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| **Podcast** | “If you imagine each researcher as a kind of a neuron in the communal brain, then people call me a connection machine.” David Baker is a true believer in collaboration. He sees mentoring as one of the most essential parts of his job. Baker spends most of his time at his laboratory and his colleagues explain his role as a connection machine as he connects “people who are working on things that are related”. He believes that progress in science is made by working together and sharing ideas.  Despite being in high demand since receiving his Nobel Prize, Baker has turned down all work trips to focus on being present in his laboratory and exploring new frontiers in science. The only work trip he has made since the prize announcement in October 2024 is the journey to Stockholm to receive his Nobel Prize. And for that, he brought 200 former students to Sweden celebrate the award with him.  This conversation was published on 29 May, 2025. Podcast host Adam Smith is joined by Karin Svensson.  Below you find a transcript of the podcast interview. The transcript was created using speech recognition software. While it has been reviewed by human transcribers, it may contain errors.  David Baker: It’s nice to have a relaxed conversation like this because normally I might have 10 half an hour meetings with students a day, then it will be a research presentation and then I often just have sort of ideas or someone has an idea about something we should brainstorm.  Adam Smith: It really was an enormous pleasure to pin David Baker down for, as he says, this relaxed conversation. Because even amongst that most focused group of people, the Nobel Prize laureates, he is particularly focused. But the interesting thing is that he’s anything but that vision that we have of the kind of elusive genius, the lone scientist, as he implied it in what he just said. He is a great collector and connector of people. His lab featuring people from all over the world is a hive of activity and absolutely enormous. That collaborative enterprise that forms the core of his science comes up really strongly in this conversation. Enjoy with me this rare timeout in David Baker’s life.  Karin Svensson: This is Nobel Prize Conversations, and our guest is David Baker, recipient of the 2024 Nobel Prize in Chemistry. He was awarded for computational protein design. He shared the prize with [John Jumper](https://www.nobelprize.org/prizes/chemistry/2024/jumper/facts/) and [Demis Hassabis](https://www.nobelprize.org/prizes/chemistry/2024/hassabis/facts/). Your host is Adam Smith, Chief Scientific Officer at Nobel Prize Outreach. This podcast was produced in cooperation with Fundación Ramon Areces. David Baker is the Henrietta and Aubrey Davis endowed professor in biochemistry at the University of Washington. He speaks to Adam about bringing 200 people to the party in Stockholm, what he’s learned from his broken ski poles and trailblazing in the field of protein design. But first Adam wants to know what it is about David Baker that enables him to ask audacious questions.  Smith: I wanted to start by just asking you what it is about you that enables you to ask such big questions?  Baker: I have always been interested in exploring new things and discovering new things, and I guess I tend to get bored pretty easily. I really like being on the frontier and protein design has been and continues to be extremely exciting because of all the really amazing new opportunities that are opening up.  Smith: But I would say that yes, certainly you’re on the frontiers, but you are almost ahead of the frontier throughout your career. You’ve been so far ahead of the game and that requires a special sort of confidence, some kind of special intellectual bravery I would’ve said, but maybe it doesn’t strike you like that.  Baker: I think one thing that is very important is I’m convinced that groups of people working together and collaborating closely, if they’re all really good and really motivated, can do amazing things and have the kind of confidence in solving new problems that comes about. I’ve worked really hard to develop what I call a communal brain in my lab and at the Institute for Protein Design, where we have really brilliant people coming from all over the world, working closely together. If you came here to walk through, you would just see people talking to each other all the time and brainstorming new ideas. That I think really gives the brain power and the confidence and the ability to continually break new ground and explore completely new areas.  Smith: What’s the secret to getting people to collaborate in that lovely way?  Baker: There are a couple things. One is when new people want to join the group, whether graduate students or others, we’re trying to look for people who would really thrive in this kind of environment and share ideas, discuss and brainstorm. Within the context of the group, we have lots of free food. There’s different food events, food and drink events every day. We have research talks several times a week. I really try and make an emphasis on everybody knowing what everyone is doing, even though it’s a fairly large research group. I basically don’t travel. I’m here all the time, so I spend all my time meeting with people one-on-one in a small group. I try to know what everyone’s doing and I connect people who are working on things that are related or where they might benefit from each other. There’s just really high density communication. If you imagine each researcher as a kind of a neuron in the communal brain, then people call me a connection machine or there’s just a lot of social engineering to make sure people are talking all the time.  Smith: Sounds great. That’s a rare self-discipline you have not traveling. It’s so easy to get caught in that mill of being elsewhere all the time.  Baker: Yes. I think I probably have set a record for Nobel Prize winners. I’ve been on exactly one trip outside of Seattle for work since the announcement in October, and that was to Stockholm.  Smith: I’m sure that is a record that’s extraordinary. How do you say no to everybody?  Baker: I think it comes back to what you said earlier. I do feel like we’re exploring uncharted territory and the unknown and the place where I’ll be able to learn the most about that exploration and achieve most is just right here. It’s going to other places in the world is not going to really help in charting the unknown because I think to some extent we are ahead and that’s really what I’m passionate about. Mentoring is a really important part of my job because the scientific advances are one thing, but really I think the bigger impact is on all the amazing scientists who are coming here to get trained and then going off and doing wonderful things. In Stockholm it was just incredible. There were almost 200 former students in postdocs, I think about 60 of whom now have faculty positions all over the world who came interacting with that group. It was very clear to me that the impact I’m having is really in the people being trained then in the particular scientific advances. If I go away for a few days, then I’m missing. I might have 10 one-on-one meetings with students and then a bunch of informal discussions a day. So I’m really missing out a lot on both exploring the new frontier and mentoring.  Smith: Yes, it must be miserable if you’re sick for a few days. That number of your former and present students who came to Stockholm to help you celebrate, that must be another record, I would’ve thought.  Baker: I think so. I think that the Nobel Foundation didn’t want to state any numbers, but they were quite surprised how many people there were.  Smith: Yes. It must have been amazing. Quite a party I can imagine.  Baker: It was! There were a couple things. One of them was in the same time the banquet was going on, there was a party in the Grand Hotel, the room in which the Nobel Prize ceremony used to be. Then after the banquet was over, we all went there and it was just great. We also had a really nice dinner the night before in a beautiful museum in Stockholm. It was very special.  Smith: That really is the kind of the actualisation of the idea that it’s a team celebration. Lovely.  Baker: Yes. I really feel that the prize was for the group, the work of a really wonderful group of people, and the prize is really as much everybody’s as mine. It was really great to be able to celebrate with so many people.  Smith: This ability to refuse trips away and to stay in the lab, we often talk about the extraordinary focus that great scientists Nobel Prize laureates have, where they can stick with a problem for 10 years and don’t get diverted from it. They carry on doing it 10 or 20 years. This is another sort of focus, the ability not to get distracted is something very particular. I’m gathering that you perhaps don’t do too much self-analysis, but it’d be interesting to know how you became so focused. Were you always like that as a child? Were you very good at concentrating?  Baker: I think it’s now more than ever. I think that protein design is getting a lot of press these days, so people are hearing about it. I do give a lot of zoom talk, so several times a week I’ll be in a different country before I come to work, giving a talk. I am communicating what we’re doing, which is an important part of being a scientist. I just don’t spend time in on airplanes, hotels and all the other things that go with traveling. I think to some extent it does tie back to other things you mentioned. In my case, it’s not so much that I’m focused on a particular discovery, but I am very focused on exploring the new frontiers opened up by protein design. I just think that the best way to do that is to be here all the time.  Smith: Collaboration, open science sharing, obviously all very important to you. Where did you learn that? Because a lot of young scientists find it difficult to navigate the boundaries between what they should tell people, what they should share. When you were starting out, was it obvious to you that sharing was the best answer?  Baker: I think I’ve always been that way, and we had to formalise it at the time when the first scientists were leaving my research group back near the beginning when we had developed the Rosetta protein design and structure prediction software, and we had to decide what to do. We decided at that time, this was around the year 2000, that we would set it up so that everybody who left my group would continue to develop the software. We were licensing it to companies, and none of that money would go back to anyone’s pocket or to any particular institution. Instead, it would go into a nonprofit consortium we called the Rosetta Commons. That money would be used to support the broader development. That worked out really wonderfully. We’ve had amazing meetings ever since then, and the number of developers news. I think there’s over 120 different research groups involved now. I think in science, you have so much more impact if you share what you do, invite other people in and encourage people who are experts in the area to join or stay in. In the case of people leaving my group, I think it’s just very obvious to me that that’s the right thing to do. Also, in terms of the impact it’s had, with a communal brain, one that’s spread over many research groups, it becomes even more powerful.  Svensson: So Adam, this all sounds a little bit like science fiction to me. How would you explain what protein design is?  