarely that just looking at the structure completely settles something. It's usually along with biochemical data and evolutionary data, whatever else. But it changes totally what people can do with that other data. And so having a structure of the system that you're working on just enables all kinds of things—designing mutations in a more sensible way, interpreting whatever other data you're looking at. And so it lets you do much better science of other sorts. And then sometimes you get big surprises like the structures of the ribosome that came out in 2000, and just totally changed what we think about how ribosomes work and how proteins are synthesized—lots of exciting stuff about RNA. Our lab's also working on RNA as well as protein now. And I should say that it really is our lab. Dave and I have worked together through this whole time.

ROSEBERRY: During those earlier times, what were you using to look at these structures to develop models?

RICHARDSON: Well, it was X-ray crystallography. And so it really took seven years to get that picture.

ROSEBERRY: So tell me what X-ray crystallography is.

RICHARDSON: Well, you have to get the molecule to grow a crystal, which of course is not its natural biological state. But if you know what keeps the protein happy—so, often the people who are working with it biochemically know a lot about what kinds of solution conditions and temperatures and pH's and so on that particular molecule is happy. That helps a lot. It has to be very pure, has to be fairly high concentration usually, and sometimes it needs other partners, like if we tried to do a metallo-enzyme

without the metal in it, it wouldn't work very well. And having molecular biology to produce the proteins has made an enormous difference, of course, as opposed to having to purify them out of natural sources, because it means that even if there were, say, only five copies of a protein in the cell, you can produce it by molecular biology, and if you're lucky at least, get enough of it to actually purify and do a structure. So in a lot of ways, preparing the sample and making it grow crystals is the hardest part, in the sense that it may just not work at all. There's some very important systems that people have been trying to get crystals of for years and no one's managed it. But there are other techniques, most notably NMR [nuclear magnetic resonance], but nowadays also cryo-electron microscopy, particularly in combination with crystallography because the EM is lower resolution. But you can get considerable good structural information from those as well. But crystallography is still the major technique for seeing these structures at the atomic level, where you really find the locations of all the atoms and their relationships to each other.

ROSEBERRY: Is that what is still used in this lab?

RICHARDSON: Yeah. Well, we don’t actually anymore do protein crystal structures from the beginning. We got off onto a whole lot of other ideas over the years. Some of it is what we would now call structural bioinformatics: looking at structures and comparing them and trying to find patterns in them, molecular graphics and representations of these structures, and protein design. We're now back in crystallography, but mainly at the later stages where you're refining the structure and rebuilding it and making sure that you have it all correct.

ROSEBERRY: So it wouldn't be—you wouldn't be waiting for that crystal to—?

RICHARDSON: Well, there are now about fifty thousand structures in the databank, and people are doing them at an increasing rate. And so at this point we can indulge ourselves and look at all these things that everybody else has done, rather than adding our one or two. (*laughs*)

ROSEBERRY: You can do comparisons between them.

RICHARDSON: Yeah. And try and help make the techniques better for people to do those structures, so as to make it easier and more accurate.

ROSEBERRY: Well, what were you doing as a technician? What would that role be?

RICHARDSON: Well, I started off actually measuring the intensities of diffraction spots by eye, comparing how dark the spots were. And fairly soon after that, we got a diffractometer that measured these things electronically with counters. And so we moved on. At that point, I was still looking at the data and trying to make sure that it was really good—looking at exactly what were you seeing, the profile of each spot and how many measurements we had of things. Dave and Ted mostly did the crystal growing and the protein preparation, and Dave was the main programmer. I helped a little bit with that in the early days, but he's really kept that on and is one of the central programmers in the lab now. But of course, we all end up discussing what it is that we should be programming and what should the software be doing and what shouldn't it be doing. And we've been particularly thoroughly involved with that on graphics programming. But while we were at MIT, that didn't exist; there was no such thing as real molecular graphics until a little while after we got here. We've actually had a very close relationship with the computer graphics lab at UNC [University of North Carolina] Chapel Hill for about twenty years, really. We were sort of consumers of their graphics

or advisory people with driving problems that they were trying to deal with, and we learned a whole lot about designing graphics and computer systems from them.

ROSEBERRY: So those were available as long as twenty years ago?

RICHARDSON: Oh, yeah—no, longer than that. This was early seventies that we started off in that with them. And so it was—that was when we got out the first structure for the superoxide dismutase here at Duke and about the time that Dave was getting tenure, and that was about the time that they were developing really good systems for doing this process of building a model into an electron density map, the data that you get out of crystallography, and doing that on the computer. And so SOD was actually the first protein that was fit entirely on the computer before we built a physical model. So earlier it was done by building what are called Kendrew models. They're brass-stick models where a protein is several feet on the side. There's one of them out in the hall here that I suppose should be part of your archives. (*laughs*) And that's a very hard way to do it, and it's not very accurate but—

ROSEBERRY: That would be built by hand, maybe?

RICHARDSON: Yeah, yeah. And so the computer models are capable of being very much more accurate, but it took quite a while to get the display capabilities and the calculations up to where they did a really nice job with it. Nowadays it's really easy to do that way.

ROSEBERRY: So is this lab working on making those computer models available on that technology or—?

RICHARDSON: Well, there's a worldwide database that does that. The Protein Data Bank, which got started also in the seventies—I guess it was mid- to late-seventies when

the databank was founded. And it still is just one set of collaborators. It's more or less one databank, whereas the sequence people have many, many different databases that don't necessarily quite relate to each other, and it's been marvelous in macromolecules we really have one database. There is a separate nucleic acid database, but everything in there is also in the PDD [Protien-Disease Database]. It isn't really just a protein database; it's a macromolecular database. And so everybody who does structures, in order to publish them, has to put their models in the database, and increasingly they're supposed to put their data in as well, which we really are trying to push for. (*laughs*) And that's gotten a lot better. And so for most structures, you not only can get the atomic coordinates of the model from the database, and you just bring this up on a Web browser and you have the coordinates in a few seconds from the database. It really is neat these days. It's one of the things that has truly been getting better and better. It's nice to enjoy those when you find them. (*laughs*) But you also—for most of the structures, the data is available so you can actually look at the electron density maps. And so you can see what the evidence was for that model. And so if there's something that you wonder about, just how certain is this particular piece, you can go and look.

ROSEBERRY: Well, that sounds like a wonderful resource.

RICHARDSON: Oh, it's really great.

ROSEBERRY: So tell me a little bit more about what the lab here does now.

RICHARDSON: Well, too many different things at the moment. We're trying to study both RNA structure and protein structure. The biology of RNA has been exploding recently. Every year when you go to the meeting, there are three whole new fields that nobody knew about the year before, and there'll be hundreds of people talking about

them. And the structure work is also really growing and trying to keep up, but the tools are not nearly as good yet as the ones for proteins. And so one of the things we're trying to do is build tools that will work really well for doing RNA structure and also analyzing RNA structure. We're part of a group called the RNA ontology consortium, which nominally is defining nomenclature, but you get into a lot of substantive issues trying to deal with a nomenclature, particularly in a very new field, and that's been really interesting—particularly, we're trying to describe the backbone in RNA.

Any macromolecule is a polymer where it has a backbone that's a chemical string of connected atoms; and then at regular intervals, there are side chains going off of it. And so in proteins there are the amino acid side chains with different chemical properties, and there are twenty of them for proteins. In nucleic acids, there are the bases that stick out, and there are only four types of bases. And they're also bigger and more rigid, whereas the backbone is longer and more flexible in nucleic acids than it is in proteins. And so in proteins, a lot of the problems, the hard parts are with the side chains. In RNA, the bases are easy to see and they have phosphates in between, but the backbone has too many variable angles. It wiggles a lot, and it's hard in these maps to tell which way it's wiggling, unless you get very high resolution. And so working at what's basically the physics of those molecules to tell you what conformations actually make sense and are possible helps a lot when you're trying to fit them through the density rather than going just on what it is that you can see, because it's not really quite good enough resolution to see the level of detail that you want. And so we're trying to help understand those conformations enough better so that we can fit them both more easily and more

accurately. And of course it gives us the chance to spend a lot of time looking at these structures, which are very elegantly fascinating and beautiful.

And then in proteins, again, we're doing very similar things. When we were doing protein design, we were doing *de novo* design, where we were trying to come up with an amino acid sequence that we thought would fold into a certain protein structure, certain 3D arrangement. And then we would make that structure—either cloning it, expressing it or peptide synthesis but producing the actual molecule, to see whether it did what we thought it would do. And of course mostly it doesn't, because we didn't really know what we were doing that well and still don't quite. But that kind of process now works some of the time. (*laughs*) It's gotten better, but it's still certainly not a solved problem. We could get approximate structures, but they were not well-ordered into unique structures. When I say a unique structure, it doesn't mean they're static. They move and wiggle a lot, but they have an equilibrium structure that's really very well defined in these complicated 3D arrangements. And the ones that we designed had multiple equilibrium structures.