Smith: I think, until recently, it was science fiction. Protein design is building new proteins from scratch. It’s envisaging a protein structure you want to make, and then working out what sequence of amino acids you need to put together in order to make that structure.  Svensson: That sounds amazing because I always think of proteins and amino acids as something that’s in nature, not something you can make.  Smith: Exactly. Until very recently, that was the case. Nature’s been doing this for a long time. It was only in 1972 that Christian Anfinsen was given the Nobel Prize in Chemistry for working out that the structure of a protein is entirely dictated by the sequence of amino acids that form that protein. Now it seems obvious to us that that’s the case that proteins work in the way that individual proteins work because of the shape they are. But that wasn’t known until then. The next problem was working out how that happens. How does this chain of amino acids give a particular shape?  Svensson: Have we managed to find that out?  Smith: Yes and no. The answer is yes, broadly a big part of the 2024 Nobel Prize in Chemistry was awarded for the fact that we have worked it out, but it’s us in collaboration with machine learning that’s worked it out. For a long time it was thought that really we would be able to understand how proteins fold, because we’d understand the rules that govern the way that amino acids interact with each other to make a particular shape. That’s not quite how it turned out. In fact, those rules are still opaque, but it was pattern recognition that solved the problem, that by feeding millions and millions of structures into machine learning algorithms, they were able to see the patterns and predict how this particular sequence of amino acids would fold up to form this shape.  Svensson: So yet another example of us being outsmarted by machines then.  Smith: I suppose. As I say, people thought they might be able to understand this and they haven’t been able to, and the machines haven’t also understood it. They can just see the pattern. I think it’s probably nicer to say that it’s us working together with the machines that it was all those wonderful scientists who got those structures in the first place and filled up the protein data bank with millions of structures, fed those into the machines, and the machines have been able to see the patterns. It’s a nice example of humans and machines working together to solve a problem that has been around for a long time.  Svensson: Peaceful coexistence.  Smith: Yes. Actually that’s an important point. There’s all this talk of the worries of AI even in this podcast series, but in this case, this is working nicely.  Svensson: How does David Baker fit into this then? What was his contribution in the field that earned him earn a Nobel Prize?  Smith: He became interested in this protein folding problem very early, but he also saw it in the reverse direction. He understood that if you designed brand new proteins that nature had not made, you could perhaps work out how to make them by knowing what amino acid sequences would go into making up that shape. He was an early adopter of this idea that you could potentially make the proteins you wanted to make that nature had forgotten about, if you like. He developed algorithms to begin to predict structure from amino acid sequences. By a lovely combination of working with the algorithms and doing the biochemistry to test his ideas, he was able to move ahead very fast in this field of designing proteins. So he was awarded the Nobel Prize for his pioneering work in that field and building all sorts of amazing new proteins that the world had never seen before.  Svensson: The way you talk about this science, it feels like this big world opening up of new avenues to explore in terms of constructing these proteins. What are those frontiers that he’s been discovering?  Smith: That’s absolutely the point that the frontiers are so broad because proteins do so many different jobs. They’re responsible for pretty much everything that goes on inside us, and they’re also doing lots of jobs out there in nature. Anything that a protein can do can potentially, I suppose, be improved on or modified by building a new protein. There’s just no end to the possibilities, whether it’s for medical use in the body or for use out there in the environment, building new proteins to help us get rid of nasty substances or going into the new realms of nanotechnology or nano machines and thinking about how proteins and small molecules can interact. This must be why you hear in David Baker’s voice this absolute excitement and captivation with this field because it just opens up your word frontiers. What could be more exciting than that? Let’s hear David Baker himself talk about some of the possibilities that he is most excited about.  Baker: There are many. I think there are some problems that I think we’ve pretty much already solved. The problem of designing proteins with new structures or new types of viral, like capsids for delivery, the design of proteins to bind to other proteins. This was a completely unsolved problem only a few years ago. Now we can do it quite robustly given a therapeutic protein target. We design a binder to it. We’ve also very recently made progress on designing catalysts proteins that can, for example, break chemical bonds or make chemical bonds. Some of the most exciting challenges ahead involve combinations of those modalities. For example, design a proteins that will not only bind to a target, but modify it, for example, destroy it for a more catalytic therapeutic. The design of machines in nature there are many different types of machines that, for example, power movement in our muscle. Now, we should be able to just combine catalysis and binding to make a whole variety of new nano machines that are intended for use, both in the body first (perhaps do quality control and circulation to help with things like chronic disease and aging) as well as for nanotechnology, finally fulfilling the vision of nano machines that can do things. Then I’m very fascinated by things that occur in nature like biomineralisation, like tooth and bone and shells, that’s proteins interacting with inorganic compounds. Now we’re trying to design proteins to template mineralisation not only of the minerals that nature’s use, but other more exotic compounds like semiconductors such as zinc oxide. I think there’s a whole new range of materials to be made there, and that’s just a small subset of the things that we’re working on now. I actually think the next five or 10 years are gonna be the most exciting of my career now that the basic protein design infrastructure works. There are so many really exciting areas that truly do sound like science fiction, but I think will become reality in the near future.  Smith: Yeah, it’s a bewilderingly large array of possibilities that your mind must be swimming in all directions all the time.  Baker: It’s really inspired by nature and evolution. If you look throughout life, there’s just so many different problems that nature has solved, and those solutions have all come about through random mutation and selection. There’s been no guiding intent. It’s just all kind of happened to happen. Yet we have all the amazing things in nature. Now if you think, well, we can actually design anything we want, the possibilities go far beyond what we have in nature, but the breadth of nature already provides inspiration for so many different things. Like, say, improve photosynthetic systems that can use solar energy much more efficiently or to a much wider range of things.  Smith: Is the technology moving so fast that there is a need for some kind of care regulation? Is it a bit like the biotech revolution where the biotech community itself held the SIMB conferences and thought we need to just keep a check on ourselves?  Baker: Right. We had a workshop last year at the IPD with government and nonprofit think tanks and all the scientists working on protein design to discuss this. What we concluded is that new methods should be kind of vetted by a committee to evaluate them, but the point of regulation should be at the level of DNA synthesis. Whenever you have a design protein, you can design something on the computer, but it doesn’t become reality until you create a synthetic piece of DNAA synthetic gene to encode it. We all collectively felt that that was the correct place to try and track and we decided probably the best way to do this would be to log all new DNA synthesis. If there is a problem later on, it can be tracked. I think overall, the other feeling is that nature has already kind of perfected ways of causing death and destruction on a really large scale, like the 1918 Spanish flu, for example. Nature already has made plenty of bad things, and the protein design has the potential to very rapidly respond to new threats, new pandemics, and perhaps even new biological manmade things. The conclusion was that the power of protein design to make the world better place far outweighed the downside, particularly since nature’s already mastered the downside, but that it would be prudent to log DNA synthesis. If there are problems, they can be traced.  Smith: Sounds very sensible and nicely put, but it isn’t always the case that the society necessarily views things the same way as the scientific community. Do you think that there is a potential of people to think there’s too much dabbling with nature as, for instance, they do when it comes to GMO foods in many cases. Is there a job to be done talking to society about what is happening and this extraordinarily rapid progress?  Baker: That’s a good point. I thought about writing a book from time to time, but that again is a little bit of a distraction from what I’m really want to do. That’s part of the reason to communicate the work and the excitement. I think there is a particular feeling about food, but in terms of medicines, people are quite accustomed to the idea that medicines will be new compounds. Almost all medicines, whether they’re small molecules or protein therapeutics are new in some way. I think there’s less objection there. I think people care naturally about efficacy and safety outside of medicine. If we’re working on enzymes to grade plastic, for example, I don’t think anyone will complain about such an enzyme being unleashed in the huge plastic piles in the ocean. I think once we have really good design protein solutions for current problems, I don’t anticipate there’ll be huge objection to deploying them.  Smith: I do want to explore you a bit, if you don’t mind, where you came from, so to speak. Your parents were physicists and you obviously didn’t go down that track, but you were a very bright student. What did you think you were gonna be when you were growing up?  Baker: I really didn’t know. When I started college, my major was initially social studies, and then I thought I would become a philosophy major. But I had sort of been interested in science actually in college. I had all these friends who knew exactly what they were going to do, and I had no idea what I was going to do. I think I took pretty much every intro class there was, which was not a good way to use the time. Then my last year I took a developmental biology class, and what came across there was how fast discoveries were being made and really the excitement and that kind of inspired me to apply to graduate school despite never having done research in a lab. Then I took a year off and kind of traveled around the world working on and off, and then started grad school the next year. I thought I wanted to work on developmental biology or how the brain works, but then I discovered that involved cutting up animals, which I didn’t really want to do, and also seemed very slow. So I got excited about working on how biological self-organisation comes about on the cellular scale. I did my PhD work with [Randy Schekman](https://www.nobelprize.org/prizes/medicine/2013/schekman/facts/), sort of understanding how cells get organised. I found during that time that I really enjoyed doing research and I enjoyed working with other people.  Smith: Just before you go on, I was with Randy in the autumn and he told a lovely story about you. He said that one time you wanted to tell him your results and you beckoned him over to your lab bench and you said, ‘Sit down there, I’m going to tell you about my results, and I’m going to explain it in a way that’s simple enough that even you can understand’.  Baker: Yes, that sounds like something I would’ve said. If graduate students said that to me today, I would be delighted. Things like that do happen. It all comes around. Randy did show me how to build a research group which was incredibly collaborative and sort of directed towards a common goal. I thought after that I would sort of ultimately come back to that area but I wanted to learn some structural biology first. Then I went to David Agars lab as a postdoc, and he was working on so many different exciting problems. As I started working on protein folding, it was really clear all the different ways it could go and all the different ways you could approach it from computer science to chemistry to biology. Then when I came to the UW, I started really completely changed from what I had been doing in Randy’s lab, but I had seen a lot of different kind of research environments. I also had a pretty broad background. I knew enough biology, so that once we started designing proteins, I started with that idea of what kind of applications might be interesting. I think even the social studies and philosophy background in college for a long time I thought that was totally useless, but a lot of what I do, you have to think about pretty general ideas and write. Clear writing is really important and I had to write so many papers on rather esoteric topics back then that’s been a very useful skill to have.  Smith: I can see how it plays in very much also in the sort of real world application of your work because you are working in a very basic science discipline, and yet you’re thinking about how to apply these to real world problems.  Baker: Yes.  Smith: Another example of you staying put is that you never left University of Washington. It was obviously the place that suited you. You went back home to Seattle and that was where you wanted to be.  Baker: Let’s see, I grew up in Seattle. I left when I was 17 to go to college. I was on the east coast for that. Then I went to California for graduate school and postdoc. Then I came back here when I was about 30. I came back to Seattle. My wife and I both had jobs here. I love the mountains. I had a wonderful day skiing and very deep powder last yesterday. I like backcountry skiing, hiking and climbing so the mountains are great. At the time we came here, we had small kids, so it was great that my parents were here and other relatives. I’ve never been very interested in leaving.  Smith: It sounds to me like you sort of know who you are. It may be a silly thing to say, but I think a lot of people spend time trying to find out where they want to be or whether they want to go down the path of being directors of institutes or whether they want to be bench scientists and all of that sort of thing. It seems to have come fairly naturally to you.  Baker: I think I am probably a little bit unusual for Nobel Prize laureates, in terms of having had no idea what I wanted to do when I was in college. At age 20, I had no clue. I think people who are friends of mine from college reading about this were probably totally surprised because I was a social studies major. I did take one chemistry class and it was by far my worst class. It’s kind of ironic in a way. I guess my advice to people is actually not worry too much about the future – just try and do what you find most exciting and interesting in any given time and that things can work out. Because it really wasn’t until I came here, I was well into my thirties before we started working on protein design. I had kind of explored a lot of different things, a lot of different areas and a lot of different aspects of biology. You can’t predict the future.  Smith: I remember watching a conversation once between a young scientist and a Nobel Prize laureate. The young scientist kept on asking questions about their career and kept coming back to that word career. After a while, the laureate sort of scratched his head and repeated the word career as if it was a word that was new to him that he hadn’t really heard before. He said, ‘yes, I never really thought much about a career, you just did the next experiment’.  Baker: Yes, I completely agree with that. A career assumes that they’re sort of like these finite different pre-ordained paths and I don’t think that’s how life works at all. Certainly for me, nothing I did was very orthodox along the way.  Smith: In the banquet speeches at the Nobel banquet on 10 December, just before your banquet speech, [Geoffrey Hinton](https://www.nobelprize.org/prizes/physics/2024/hinton/facts/) gave a speech and he said he used basically those two minutes to warn the world of the dangers of AI. Then you gave a very hopeful speech, not specifically on AI of course, but talking about the potential of protein design and understanding protein folding and combining techniques to solve problems in the world. How do you view the dangers potential of AI generally?  Baker: AI is clearly a very powerful technique and the problems that are being solved, protein structure and protein design, obviously far others is really impressive. The language models with these incredible answers to complex queries. I view AI though as just the latest in millennia worth of advances that humanity has made. New tools, techniques and things come about ranging from fire a very long time ago, which was very useful, for example, through nuclear power and nuclear weapons. I mean nuclear weapons, the destructive capabilities are obviously far outweigh those of anything else that have been developed. All these things have upsides and downsides. With AI, I think the biggest dangers probably are systemic misinformation and hacking. I think AI powered weapons, both at sort of physical weapons and just sort of sabotage of infrastructure are all very dangerous. But the upsides of AI are also very clear. It’s just the latest of many advances made by humans. I am not one of the people who’s worried about the existential threat that AI is gonna become smarter than us and control us. I think AI is just a tool that humans will use. I’m much more worried about bad humans getting a hold of very powerful AI tools and doing bad things, and the same way that one worries about bad actors having access to nuclear weapons, but the extensional threat I am less concerned about.  Smith: I suppose you’re somebody who makes use of tools as they come available.  Baker: Yes, and I think that’s what humanity has done generally. New things come about and they seem really revolutionary, and then people take them in stride and you consult chatGPT on your phone every time there’s something that you don’t remember. When I can get chatbot to take care of all my email and all the other stuff I don’t really want to do, then I’ll be happy. I think there’s a lot of potential for freeing people up to do more interesting things.  Smith: Yes. I suppose you could be characterised as the ultimate early adopter, I’d say.  Baker: Yes, that’s right. That’s true.  Smith: I also wanted to come back to this point you made about the diversity of people in your institute and how people come from all around the world. It is so important that there is free movement and free exchange of peoples, isn’t it?  Baker: Absolutely. There’s so many different places in the world that people come from and so many different viewpoints, although it’s currently not a popular topic. The people who run the US government, they’re clearly wrong historically. I think having a diverse research group just makes it more vibrant and fun. I think there’s more problems you can solve since you’re more aware of more different things going out in the world.  Smith: Your institute is the embodiment of an open country. Do you get involved at all in politics and talking about the need to maintain that?  Baker: Right. I think the particular issue I remember when Randy Schekman got the Nobel Prize, I asked him what his issue would be and he asked me what I meant. I said, well, now you have some increased stature, it’s your sort of obligation to try and use this to do good. For me it’s very clearly immigration. I have talked a lot with government leaders about immigration and I’m certainly trying to emphasise the importance of open immigration policy wherever I can. I brought it up in my Nobel speech for example, and I’m trying to help people who are running into immigration issues. I think that’s really important. Having barriers that prevent people from being able to do what they want to are just, it’s just really bad. It hurts everybody. It hurts the person, it hurts the United States most of all. Almost everything that’s ever happened in the US that’s been great has come from an immigrant or a descendant of an immigrant, and it’s just not good for the world either.  Smith: You strike me as somebody who’s very optimistic though, and I imagine that in the current climate you’re not feeling just ultimately depressed by it, but just feeling that things will change.  Baker: I think for a lot of these issues, there’s a sort of a continuum, so if you look at US policy on immigration, say the Trump direction is going to considerably less open, more restrictive, but still on the scheme of things the US is a relatively open country compared to many others. I imagine that there’s going to be the swinging back and forth as really the US public’s general opinion changes and new leaders come about who can make compelling cases for the other side. I think we’re seeing slipping in one direction. I think we’re going to see a return, it’s going to be shifting back and forth.  Smith: I wanted to ask you about those gifts you gave to the the Nobel Prize Museum? A broken ski pole.  Baker: The first gift was a broken ski pole. As I said, I spend a lot of time backcountry skiing, in the middle of nowhere, considerably away from civilization, climbing, hiking and backpacking. I have broken many ski poles. When I first heard of that I needed to give a gift. That was what I came to. It sort of symbolises a couple things. One is overcoming adversity, because when you break a ski pole, you still have to get out and it’s not always easy. Then it also sort of symbolizes my love for the mountains. The second gift was a pair of the orange glasses you saw me wearing at the beginning. It also symbolizes overcoming adversity. I had an eye injury a couple years ago and I couldn’t look at computer screens and it was absolutely terrible until I discovered these orange glasses of mine. They completely solved the problem. There was an even upside, because I had a new persona and I got these wonderful pictures from colleagues of rooms of people all wearing these glasses.  