And so we set out to try and solve at least one of the problems that we thought was causing that. There are a number of them, most of which it wasn't obvious what to do to fix them, but one that we thought we could fix was really describing and quantitating numerically how good the packing was between the atoms on the inside of the structure. And that sounds really simple. It seems as though it should be straightforward geometry, but actually there were no techniques that really did it properly. And so we took off about five years and developed something that works quite well. It's not perfect but it's good, quite effective. And the big step in it, which tends to

sound peculiar to someone not in the field, was that we actually are looking at all of the atoms instead of half the atoms. Traditionally, people don't pay attention to the hydrogen atoms in these structures, for some good reasons and some bad reasons. The good reason is that in X-ray crystallography, you really don't see them. They don't diffract X rays very well, and so you have to have superexcellent data in order to see them at all. And so trying to be conservative, people don't put them in the model. They know how many hydrogens—and you know that they're there and what they are and what their geometry and bonding and so on is, but since you can't see them, they're normally just allowed for in volume. And so you take the atom they're attached to and make it enough bigger to account for the volume of those hydrogens. But you don't account for which direction they're pointing. And the bad reason is that it makes the pictures harder to look at and the calculations take a lot longer. And until recently, the computer power wasn't really good enough to put all those extra atoms on these huge structures. And they really are enormous. You can get thousands of residues and hundreds of thousand of atoms in one structure. And the hydrogens are about half of those atoms, and so leaving them off really helps at that moment. But now we can really use all of them, and definitely we've shown that it makes an enormous improvement to put them in, because they're making a large part of the interactions either on the inside of a molecule or its interactions with something else, like a ligand or a drug molecule, or between protein and nucleic acid, or whatever interactions. Those use these same properties and can be described by this system that we invented that describes the packing. We call it all-atom contact analysis.

By the time you put all the hydrogens in and look at these details of the packing, you have so many constraints on what model you can build that it almost becomes a

search problem rather than a model-building problem. If you can find the right answer and it really fits all of these criteria as well as all the data, then it's probably the right answer, even at moderate resolution. But—and so a lot of what we've been working on is the techniques for finding that right answer, and also analyzing an approximately structure and saying, Okay, here, this thing has to be around backwards. You don't really worry about the ones that are off just a little bit. If the density was ambiguous and you fit a side chain around in one direction, but we can tell by these diagnostic criteria that it really should be the other way around, changing it really makes a difference. And sometimes if this is near an active site, it may totally change what atoms you think are next to the active site. So it's not anything we set out to do. We didn't know that this technique was going to be really good for improving the experimental structures; we were doing it because of the design. But now that we've found that out, we really feel obliged to try and help make them more accurate. People are going to be putting all of this effort into doing the structures and seeing them as fundamental to biomedical research and to all biological research actually, then if we can make them better, we ought to. And so that's a lot of what we're obsessed with at the moment. (*laughs*)

ROSEBERRY: So has the design become a secondary piece then?

RICHARDSON: At the moment we're not really actively doing design. There are other people here at Duke that are—Homme Hellinga in this department and Bruce Donald across the street are actively doing protein design, although not of entire proteins. What they're doing is redesigning binding sites, or active sites, small pieces of a protein, getting new functions. And so we spend some of our time interacting with them and thinking

about how we can be helpful, but we're not actually doing designs in this lab at the moment.

ROSEBERRY: Well, I know the designs are kind of what this lab and you, yourself became known for. And I wonder if you could—?

RICHARDSON: Well, part of it—although actually, the thing that I'm most known for is those drawings. (*laugh*) So way back, I guess it was 1980, Chris Anfinsen asked me to do a review article for *Advances in Protein Chemistry* that he was an editor of looking at all of the structures that had been done so far of proteins. At that point, there were about seventy-five protein structures known, of ones that were significantly different. So there are a number that were really very closely related that I was counting as one in that scheme. So for instance, if you think about hemoglobin, hemoglobins from different species or even hemoglobin and myoglobin are very, very similar folds. And so the subunits of them look a whole lot alike and are related. Their sequences are similar, they're evolutionarily related, and so I count them as one in that group. By that kind of counting, there were about seventy-five. And so the idea was both to define a taxonomy of overall folds and to describe the local patterns that I was calling the anatomy. The title of this was "The Anatomy and Taxonomy of Protein Structure." And so the anatomy—Oh, partly that's a joke because when we came to Duke, and particularly I didn't have a degree, I was sort of a hanger on—Dave was the one who was hired. And they had a nepotism rule at that point. So he was hired in Biochemistry, and they found me a job in the Anatomy department.

ROSEBERRY: So you couldn't be in the same department?

RICHARDSON: Right. And it was a very useful contact, because they were not only doing larger scale structures, but they were using a lot of techniques that were related to things that we were doing. So it was a good set of contacts. But anyway, I used the anatomy metaphor. And then I had actually—when I was supposed to be studying philosophy, I spent a lot of time in the Botany Department at Harvard and took taxonomy courses. So anyway, the idea on the anatomy side was to describe the local motifs in the structures—things like, what does a helix really look like and what happens at the end of it and when does it bend and types of turns, what patterns do disulfides really have, and then somewhat higher organization, like beta strand relationships—this sort of detail in the anatomy part. And then the taxonomy was a description of overall protein folds—what kinds of patterns did they have and what ones were similar to each other and what ones were different?