Smith: Yes, I can attest to the fact that they certainly make you look cool.  Baker: Which is not something I’ve been generally very good at.  Smith: It’s nice to hear that you go skiing and you take Sundays off. How hard do you work?  Baker: I have quite a few graduate students in postdocs. I feel it’s my job to really know what everyone’s doing all the time and to be connecting people. Also there’s always new manuscripts being written up. During the week I am pretty much on, it’s nice to have a relaxed conversation like this because normally I might have 10 half an hour meetings with students a day. There might be a research presentation, then I often just have sort of ideas or someone has an idea about something we should brainstorm. There is a lot going on during the week. I find on the weekend having a day to just get out in nature. When you’re skiing, you’re just looking at snow and you’re trying to decide which direction you should go. You have to make decisions, but the number of bits coming into your brain is far fewer. I find that an important part of my job actually, to give my brain some chance to recover and recharge for the next week.  Smith: I’d like to think that this conversation is giving you a chance to recharge for the conversation you are about to go into no doubt immediately.  Baker: That’s true.  Smith: It’s tremendously exciting. Even just getting a glimpse into this dynamic world you’ve created. Your institute seems pretty unusual actually. Lots of people try and get this environment. I remember in a previous life I used to visit lots of pharma companies and everybody talked about doing exactly what you have done, which is getting a small space where people have sort of crammed in and need to be talking to each other and are just buzzing with ideas. But it’s very difficult to actually make. Do you feel your institute is something very special?  Baker: I think it is very special and I think there are a couple factors. One is we’re just at the historical moment in history where the protein design problem is being solved and this is kind of the grand central station for that. We just have this culture of bringing in brilliant people from all over. I think we’re constantly getting queries and new graduate students want to come in, new postdocs want to come in. I think there are 35 first year graduate students who are doing stints in the lab this year to see if they like it. We have post-doc candidates coming and visiting all the time. I think what makes it unique is probably just the incredible collection of people who are here. The huge opportunity to make the world a better place with protein design. We’ve been really fortunate to be able to attract philanthropic support, which is of course, important to keep this whole thing going. That is one of my jobs too, to try and continue that because that is really important. I think it’s just the right time in history for this problem. I think that’s recognised by the world and by people around the world. You need that to create this kind of environment and then you need to set up the culture where it really works.  Smith: Last question before I let you go back out into the concourse with all your brilliant people, you spin out a lot of companies and that’s also an important part of your work, do you see that as making the ideas work? Do you see it as getting money for the institute? What’s the rationale behind it?  Baker: Primarily what we’re doing here is we’re making sort of advances, but in sort of an academic setting. To really bring these things out in the world they have to leave the institute. As I said, we have all these brilliant, incredibly energetic people coming in, and many of them get so attached to the ideas that they’ve had and the proteins they’ve designed that they want to continue and bring them out in the world. Then they start a company to do this. That’s happening all the time. Literally as we speak, new people or people after they’ve been here for a couple years have made some new advance and then they want to start a company to really bring it out in the world. That’s why it becomes sort of the career of the person who came here to make a discovery and it’s really important to get things out in the world.  Smith: It’s truly an incubator. Let me release you back to those who need you. It was really lovely. Thank you very much indeed.  Svensson: You just heard Nobel Prize Conversations. If you’d like to learn more about David Baker, you can go to nobelprize.org where you’ll find a wealth of information about the prizes and the people behind the discoveries. Nobel Prize Conversations is a podcast series with Adam Smith, a co-production of Filt and Nobel Prize Outreach. The producer for this episode was me, Karin Svensson. The editorial team also includes Andrew Hart and Olivia Lundqvist. Music by Epidemic Sound. If you’d like to hear from another scientist who has pushed the boundaries of our human understanding, listen to our earlier episode with physics laureate [John Mather](https://www.nobelprize.org/prizes/physics/2006/mather/podcast/). You can find previous seasons and conversations on Acast or wherever you listen to podcasts. Thanks for listening. |
| **Telephone**  **interview** | [DB]  David Baker: Hello?  Adam Smith: Oh, hello. Is this David Baker?  DB: It is, yes. I’m still listening. I’m in the press conference.  AS: Oh, I do apologise. If you want to finish listening to the press conference, I can hang on,  DB: Let me just go through the rest of the press conference and then then we can talk. Would that be all right?  AS: Certainly. I’ll phone you back as soon as it’s finished.  DB: Hello?  AS: Hi, it’s Adam Smith again from the website of the Nobel Prize. Many congratulations.  DB: Thank you.  AS: Can you just tell me how the news reached you?  DB: Let’s see. Well, actually I think it’s kind of funny. I didn’t realise this till afterwards, but I think they had the phone number for my son who then gave them my phone number. And so I got a phone call, and my wife promptly started screaming, so I had a little hard time hearing, but then they got the news across  AS: I like that she twigged before you did.  DB: Yes.  AS: I mean, people always said there’d be a Nobel Prize for the people to solve the protein folding problem, and here it is. How does it feel?  DB: It is well, of course it’s a great honour and it is very exciting and it’s great to share this with [Demis](https://www.nobelprize.org/prizes/chemistry/2024/hassabis/facts/) and, really [John Jumper](https://www.nobelprize.org/prizes/chemistry/2024/jumper/facts/) in particular, who really solved the classic structure prediction problem. You know, for protein design, I always thought that if there was a Nobel Prize, I’d be sharing it with Steve Mayo and Bill DeGrado. So I’m a little sorry about that. But yes, I think it’s neat to have you know, there’s always been two sides to the protein folding problem going from sequence to structure and then back from structure to sequence. And I think it’s neat that that there’s a Nobel Prize for them together.  AS: Yes, united. What do you think is going be the most beneficial effect of protein design in the foreseeable future?  DB: I’m really optimistic about really a wide range of applications. So just thinking about the things that we’re working on now, in health and medicine, I think smarter therapeutics that are more precise, and act only in the right time and place in the body, could get around a lot of the problems of systemic drugs. We have the first really *de novo* design medicine that’s been approved for use in humans. That’s a vaccine designed by my colleague Neil King at the Institute for Protein Design. Then outside of medicine, I think we’re making great strides now in developing new catalysts, and that could be for things like breaking down pollutants and plastics and things in the environment to coming up with sort of greener chemistry, you know, better routes to new molecules. I think there’s a lot of sustainability applications, you know, once you start just thinking about all the different things proteins do in nature that, and they really just evolved over random chance over, you know, over millions of years of natural selection. Now with the ability to design new proteins, specifically to solve problems there’s just so many possibilities. It’s really exciting.  AS: It’s a whole new world, isn’t it? Gosh.  DB: It’s a whole new world. Yes, it really is.  AS: Yes. Just lastly, on the protein folding question, how does it feel being awarded with basically your competitors? Because you know, for a while, RoseTTAFold and AlphaFold were sort of, you know, competing with each other. How does it feel to be united in this prize?  DB: I’ve never really felt that DeepMind or John or Demis were competitors. I think it was very inspiring. We were developing physically based methods for protein structure prediction and protein design for many years, and we were making progress on protein design and being able to design, you know, more complicated protein functions. But it was continued progress. But then, when John developed AlphaFold2, it was really kind of a wake up call for me to the power of deep learning, so rather than competitors, I really would say they’ve been great inspirers about the power of deep learning. I think that a lot of the most exciting things that we’ve done in the recent years have come from the deep learning methods that we’ve developed who really you know, really inspired that machine learning to have so much power in this field from John and Demis’s work.  AS: It may be too big a question for now, but as you said, basically the protein folding question was going be solved by understanding, but in the end it got solved by not understanding the rules. Does it matter that the rules are not understood? But it works?  DB: That’s a big question. I think for the many, many uses that protein structure prediction has had, that knowing protein structures have, it doesn’t really matter so much how you get there. And humans are very comfortable with solving problems every day with a very, very complicated neural network that we really don’t understand at all; our brain. We’re quite comfortable with the solutions we come up with, and we don’t have a lot of anxiety about not understanding exactly how our brains work.  AS: All fascinating. Thank you. Just for now, it’s crazily early in the morning there, what happens next?  DB: I think while we’ve been on the phone, I think I’ve had to decline about a hundred phone calls and the messages keep cropping up. I think I’m gonna try and get some sleep. I don’t know if that’s possible. But yes, it’s going to be quite a day.  AS: It will, it would put you among a select group of laureates who’ve managed to do that. So good luck. I hope it works.  DB: Yes, I’m not very optimistic, so … [laughs] it’s very exciting.  AS: Okay. Once again, congratulations David.  DB: Nice talking to you.  AS: Thank you. Bye. Bye. |
| **Interview** |  |
| **Q** | What influence did your parents have on you? |
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| **Q2** | How did you become interested in biology? |
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| **Q5** | Did you have a plan for your career? |
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| **Q18** | Why do you find proteins interesting to work with? |
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| **Q2** | How important is it for scientists to address the world’s biggest challenges? |
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| **Q1** | How does it feel when your work has an impact? |
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| **Q2** | Why is collaboration in science important? |
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| **Q10** | How important is diversity and representation? |
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| **Q7** | For you, what makes a good lab? |
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| **Q17** | Why is it important for science to be open access? |
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| **Q8** | How important is building a community among colleagues? |
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| **Q2** | Do you enjoy mentoring? |
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| **Q2** | How do you maintain your work-life balance? |
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|  | How do you keep going when nobody believes in your ideas? |
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|  | What message do you have to others that think outside the box? |
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|  | How do you deal with failure? |
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|  | What advice do you have for young scientists? |
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|  | How has AI transformed your research field? |
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|  | How did you celebrate receiving the Nobel Prize? |
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| **Podcast** |  |
| **Telephone**  **interview** | [DH]  Demis Hassabis: Hello, Demis speaking.  Adam Smith: Hello, Demis. This is Adam Smith from the website of the Nobel Prize.  DH: Great, great to hear from you.  AS: Many, many congratulations.  DH: Thank you so much.  AS: You have had so many achievements and accolades, and you’re so young, but what does this prize mean to you?  DH: Well, it’s unbelievably special and, you know, it’s actually really surreal, to be honest. It hasn’t really sunk in, but it’s an incredible honour. You know, it’s the big one, really.  AS: What were your first thoughts on hearing that you’d been awarded the prize?  DH: I couldn’t really think at all, to be honest. My mind went blank. It was just so incredible. It’s just an unbelievable experience.  AS: I imagine a party’s about to break out at Google DeepMind.  DH: I guess so, yes. I haven’t really even thought about that, I suppose, but I had a whole day of normal work ahead of me, but I guess all those plans will have to change now.  AS: I’m afraid so. But, or rather, I’m pleased to say so. But, AlphaFold, AlphaFold2, now AlphaFold3, ushers in a whole new world in science. How do you see the relationship between these tools and the individual scientist?  DH: The reason I’ve worked on AI my whole life is that I’m passionate about science and finding out knowledge, and I’ve always thought if we could build AI in the right way, it could be the ultimate tool to help scientists, help us explore the universe around us. I hope AlphaFold is a first example of that.  AS: But in terms of how, where this leaves the individual, if you like, because the power is so extraordinary and just mind blowing. But there are still individual scientists asking individual questions. So what’s the interplay like?  DH: I think that, at least for the next foreseeable future, I feel like this allows individual scientists to do so much more. Because, these systems, they’re tools. They’re very good for analyzing data and finding patterns and structure in data. But, you know, they can’t, figure out what the right question is to ask, or the right hypothesis, or the right conjecture. All of that’s got to come from the human scientist. I think the best scientists paired with these kinds of tools will be able to do incredible things, perhaps even in smaller teams than they used to be able to, because, they can rely on the tools to do a lot of the legwork.  AS: Just tell me what it’s like, what the environment of Google DeepMind is like.  DH: We tried to design it from the very beginning as sort of the perfect environment really to do cutting edge research work, and bring together world experts in many different disciplines. Obviously, machine learning and AI of course, but also engineering, also physics, biology, and even things like philosophy. So kind of bring that all together and into an incredible melting pot, and provide them with the resources, compute resources and other things. Great things will come out of that. We’ve seen that in the past with places like Bell Labs, and I was inspired by the stories of the golden eras of those kinds of places. I wanted to try and create something like that myself.  AS: How beautiful recreating Bell Labs in Kings Cross. Lovely idea.  DH: Yes. Exactly.  AS: Last question. Does it matter at all that this is held privately, that this is Google DeepMind, this isn’t a university. Does that make a difference?  DH: I don’t think so. I feel like you can do great science anywhere as long as you’re approaching it in the right way with, and doing fundamental research. You know, a lot of these new sciences and new areas and new fields of study and discovery require a lot of resources. In our case, a lot of computers. And, you know, that costs a lot of money, so why not tap into private sector in order to fund those kinds of things. As long as you are true to the scientific method and approaching it with real scientific rigor and going after the big questions, which I feel we do it at Google Deep Mind.  AS: Thank you very much indeed. I shall leave you to get on with enjoying what should turn out to be quite an exciting day.  DH: Thank you. Thanks for taking the time.  AS: Okay. Thank you. Demis. |
| **Interview** |  |
| Q1 | What sparked your interest in science and AI? |
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| Q2 | What inspired you to move into biology |
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| Q3 | How has your interest in gaming shaped your career? |
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| Q4 | Did your game Theme Park influence your career in AI? |
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| Q5 | Do you still play games |
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| Q6 | How important is it to use science to help solve challenges? |
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| Q7 | How does it feel to see your work have a real impact in people’s lives? |
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| Q8 | Have you had any failures or mistakes in your career? |
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| Q9 | Is failure important in science? |
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| Q10 | What keeps you motivated? |
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| Q11 | What would you like to explore next? |
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| Q12 | Who has influenced your life and career? |
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|  | Was there a teacher who was important to you? |
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|  | What is your advice for young researchers? |
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|  | What advice do you wish you had received when you were younger? |
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|  | How do you continue when nobody else believes in your ideas? |
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|  | Why is it important to make scientific research open for all? |
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|  | How important is diversity in research? |
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|  | What are the greatest possibilities for AI? |
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|  | How can we ensure AI benefits everyone? |
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|  | What are your biggest concerns around AI? |
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|  | What are your hopes for the future? |
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|  | What do you do in your spare time besides gaming? |
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|  | How do you balance life with work? |
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|  | How did it feel when you found out about the Nobel Prize? |
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|  | How does it feel to be a Nobel Prize laureate? |
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| **Podcast** | “I really love the notion of contributing something to physics.” Chemistry laureate John Jumper has always been passionate about science and understanding the world. With the AI tool AlphaFold, he and his co-laureate Demis Hassabis have provided a possibility to predict protein structures. In this podcast conversation, Jumper speaks about the excitement of seeing how AI can help us more in the future.  Jumper also shares his scientific journey and how he ended up working with AlphaFold. He describes a special memory from the 2018 CASP conference where AlphaFold was presented for the first time. Another life-changing moment was the announcement of the Nobel Prize in Chemistry in October 2024 – Jumper tells us how his life has changed since then.  This conversation was published on 19 June, 2025. Podcast host Adam Smith is joined by Karin Svensson.  Below you find a transcript of the podcast interview. The transcript was created using speech recognition software. While it has been reviewed by human transcribers, it may contain errors.  John Jumper: The moment you get the Nobel Prize and the moment the Nobel Prize’s announced, you immediately get an email from everyone that you’ve ever interacted with in your life. You find out exactly who you’ve impacted in your life because they all send you a message.  Adam Smith: It sounds slightly overwhelming, doesn’t it? Lucky that John Jumper, who was just 39 when he got the call from Stockholm. So at least being so young, that must have limited to a certain extent the number of people he’d interacted with over the years. But it’s nice that it emphasises the social side of science, which so often comes up in these conversations, dispelling the myth of the scientist as the sort of lone maverick. Rather, there’s a great community around them. Alongside the competition, there’s all this collaboration and communication. Please join me for this conversation and take the chance to become part of that group of people who have got to know John Jumper.  Karin Svensson: This is Nobel Prize Conversations and our guest is John Jumper, recipient of the 2024 Nobel Prize in Chemistry. He was awarded for protein structure prediction. He shared the prize with [David Baker](https://www.nobelprize.org/prizes/chemistry/2024/baker/facts/) and [Demis Hassabis](https://www.nobelprize.org/prizes/chemistry/2024/hassabis/facts/). Your host is Adam Smith, Chief Scientific Officer at Nobel Prize Outreach. This podcast was produced in cooperation with Fundacion Ramon Areces. John Jumper is a distinguished scientist at Google DeepMind and leads the Alphafold team. He talks to Adam about how his optimism won him, his job at one of the world’s most coveted workplaces, how he learned chemistry in a week, and how a fresh approach made the same data a hundred times more useful and secured him the Nobel Prize. But first we go back to the moment of the prize announcement when Adam reached John, who was on a conference call with his colleagues.  