And so it was for that second taxonomy half that I invented the system of what are called ribbon schematic drawings or ribbon drawings of proteins. I wasn't the first person to do something like that. There were several versions of similar drawings that people had done one or two of to illustrate a particular protein. But they were all slightly different, and they were all done from different viewpoints and with slightly different conventions. And so even for proteins that were very, very similar, if you looked at two of these drawings, you wouldn't know that. And so what I was trying to do was make a uniform set of conventions and to draw all seventy-five of the structures that were known. And so for related ones, I would draw them from the same viewpoint, so that you could see what was the same and what was different. And of course the big challenge is to take something where the three-dimensionality of it and even the handedness of the

structures and how they relate in 3D is really the important part. And to put that on a 2D page is not easy. I'm no good at drawing other things, and so it took me a whole year to work out how to do this, and I did an awful lot of drawing and erasing and drawing and erasing.

ROSEBERRY: Did you do this on your own, or were you studying art?

RICHARDSON: No, this was sort of my own project. And I didn't do anything else that year; that was it. And that was an incredibly productive wonderful year. But as I say, this is part of what's so wonderful about being invisible. The idea that anyone would be allowed to take a year off with, you know, not only no publications, but no real research results exactly. The ribbons have been enormously empowering to everybody doing research, but most people don't really quite count it as research, you know, working out how to represent these things and how to relate them. I suppose these days one might get away with calling it bioinformatics, but it isn't mostly what people think is respectable. And so I find it sort of ironic that that is what I'm known for but it would be almost impossible to do it now. We're all under too much short-term pressure.

ROSEBERRY: Were you on faculty at the time?

RICHARDSON: Sort of. (*laughs*) I had a lovely kind of position called an associate, I guess. It's kind of like an instructor, but it actually accrues tenure years, although you don't ever have to get sent away, they don't ever have to make a tenure decision. And so again, you don't have tenure in this position, but once I got in the National Academy, Duke decided it was embarrassing not to give me tenure, and they finally did, and they were able to do that. I really hadn't thought they ever would. (*laughs*) So I don't think I

was actually on the graduate school at that point. So I couldn't have my own students, but that really didn't matter since we had a joint lab.

ROSEBERRY: So you were interacting with the students—?

RICHARDSON: Oh, yeah. Interesting kind of position. I'm not sure it exists anymore.

ROSEBERRY: Well, tell me about these folds. You had talked about the protein folds and their being represented by the ribbon. Is that accurate?

RICHARDSON: Well, for instance, an alpha helix is a spiral where the backbone goes in a right-handed spiral with a repeat of 3.6 residues. And each turn makes interactions, hydrogen bonds and also just atoms touching, what are called Van der Waals interactions. And it's a very favorable, stable confirmation. And so both the long-range structure is a good one and also the local structure that makes that is also a good local structure. And so they're very common and quite regular and quite obvious when you look at the structure; they're the best understood and most studied piece of protein structure. And the way of representing them was as though you had ribbon like the ribbon on a package where you could imagine wrapping it around the cylinder and showing that as this spiral path.

Well, I guess I should say that the plane of the ribbon is the plane of the peptide bond. The place on the backbone where the side chain comes off is the alpha carbon. And between two alpha carbons is what's called the peptide, which is a set of five atoms that are all in a plane, because they have a peptide bond as a partial double bond for the chemistry people, and so it's constrained to stay in a plane rather than moving around freely. And so this plane or unit has an oxygen and an NH that like to hydrogen bond to each other. And those stick out in opposite directions of this flat plane on the backbone.

And so that arrangement and the way those interact with each other is a lot of what determines how the protein folds up. And in the helix, all of the NHs on all the peptide points in the same direction, and the carbonyl oxygens all point in the other direction, and they're all lined up so that on adjacent turns, they interact with each other. And so all of the backbone hydrogen bond groups are satisfied. They all form hydrogen bonds, except on the ends. And in general, the idea of the ribbons is that they should follow these planes of the peptides. And that works very naturally in the helix. And so each peptide is more or less lined up with the next one and the ribbon sort of just goes continuously between them.

Then the other common structure is what's called a beta sheet, which is made up of individual beta strands, and in the beta strand, the backbone is pretty much pulled out straight. Not quite—it wiggles back and forth, so they're called pleated beta sheets. But it's as extended as it really can get comfortably. And so there, all of the peptide planes are more or less lined up in the same direction, except they actually flip 180 degrees between each pair. And so if an oxygen is pointing to the left on one, it'll be pointing to the right on the next one. And so the definition of this ribbon convention is actually different in helix and sheet. In helix, it actually follows the same direction, as the carbonyls point the same way in between. But in beta sheet, you take whichever is the shortest distance, and you don't make it flip over by 180 degrees. There were some early things in computer graphics where people took it too literally, and they made a ribbon that flipped over every residue, and it looks awful. You just can't make sense of it, because it just spins around like a corkscrew much too tight, and you don't see the overall pattern. And also, you don't see the relationship between adjacent beta strands, which is

what makes the sheet. So in beta strands, the hydrogen bonding groups stick out to the side, and they interact with a neighboring, similar strand.

Then you have what are called loops or coil regions that are nonrepetitive. Those are harder for people to understand. They have often very well-defined, definite interactions, but they're a little harder to describe. And so what I was after was a convention that made sense to people when you looked at it, not necessarily the one that *a priori* was a single translation from the model into the ribbon.

ROSEBERRY: So you had mentioned kind of before we turned the tape on that there's a little bit of subjectivity to that.

RICHARDSON: Yeah. Because you have to decide that helices are important and that you want to represent the peptide plane and the hydrogen bond direction. There are other things you could do in showing a structure. For instance in a beta strand, I had to decide that I wanted it to stay fairly flat and quiet and smooth it in a certain way rather than making it show all the zigzags, or twist over every turn. And so a lot of what's happened, people like the ribbon drawings a lot and they got very common even early on. But what really has made them ubiquitous was computer graphics, where once we could show more than a few lines on the computer and could actually show something as complicated as a ribbon, that got to be the way that people showed these structures. And so all the people writing graphics programs, like my husband Dave, had to work out how to actually do that from the structures. And people tried a number of different systems early on. There are still some variations to it, and it's not absolutely uniform. And so there the subjectivity comes in how you decide to write the program. Different people define where the end of a helix would be slightly differently, and they won't absolutely agree.

And deciding whether a strand is long enough to really count as part of a beta sheet or a little tiny curl, is that really a helix, so do you show it as a helix or do you show it just as a piece of coil? That's all fairly subjective in deciding what are good viewpoints. And so it was salutary for people to remember with the drawings that this is somebody's interpretation. And of course any interpretation in science, if it's worth anything, it emphasizes some features and drops other features. And what makes it good or bad is how good a job you do of that. But it is worth remembering that it's a choice. (*laughs*)

ROSEBERRY: But people are still using the conventions that you set up to—?

RICHARDSON: At least pretty much, yeah. They're slightly different, and some people do them slightly differently but pretty much they're the same ones.

ROSEBERRY: I know that these are now called Richardson images or—?

RICHARDSON: Well, sometimes, but more often just ribbon drawings.

ROSEBERRY: So when you started, you were using colored pencil and then they—?

RICHARDSON: Well, the way I made them originally— I've done some colored versions that used pastels or colored pencils, but the main system was in ink actually on tracing paper, because I had to do it on top of a printout from the computer version. And so I originally commuted up to NIH for—there was a very early computer graphics system which was incredibly primitive compared to anything that you would have on your wristwatch these days, but it was really valuable for what I needed. And we were putting up just stick figures that had one bond from a C-alpha to the next C-alpha—a very, very simplified picture of the protein, but it was accurate, so the coordinates were in the right place. And I would move it around and find a good view and get a printout of it at a given scale, so they were all a consistent scale, and then of a stereo pair much smaller

that I could look at while I was making the drawing. So I was looking at it in stereo while I was drawing on top of this printout. And the originals were line drawings in ink that we then photographed, and Dave actually spent a lot of effort making really, really high-contrast clean photographs of both the color and the black-and-white ones.

ROSEBERRY: It sounds pretty labor intensive.

RICHARDSON: Yeah. And I'm glad I don't have to do them anymore. My eyes aren't good enough, I don't think, to do that level of drawings. And I certainly wouldn't want to do forty thousand of them. And so these days both our programs and everybody else's programs have ways of setting these up and doing them. And again, you've got to make choices about the representations. In a really big structure, for instance, you might want to show the helices as solid cylinders instead of ribbons, because you want the right level of detail for the size thing that you're looking at.

ROSEBERRY: So what was your husband doing at the time while you were taking this year off and working on these—?

RICHARDSON: Oh, we were still pretty much in crystallography at that point. We were still working very actively on the superoxide dismutase structure, getting higher resolution data and studying the active site, how the substrate came in and—but that was about the time that we started thinking about design, but we really hadn't gotten into it quite yet at that point. That article came out in 1981.

ROSEBERRY: So was your hope to help him in his work, or were you hoping to influence the field and do your own—?

RICHARDSON: Well, it was really getting out to the world things that we had done in looking at our structures and comparing them to other people structures. And so it did

end up being helpful in the future, but we were thinking of it as a publication, both of our work and also sort of a review of the field.

ROSEBERRY: But it wasn't until the computers that this kind of became—that the technology was able to use this, that these drawings became—?

RICHARDSON: Yeah, it became a whole lot more easy to do and popular at that point.