Audio recording from announcement day: “…Demis Hassabis and John Jumper…” Glad you guys are all caught up now!  Smith: It was wonderful to see that video of you sharing the moment of the announcement with your team. Thank you for sending it to us!  Jumper: And not realising that you were going to post video so there’s that up the nose shot!  Smith: I think people adored that moment. It was so nice because in a way it’s also mysterious what goes on there. People just love being able to feel that they were somehow coming close to it. Since that moment you’ve had months, but you’ve had Nobel Week in particular. How did you find that trip to Sweden?  Jumper: It was extraordinary. The part about it is the amount to which this is a celebration by the whole country of science, the experiences and just the massive amount. In terms of the pump and the circumstance and the formality. I like to explain to people that I got a little bit of a pull in my shoulder from standing up straight so much. The part that absolutely got me is, we arrive and there are people asking for your autograph, kind of stalking outside the hotel. There’re the beautiful Nobel Prize vehicles and I signed someone’s napkin in a restaurant. There are kind of just moments as a celebrity and you meet all these exceptional people, but it’s just such a part of the Swedish national identity and culture. I thought that was a very beautiful thing.  Smith: You’re sharing it with so many people because you’re sort of sharing it with the Swedish public and you’re also sharing it with your colleagues and your family. There’s a whole mix of people there.  Jumper: Yes, it’s worlds colliding. You invite your family, you invite your friends, you invite your colleagues. We had lots of colleagues and I had someone quite a senior in our company, Google DeepMind, head of a division saying, “Oh, I was talking to your mother last night”. I’m thinking, “Oh, good, my mother’s great”.  Smith: It’s good that you were thinking, “Oh good”. You might be thinking, “Oh no, what did she say? What stories? Help!”  Jumper: Oh yes, apparently one of my teammates ended up sitting next to my mother on the flight and discussing my history. So it’s all these people. The moment you get the Nobel Prize and the moment the Nobel Prize’s announced, you immediately get an email from everyone that you’ve ever interacted with in your life. It takes a couple weeks just to respond thank you to all the emails, messages, chats and texts that you get.  Smith: It’s a nice way of looking at the Nobel Prize, that it’s the social network.  Jumper: Yes. You find out exactly who you’ve impacted in your life because they all send you a message.  Smith: Fascinating. That’s a really nice perspective. Simon Johnson told me that he told you that given how young you were and how much you’ve done already, he wanted to put a bet that you’re going to be the first person to get three or four of these things.  Jumper: He’s very kind. I hope I do the kind of work that, if I get lucky again, puts me in contention. I’d be happy to be in contention a second time for a second prize. Of course there are some incredible people, Marie Curie who’s gotten two, but I think it’s just I want to do good work again. There is this wonderful challenge of the Nobel Prize that you become a public intellectual. There’s so many good things for you to do then you have to think about what is the right thing to do? Do I go to the lab? Do I try and do the next thing? Do I just put my head down and try and shut out the noise? Do I go to this very worthy thing? Do I engage with these young scientists and talk to them and give them what lessons I can give them? Actually, like very recently I went to an event for Marshall Scholars. I had been a Marshall Scholar previously, and I just told them the story of my history and how nothing went the way I expected it to. All these opportunities to tell people this. I don’t know what’s the best use of my time, but I’m trying to figure it out and have some fun along the way.  Smith: But given that you are part of this rather exclusive group of people who got the prize very young, getting the prize before you’re 40 is very unusual, especially in chemistry. How do you feel about that? Is it in a way a relief to get it, if you like, get it out of the way ? Does it exert extra pressure, which you possibly don’t need at this age? What do you think?  Jumper: Not only was I fortunate to get it young, but I was fortunate to get it so close to the discovery. Like if you date from the published paper that was 2021. I remember thinking at the moment, the week before the Nobel Prize, that I’m finally starting to kind of get my time back and AI is having such a huge moment in talking to people. I’m finally kind of getting ready to fully launch into the next research initiative and work. Then this comes and this comes as this kind of wonderful bomb that destroys all the plans that you had before it. If I work out the numbers I’m at about the midpoint of my career in terms of productive years maybe 20 to 60 ish with some bounds. Some people are productive much longer. But I’m at about the halfway moment of my research career. I need to solve the second half. I have both a wonderful platform and all these distractions. I think it’s not hit as many people in the modern age. I’m very fortunate. I look back on Bragg that got it at 25. I think he might be the youngest of the scientific prizes.  Smith: Exactly so.  Jumper: What I really wonder is what will it be like in five years? Will it be something where it’s something that people occasionally notice, it’s a Nobel Prize winner. Will it still be a defining attribute for people meeting me?  Smith: From looking at what happens to others. I think it will be the source of constant invitations and constant demands on your time, which you either accept or refuse. But yes, it’ll be there. I don’t think it’s going to go away.  Jumper: I’ve never taken so many selfies in my life. I cannot, leave an event or whenever I talk to someone, they always sheepishly ask at the end, “Do you mind if we get a selfie?” I always say, “Yes, just be quick”. But it shows you how aspirational the Nobel Prize is. I think it’s a beautiful symbol of what we want science to do for the world. I think it’s earned that distinction, but it’s such an interesting thing. It makes conferences exhausting. I love going to them, but that means I work 16 hours of just talking constantly to people. It’s a different experience. In my personal life it’s kind of easy, friends know I have a Nobel Prize but not like random people I meet on the street. I’m not a TV celebrity, but in terms of my scientific career, I’ve basically met all the scientists I’m going to meet who don’t know I have a Nobel Prize for better or for worse.  Smith: Yes. It does make you sort of public property. You mentioned that it came very close to the discovery and that in a way must be very nice because often one talks to laureates who have been awarded for something they did a long time ago and they like to talk about it. But honestly, I’m a bit more focused on what I’m doing now and in your case it is what you’re doing now. That’s a nice sort of compliment.  Jumper: I remember seeing the Museum of Industry in London and it’s got a wonderful hall of steam engines, as you should in a museum celebrating British science. But they also have on the side what James Watt did after the steam engine, which was a device for copying sculptures. I’m imagining him, everyone wanting to talk to him about the steam engine and he wants to talk about his device for copying sculptures.  Smith: Yes. There have indeed been a couple of those announcement phone calls that I’ve made bringing people who’ve just heard the news and frankly they’ve sounded slightly annoyed that this is interfering in the day’s experiments. It’s integral to who you are and how you work, that you’re focused on what you’re doing now.  Jumper: I also talked to a lot of people who felt like they were never going to get it. It’s nice to get, but I can almost feel, maybe not resentment, but certainly kind of exhaustion. I was thinking myself, I knew that the work had been talked about in the light of the Nobel Prize, but they often come later and I was thinking I was going to hate early October every year. Every year was going to be the time I get disappointed yet again that my 10% chance to get the Nobel Prize in a particular year didn’t come through. I couldn’t imagine having done that for say, 20 years that a lot of really deserving laureates do.  Smith: It reminds me that [Jim Rothman](https://www.nobelprize.org/prizes/medicine/2013/rothman/facts/), who got the medicine prize, I think in 2013. He sent me a photograph of him getting the call from Stockholm that told him that he’d been awarded the prize. I suppose now everybody has a phone with a camera. But back in 2013 it was a little unusual for somebody to be able to take a photograph of themselves instantaneously. I said, “How come?” He said, “Actually I have a phone on the bedside table every year that night when the medicine prizes announced”. Then he said, “I’m Jewish and in our house we call that night Passover.” He’d been waiting for a while. Yes, it is a pressure.  Jumper: Yes. That resolves it in some way. I think the other nice part of getting this prize so soon to the discovery is it makes it really easy to say, and now I am turning the page. Now I have my post Alphafold career and not post AI. I’m still doing AI, science and others. But I think it’s a nice reason to say this is a beautiful chapter of my life’s book and now I can move on to the next chapter, which is probably called dead ends and failures. But still, I think getting to this next chapter on how you go after the next thing and not be tied. One of the things people always worry about is how these great discoveries tie you to the past, tie you to the questions, the techniques. You were doing the right thing and had this great discovery and how do you let it go and be a great scientist in a different way going forward.  Smith: You talked about lessons, but I guess that is a very important lesson to learn, not to be tied to ideas, but somehow be flexible enough to adapt to whatever’s happening in front of you. That’s not so easy.  Jumper: Yes, it’s not so easy. The Nobel Prize gives you an incredible kind of authority and power to talk about things you know, and things you don’t. It gives you a platform. But I think to use it well, to support your own work, to support the work of others, that’s important. Your voice carries more weight, even in things like policy discussions and all this. I think these are all interesting side aspects of these prizes and kind of has a different kind of character and flavoured to my age. Honestly even Demis’ age, he is not that much older than me.  Smith: Of course. You’ve been very directed so far and I wondered whether you were directed as a child, whether you were a very focused kid?  Jumper: I would say directed is an assumption. I think passionate, competitive, but kind of shoot off in directions and then shoot off in other directions. I think I’ve always been deeply passionate about learning about science, loving this notion of understanding the world, of pulling apart the world with intellect and experiment.  