ROSEBERRY: And then af—you mentioned that you—

RICHARDSON: That was, I guess, maybe early nineties when the graphics really were able to do that.

ROSEBERRY: So you mentioned that maybe there was a phase that you were—the lab was doing the modeling and the graphics, kind of after the crystallography or—

RICHARDSON: Yeah, that's pretty much been a major aspect of our lab since—well, I don't know. We had to do some primitive kinds of graphics even for the early crystallography, but it really got serious after we got here at Duke. And certainly since the late eighties, we were really involved. No, it was sooner than that. We really did get into a good deal of it in the seventies. And some of that work was with the UNC people, and then some of it was our own graphics here.

ROSEBERRY: And that again is to kind of help people see it—?

RICHARDSON: Well, that one really is both directions. It's both something that we absolutely have to have to do our own work, and that really is where we got started. But some of it is trying to reach out. For instance, one of the other things that we've done is I guess the drawings are sort of more mine but Dave was involved; then, this graphics program is more his, but I was involved. We invented a system called Kinemages (for kinetic images), which was one of the first two molecular graphics systems for

macromolecules that you could really do on small computers. And that was 1991, '92 with the launch of the *Protein Science* journal. So we did that along with the Protein Society. And the journal had these kinemages available as supplementary material on floppy disks that went along with the articles. So some of the articles had 3D movable interactive illustrations to them. For about five years, I made those for the articles.

ROSEBERRY: Well, it sounds like it's a very cooperative lab.

RICHARDSON: Oh, yeah, among the students and post docs as well. So a lot of our projects are jointly shared among a number of people.

ROSEBERRY: How many students and post docs do you have?

RICHARDSON: Right at the moment, the lab's very big. We usually try to have a small lab because we both enjoy doing stuff ourselves. But we have a wonderful group of people at the moment. I don't know, it's about nine or ten people total.

ROSEBERRY: Well, what was Duke like when you first came in 1970?

RICHARDSON: Well, the whole area was just so much smaller. You know, when we came, the airport was like a little Caribbean airport, and you went outside to the luggage place and it was a big shed with no walls, and there was certainly no traffic until much more recently around here. One of the things that attracted us to Duke was that it was a major university where we could do something as technologically demanding as protein crystallography but where we could live out in the woods. And Duke was—has always been a really respectable high-quality university, but not quite as high-pressured as Harvard or MIT. I don't know that I can really say that anymore. Everybody seems to be high pressure these days. (*laughs*)

ROSEBERRY: So Dr. Hill was chair at that time?

RICHARDSON: Yeah. We came just right at the time when he took over from Phil Handler. So when we came down, I guess to interview, we got introduced to Phil Handler when he was on his way off to head up the Academy [National Academy of Sciences].

ROSEBERRY: Can you tell me a little bit about Dr. Hill?

RICHARDSON: Well, he's certainly been a major influence on the department all along, and he and Charlie Tanford were the two people who came and found us and persuaded us to come, and who really wanted to get structure here. And so we interacted with both of them very strongly. Bob Hill was the one who was doing, well protein chemistry—not that a lot of other people weren't, but studying enzymes and also doing—even sequences were difficult in those days and a real effort. And Charlie Tanford was doing the biophysics and theoretical understanding of protein folding and later membranes, and we interacted very strongly with him.

ROSEBERRY: Were there other women in the department?

RICHARDSON: Almost all of us were sort of around the edges one way or the other. I mean, Molly Bernheim was definitely around, but I'm not sure actually whether she was officially in the Biochemistry department or not. But there weren't very many women. It was really very noticeable a few decades ago when the women's room was sometimes crowded; it never used to be. (*laughs*) And there were a few students back in those days but quite small numbers of women, and of course now for quite a while it's been half and half or even sometimes more women. And now for quite a while we've had a lot of women faculty. And these days most of the women come up through more normal

channels, whereas when I was first getting started, an awfully large percentage of the women had some sort of oddball career track—not necessarily the same as mine, but very often there was something unusual about it.

ROSEBERRY: Do you think that's out of necessity or—?

RICHARDSON: Yeah, pretty much.

ROSEBERRY: There weren't the normal avenues available to women?

RICHARDSON: It was much harder obviously. But it wasn't necessarily a bad thing: if you managed to get a route like that that worked, then it was very nice. As I say, I really treasured my time when I could pretty much do science without having to do administration and not being quite as obvious and having a lot more choice. But that was because I managed to get this nice arrangement where Dave was the one who took care of the lab. (*laughs*)

ROSEBERRY: So we had talked before that you didn't get a PhD. Did that ever become an issue here or—?

RICHARDSON: Well, I was certainly a real embarrassment to the university for a long time, once I became at all well known. There was a stage where Dave was really trying to persuade me to get a PhD in something, and I was very seriously considering getting one in alpine ecology for a while. There was some really neat work being done here that would be fun. And once you have a PhD, certainly no one cares what it's in. And so that wouldn't have mattered. But I would have had to take off at least one whole year and probably more than that in order to do it, and so it never seemed quite the time to do it. And then also at that same stage, Dave had me do a bunch of publications by myself, which in one sense was unfair to him, but it made me much more obvious. And by the

time of the *Advances* article even, he decided I was well enough known that he didn't really have to worry about it. So I never did.

ROSEBERRY: And you're a James B. Duke professor, so obviously—

RICHARDSON: Yeah, you know—the thing that I thought was really the turning point was getting the MacArthur fellowship. And I think that's what got me into the National Academy, that and the drawings. Because lots of people had seen my little byline (*laughs*). But it was after I got into the National Academy of Sciences that Duke decided to give me tenure. It still took a while, because I obviously was not really quite respectable.

ROSEBERRY: So tell me about that McArthur—you mentioned that.

RICHARDSON: Well, in 1985, I had this mind-boggling surprise of getting called up and told I had won the McArthur, which is just amazing. And I think one of the best parts of it—I guess there were two really great parts of it. One was going to the reunions and meeting all these fascinating people, and then the other one was that if somebody in the university was saying, "Well, shouldn't you have more than one grant or shouldn't you run a bigger lab or work on something more medically relevant"" or something at that level. I could get away with it, saying, "Well, maybe not." (*laughs*)

ROSEBERRY: Is there anything specific that you were working on for that award?

RICHARDSON: Well, it was presumably mainly because of the drawings. The design work and the graphics were later. I guess at that point we were starting to do the design work, but that wasn't the main thing that people knew about yet. I think they very much—I mean, for that it was a real advantage not having a degree. They're looking for people who do something unusual or from an unusual background.

ROSEBERRY: You had kind of mentioned that this circuitous route was useful to you. Do you feel like overall it's been—?

RICHARDSON: Well, for instance, I think my philosophy background is actually useful, mainly in questioning absolutely everything. (*laughs*) And also it's useful to have had a different background than other people. That's sort of hard to keep that up after all these years and make it sound convincing but I try (*laugh*s) to go at things from a different angle than typical.

ROSEBERRY: Do you think that that's something that's looked well upon—that people might have a different way,of going at them at a different route

RICHARDSON: Well, it's sort of like interdisciplinary studies—everybody says they want that, but in fact, it's hard to do because you don't really get full credit in either side. And so I think people like the idea but they don't always like it in practice. (*laughs*) But one of the things that really is nice in science is that although it's certainly not perfect, if you come up with something new that really is useful and interesting and people are convinced by it, at that point it doesn't matter very much how you did it, or who you are.

ROSEBERRY: So are these drawings to you—is that something that is kind of your—you would consider to be a legacy of yours, or is there something else that you feel more—?

RICHARDSON: Oh, yes. I mean, I think there are other things that are equally important, but that one I think of as a major thing. As I was telling you earlier, there is this odd feeling that everybody in the field looks at molecules through my eyes, which is a very neat thing, but it's also kind of scary. (*laughs*) If I didn't do it quite right, they're all stuck with my misconceptions. (*laughs*)

ROSEBERRY: So were there other women? You mentioned Dr. Bernheim. Were there other women kind of in the medical center, maybe, that you can think of early on that—?

RICHARDSON: Well, I suppose one of—I don't know whether it's a virtue or a failing, but I never pay much attention to who anybody is, and so I don't necessarily think of them as a student or a department chair or men or women or whatever. And so I'm not sure that I really can even remember who was an influence and who wasn't. So I'm not sure I'm the right person to ask. You might try Irwin Fridovich, who is very good at that sort of history and—. (*laughs*)

ROSEBERRY: Is there anything that you remember about Mary Bernheim, that—?

RICHARDSON: Well, she was definitely a real presence at that point, but I didn't really know her well and didn't interact with her all that closely.

ROSEBERRY: Did she have a pretty strong scientific reputation?

RICHARDSON: That's my impression. And I didn't know her well enough to know what this was like for her or—certainly everybody knew Molly, and she was part of the community at Duke.

ROSEBERRY: So is there a sense—you kind of talked about that feeling of—the nice feeling of being invisible. Is there a sense of that women were treated any differently in science?

RICHARDSON: Um, well, not necessarily any more so than somewhere else. But it definitely in those days was much harder to be a professional in almost anything. Now I think people pay too much attention to me as opposed to Dave, and he's the one who's more invisible than he should be. I think one of the real problems now is that people insist that everyone has to be completely independent, whereas I think a lot of our

strength is that we complement each other and have worked so closely together. And people ought to be willing to say, Well, okay if the combination of the two of you do more than enough for two people, that ought to be okay. But people seem to have this feeling that they have to sort out for each thing, that one person was responsible for it, which usually isn't true. (*laughs*)

ROSEBERRY: It's a lot of collaboration.