Smith: Where did that come from? Was that part of your upbringing? Was it just innate in you that you had an interest?  Jumper: I’m the son of two engineers. My father’s a mechanical engineer and my mother is a civil engineer. I grew up in kind of semi-rural Arkansas, near the city but not in it. I think innate for me was drive and competitiveness. I was going to be the best. I hated losing from a young age. That was definitely innate. I think from my parents really came a notion of utility to others of doing work that it was kind of meaningful. My wife sometimes calls me or accuses me of being puritanical in my view toward like doing hard work to achieve good things, to kind of contribute to the common good. I think all of these were really probably instilled values into me. I remember actually my parents were less sure about science probably because they weren’t sure it was as practical as engineering. So it was like you have to go to a school that has a good engineering program in case you decide you don’t want to do science. I remember my mom saying reasonably from her understanding, like physics, are you sure you can make money doing that? But I fell in love with the world we didn’t see, the cosmos, quantum mechanics, like all these things that we almost like as humans didn’t have a right to know, didn’t have a right to pull this apart. I loved all those things and I was really driven to learn and understand. I grew up in this wonderful time. I was born in 1985, so really a lot of my formative years around academics in high school were in the nineties and early two thousands. The internet was new, it was wonderful and weird and gave you this connection out to the technical world or out to reading about science, out to computer programming, out to all these things. It gave you all these wonderful connections that I would like look in the books and library and say they’re not nearly at this level of depth and understanding that I can get just by kind of searching the internet.  Smith: How fascinating! What an interesting perspective! Because of course older scientists, maybe some of them, found it more difficult to transition and felt that that somehow this was a dangerous time, that the information maybe wasn’t as good as it should be or whatever. But seeing it in with that perspective that I’m at a moment when things are connecting and you can get access to so much more. That’s really interesting.  Jumper: I very quickly realised that pop science wasn’t really a representation of what the science really was. I think if you grow up in a big city, Arkansas itself is a state, it’s like a couple of million people. I went to a good high school, but I got my best education in writing, politics and these kind of things. But when it comes to advanced mathematics, advanced physics, the access grew so rapidly, access to educational materials, access to nerdy subcultures or people who would write about this grew so rapidly because of the internet. It makes such a difference. My wife grew up in New York and what she had access to in terms of special classes or ability to learn was so differentiated compared to what was the typical experience in Arkansas. Even though I grew up in a a relatively privileged household, it’s just really great for connecting and for making education available.  Smith: Is it special to Arkansas that you came from Arkansas? Are they proud of you?  Jumper: I believe so. Honestly I haven’t been able to go back since the Nobel Prize but they are proud. I’ve received some nice letters from the government and I’m the first laureate from the state.  Smith: Exactly, that’s what I was getting at. Obviously your alma mater will always claim you and the university says yes of course, but where you came from, where you grew up, that also matters.  Jumper: A few days after the Nobel Prize, my high school put up a blog post about the Nobel Prize of course and included my high school yearbook photos. That moment at which your coworkers discover your high school yearbook photos posted on the internet is an interesting moment. I regretted some of my decisions. The other part about being kind of a public celebrity. I don’t know if you saw the BBC posted an article on how Wikipedia is working to fix some of the worst images. Somebody sent me this and I thought “Why did they send me this?” I scroll down and I see my old Wikipedia photo, it was listed by the BBC as one of the worst photos on all Wikipedia. That was replaced with a much better one thanks to the photographer who showed up in Stockholm.  Smith: I think that’s an accolade worth talking about that you should add that to your list of prizes and awards. Alongside maybe an Ignoble prize if you’re going to achieve that but there’s only been one laureate who’s managed to get one of those  Jumper: Andre Geim.  Smith: Exactly. That utilitarian interest that came from your parents is sort of manifested itself in your approach to learning because you, you’ve transitioned between academic environments and private environments and companies. Was that very directed? Did you want to see both worlds or was it just the opportunity that arose?  Jumper: No, I wanted to live forever in academia. I worship the notion of a PhD. I really love the notion of contributing something to physics. I remember very distinctly, I wanted to have one sentence in a textbook, describe what I did for science. I had this belief through undergrad. I did some undergrad research. I enjoyed it at Vanderbilt and toward the end you apply for kind of scholarships to support study because that’s what good students do; they apply for prestigious scholarships. Then I was accepted to the Marshall scholarship, which is given by the British government and thanks for the Marshall program. I remember, okay, well this is a prestigious scholarship so I should do it. I’m going to go to the UK. I kind of applied by email trying to find the right advisor because you have to pick an advisor when you enter Cambridge. I ended up in kind of the wrong area of physics for me. I just didn’t love it. I didn’t grab it. I didn’t see myself doing this for years. About one year into a PhD, which normally takes three or four in the British system, I decided I just loved it so little that I was going to drop out. I walked into my advisor, I talked to my wife and I walked into my advisor’s office and I said that I’ve decided to leave. He said something like, I must say I’m surprised. So I quit my PhD about a year in and took what I call the consolation prize. I wrote an infill thesis and I received an infill.  Smith: This was condensed matter physics that you were looking into.  Jumper: Condensed matter physics at the Cavendish.  Smith: That shows great self-knowledge and in a way self-confidence to say this isn’t for me.  Jumper: It didn’t feel like self-confidence at the time. It felt like being dejected. I was on the rails of my chosen academic path. I shall do this and then I shall do that and I’ll be a professor and I’ll think great thoughts and I’ll do great computational physics. I loved computers, I loved playing with computers and I was doing physics. It felt like a failure. It felt like a real rejection, I had chosen wrong at the beginning. I wasn’t happy and I left. I left in the summer of 2008 I believe and it was much too late to apply to US grad schools because I thought maybe I didn’t like Cambridge and maybe I’d picked the wrong area of physics. I’ll just roll the dice again. But it was too late for that. So I said, “Well, I’ll work a year or two and I’ll make a little money. I don’t want to end up in industry but I can work a year or two and then I’ll go back to grad school.” So I was an unemployed skilled physicist. What does an unemployed skilled physicist do? They apply for quant finance jobs. I applied to a bunch of hedge funds and quant trading shops and had some interviews but of course it was also 2008, the year of the financial crisis. I applied to D.E. Shaw, the second largest hedge fund in the world. They said, “We don’t have anything but do you know about our private biomedical research group who’s designing custom computer chips to simulate how proteins move?” I said “No and do you mean I get to stay in science and get paid a real salary? This sounds great.” That’s how I got into proteins in biology at all was this happenstance of leaving a program and then happening totally at random into this role.  Smith: It’s fabulous. If you’re just open to possibilities, things can happen. That’s an extraordinary way into what turned out to be absolutely the right avenue.  Jumper: It led me directly into AI. It also made me a chemist. That’s another funny story. They hired lots of physicists and I learned a tremendous amount of also computer science there. Because they had like real and proper high performance computing people. I learned how you really do this thing. I worked there for three years. I really enjoyed it. It’s a really wonderful time. They built these custom chips. I said “Okay, I should go back and get a PhD.” My wife Carolyn, who had done an infill in finance said, “I really want to be a geneticist. I want to get into this”. So she starts reading genetics books and so she’s going to apply for a PhD and I’m going to apply for a PhD. We just applied all the same places because we weren’t going to live apart for the whole PhD. That’s just not something we’re going to do. After we applied and we get accepted, she has a really great offer from Chicago human genetics. I had some other great offers, but I had missed the application to Chicago. I applied to the physics department. I had failed to apply because they closed their application at five and I thought it was going to be midnight.  Smith: That sounds very familiar. That sounds like my approach to doing things. If it’s going to be midnight, do it at 11 o’clock at night, not earlier.  Jumper: Exactly. I need that forcing function. I spent like a month trying to convince them, “Hey, can I apply please?” They said, “No, go away. You can apply next year.” I’m telling this story to a colleague, Albert Pan. I’m saying, “I don’t know what I’m going to do”. He goes, “Do you think you could be a chemist? I know this professor in Chicago chemistry, I could refer you to him”. I said, “Sure, I can be a chemist”. I hadn’t taken a chemistry class since high school and he must have said a very nice thing to this professor. I talked to this professor the next day they say we’re gonna open the application for one day. Submit right now. A week later they accept me to become a chemist. That is why I have a PhD in chemistry. But I had to learn general chemistry one week ahead of the students.  Smith: It’s funny, chemistry seems to attract people like that. A lot of people drop it at some point and then they come back to it. There are chemistry laureates out there who are proud of having failed chemistry at high school.  Jumper: The other part is, and that’s how I got into AI. I had worked at this place with these incredible custom computers and enormous amounts of computing resource. I loved working on protein problems and biology problems. But I remember thinking I was doing more simulation in a single day than most people do in their PhDs in kind of protein simulation. I don’t want to go to my PhD and have just a thousand fold list resources than I had before. So I’m going to try to do algorithms and math. I’m going to try and rebuild kind of the ideas using ultimately AI to kind of capture in algorithms what I no longer had in computer hardware. That’s why my PhD was kind of how do we use AI to do protein simulation?  