RICHARDSON: Well, it's hard to do the collaborations nowadays. If you try to do that, you won't get credit for it, and you may not get tenure. Really couples these days are forced to develop independently, or at least give the impression of doing it. That seems a shame.

ROSEBERRY: So have you two had to kind of do that—?

RICHARDSON: No, we've gotten away with it because we were in it forever, (*laughs*) or at least mostly get away with it.

ROSEBERRY: So you're able to keep up that collaboration?

RICHARDSON: Yeah.

ROSEBERRY: Well, it sounds like at some point there was a relaxation of that rule—

RICHARDSON: Yeah, of the nepotism rule? Yeah. And so now for quite a long time I've been officially in biochemistry.

ROSEBERRY: So when did that—?

RICHARDSON: The story is that there were two people in the same department who wanted to get married and the administration decided it was not a good idea to force them to live in sin. (*laughs*) I don't know whether that's really true, but it's a good story. (*laughs*)

ROSEBERRY: So they changed the rule.

RICHARDSON: Yes.

ROSEBERRY: Okay.

RICHARDSON: It's probably not quite that simple.

ROSEBERRY: But it makes a good story.

RICHARDSON: It may have been one of their considerations. (*laughter*)

ROSEBERRY: Well, it seems like there are quite a few—

RICHARDSON: So I suppose you could say whoever that woman was, she had a real influence.

ROSEBERRY: She changed the rule.

RICHARDSON: Yes. (*laughter*)

ROSEBERRY: Well, it seems like there are quite a few pairs at Duke, and I don't know if that's true in science in general, but it does seem that there's—

RICHARDSON: Oh, yeah. And some of them very illustrious.

ROSEBERRY: Do you know if that is a common theme in the scientific world or in—?

RICHARDSON: Well, I know an awful lot of pairs of crystallographers.

ROSEBERRY: That's interesting.

RICHARDSON: I guess the—maybe the best-known one is Jerry and Isabella Karle. But there are quite a few.

ROSEBERRY: Is there something about the field that might—?

RICHARDSON: I have no idea, and I'm not at all sure that this is actually statistically significant; it's just my impression. I'm sort of primed to look for them, after all. (*laughter*)

ROSEBERRY: Well, is there anything—I mean, obviously your work has changed quite a bit and the field has changed, but is there anything that we've missed talking about, about those changes, about—?

RICHARDSON: Oh, probably lots and lots of things, but—certainly all of the things connected with computers and maybe even more so with connectivity, with being able to talk to anybody all over the world and work with them very easily to get at all the databases instantly even sitting at your laptop, not to be tied to mainframe computers when you were computing things. These days, we can do real research and have been able to for a long time on our laptops, really take advantage of that. And some of the new kinds of data that are available now are very empowering. But sort of in the other direction, as I say, there's much too much short-term pressure and insistence that everything should have value in the short-term, and overall that's not a very good idea because most of the big ideas come from long-term things. They tend, fortunately, to happen even when they're not encouraged, but I think science would be a lot more efficient if we were given a little time to think of about what we were doing.

ROSEBERRY: So do you think there's aspects of creativity that are important in science?

RICHARDSON: Oh, definitely, for sure. And this kind of atmosphere does make them harder. The raw materials for doing new things are better, but the sort of social conditions for doing them are much harder.

ROSEBERRY: Why do you think that pressure is there?

RICHARDSON: Well, some of it is a direct bad result of the good connectivity. You know, everybody in the world is competing with everybody else in the world and talking

to them every two minutes and everything is expected to be done instantly, since sometimes you can. And there are too many of us.

ROSEBERRY: So you were able to kind of nurture that creativity by—?

RICHARDSON: Yeah, by having a little space and peace and quiet occasionally. (*laughs*)

ROSEBERRY: Well, are there other women here at Duke that—who might be still working or in the past who might be worth mentioning for historical purposes that I should look at?

RICHARDSON: (*laughs*) Well, I'm not sure whether you specifically mean people who were here for a long time. Certainly developing more real, I guess, official full-time faculty in this department and others as women has been important. It's nice having Lorena across the hall, watching her structures and interacting with her students. And I'm glad to have Nancy Andrews here as a dean—that looks as though it's going to be interesting. All kinds of women lots of places now doing good things.

ROSEBERRY: Well, are there any questions that I have not asked you today that I should have asked?

RICHARDSON: (*laugh*) Well, not anything really obvious that I can think about. I've done an awful lot of talking, so probably more than you wanted.

ROSEBERRY: Oh, it's been a pleasure. Well, thank you very much.

RICHARDSON: Sure.

ROSEBERRY: I appreciate it.

(*end of interview*)