Smith: Right. That’s interesting. It’s kind of resources forcing the approach. Fascinating. I’m getting the distinct impression that my use of the word directed is completely wrong.  Jumper: Yes, I’d agree.  Smith: Okay, so that got you your PhD in chemistry and then back into industry again.  Jumper: Then what happened was, honestly my publication record wasn’t that stellar. I had kind of two papers. I think there were pre-prints, but I was finishing them as papers. The work was good but it was no way it was going to get me a professorship. At that point Carolyn and I had had two children and I wasn’t going to do a postdoc and bounce around the world. Also it was clear that this AI thing has legs and that I really did want to work in it probably more than I wanted to work in computational. If I had the choice between pure computational biology and pure AI work, I was going to go to the AI side. This was about 2017 and I heard this rumour that DeepMind was getting into protein structure prediction. Then I found out I had a friend who knew someone there. That’s how I ended up back in industry. All of this is kind of local optimisation for whatever I needed to do at the moment, whatever seemed interesting. I think what I have had for a long time is somewhere between confidence and a bit of arrogance that whatever the problem was, I could probably do well at it. I was willing to jump into whatever I thought might need clever people.  Smith: It’s a beautiful story and I can quite see why telling that to the Marshall Scholars is inspiring. And it’s a very lovely example of how talent will flourish sort of wherever you put it.  Jumper: Yes or you don’t talk to them.  Smith: It reminds me of a funny story. There was a drug discover called Paul Janssen who started Janssen Pharmaceutical a long time ago. He was possibly the person who put most drugs on the market. It was a long while ago, so maybe it was because it was easier then, but who knows. But he had this policy, he was Belgian and it happened at the Belgian Congo was gaining independence and stopping being the Belgian Congo. So all these Belgians were returning to Belgium from there. A lot of them were very talented and he just picked these talented people up and brought them into his company. Some of them had absolutely no experience in drug discovery, but he just thought they were clever and he wanted clever people around him. Talented people who had some track record in doing something and they turned out to be very good gets, sort of parallel that you just go out and pick up good people and somehow they’ll find their place.  Jumper: Also try and create the kind of place that lets them grow. I do think a lot about the Alphafold work. It was about a team of around 15 and we mostly got physicists, computer scientists, AI researchers, very few. I was considered one of the two real biologists of the group. I’m a different kind of biologist, certainly not classically trained. Very smart people capable of learning and diving into these subjects and then all became kind of very good and understood well enough to then have the ideas and do the work on how do we do Alphafold. I think that getting adaptable people because as fast as this field and world is changing, you really need adaptable people. We should down weight experience because after all the field we’re in, AI keeps changing so fast that nothing from four years ago is all that relevant to today. Like 10 years of AI experience is still only really three years of AI experience in that way.  Svensson: Adam, John Jumper was 39 years old when he received the prize. How common is it to become a Nobel Prize laureate before turning 40?  Smith: First of all, it’s not so common to become a Nobel Prize laureate. They’ve only been a thousand since the prize began. But those below 40 number about 5%. That’s across all categories.  Svensson: Is there a common denominator for them?  Smith: Yes, I suppose there is. That’s that their work has to have made an impact very quickly. Many people who get Nobel Prizes have done that work quite young, but it then takes many years for the true significance of the work to be recognised. In the case of those who get it below 40, things have to have moved pretty fast. There has to be a wide recognition of the importance of the work very fast.  Svensson: But it also says something about the pace of AI research, doesn’t it? That it’s connected to that and that’s also moving very fast.  Smith: Absolutely. I suppose that things become outdated very quickly in artificial intelligence. So if you’re going to have an effect, it’s probably going to be pretty immediate. That was certainly John Jumper’s experience that he came in and he had a big influence on Alphafold, this program from Google DeepMind. The influence was widely recognised quickly.  Svensson: What is Alphafold that he was given the prize for?  Smith: It’s a tool for predicting the structure of a protein from the DNA sequence. Now it’s been a longstanding problem in biology that we know that a DNA code gives rise to a protein of a particular shape. But we haven’t been able to predict the shape of the protein from the code nature does it. It knows that this code means that it’s going to fold this protein up in this way and it’s going to look like this. But working out the rules that govern how the protein’s going to look has been incredibly difficult. Many people have been working on it for a long time, very hard to try and work out how protein folding works. In the end it turns out that Alphafold and its successes Alphafold 2 and now Alphafold 3 are absolutely the best at predicting how a protein will look.  Svensson: How does it do it?  Smith: Somehow it has learnt the rules of protein folding. It’s a machine learning algorithm which was trained on all the known structures of proteins. There has been this marvelous community effort by scientists over many years to deposit all the known structures of proteins in something called the protein data bank. That provided, if you like, a training data set which Alphafold was able to use. It works out somehow the interrelationships between all the residues in those proteins, all the different amino acids and how they position themselves in space. It has come up with its own set of rules for how to fold things up, which very accurately mirrors the way that nature does it.  Svensson: Alphafold 2 had its big moment at the CASP 14 conference. Can you tell me about CASP is?  Smith: Yes. CASP is a competition that’s held every two years to see how different groups in the protein folding community are doing and who’s got the best model. It started back in 1994 and it stands for the critical assessment of structure prediction. They hold a meeting every two years where people come together and they’re given a set of sequences for proteins for which the structure is known but those structures haven’t yet been published. All the different groups would put those DNA sequences into their models, see what kind of structure they got out, and then compare it with the actual structure, which is known to the organisers but isn’t known to all those different groups.  Svensson: So protein folding Olympics.  Smith: Exactly. I think a little bit like the Olympics, healthy competition and a friendly atmosphere. It was at the 13th CASP meeting in 2018, that Alphafold made a big impression by winning the competition. Then two years later in 2020 Alphafold 2 came along and it smashed the competition and was about 90% accurate in structural prediction. That did surprise everybody. Basically the protein folding problem had been largely solved by Alphafold 2. Actually I spoke to John Jumper about how it was at CASP 13 in 2018 that he was given the instruction to really turn the heat up under Alphafold and dramatically improve it.  MUSIC  Jumper: I get on this call with Demis and Cory, and they’re saying, “Okay John, we want to scale up this effort and we want you to be the sole lead and you better go solve this problem”. I was told that from a hotel room in Cancun where the CASP conference was happening. Actually I had some research successes, like personal research successes in the middle that made it more likely we were going to go solve this and this first version of direct structure prediction. But still, I remember sitting there going, “Well crap, it’s all up to me now.”  Smith: In a way that’s more of a moment or at least as much of a moment as being phoned by the Nobel Prize Committee. I mean it’s a life changing event.  Jumper: It starts very mysterious. It’s like, Demis would like to have a call with you at 11:00 PM tonight. I’m like, okay, I guess we’re doing a call at 11:00 PM I remember going back and saying, “What in the world are the ideas that are going to take us from where we are to where we need to be?” Trying to make a list and thinking who am I going to recruit? Who am I going to grab? How am I going to get 15 or 20 people? I got to go find those people. How do I do all this? It’s this almost lowly moment. I remember sitting on this flight making this list, what are the ideas we’re going to try? What’s going to get us there? Thinking no one else knows on this flight how much pressure I’m under trying to figure out how to do this thing. That would’ve been somewhere around 5 December, 2018.  Smith: Turns out that Demis is a good spotter of people.  Jumper: He saw something in me, part of it was an optimism that we could solve it. I had a big research breakthrough in terms of this kind of direct structure prediction, but I remember that kind of came after they told me I was co-leading the group. I felt a little better about it afterwards because I had landed some decent things and some enormous kind of speed ups and simplifications to the CAS 13 system during the middle of CASP. But nothing that fundamentally improved the accuracy by much.  Smith: It all worked out very beautifully  Jumper: Yes, I guess he was right.  MUSIC  Jumper: It’s hard to give outsiders of the field an appreciation of how much computational biology wasn’t that well respected by experimental practitioners before this. There were molecular dynamics and it was used and it sometimes was used very well, but it was not thought of as an incredibly highly predictive technology that you don’t predict. You go solve the structure, you get the answer, you do these things. I think this is really opening the door to, we have these computer tools to predict biology and we’re going to use it for lots of problems. I’m very interested in what’s the radius of this? How much of biology can we get really incredibly predictive tools for?  Smith: One limit there might be the quality of the data I suppose because AlphaFold’s success was in part that the data that went in was very good. Those 200,000 protein structures was solid data. In biology things are a bit messy. People talk a great deal of course about the reproducibility problem in biological research. The fact that you can’t necessarily know whether everything is right. Do you think that that might potentially be a limitation to things in the future?  Jumper: Certainly data is going to be a challenge. I think one illustrative study that was done on Alphafold by the Alqaresi group, they reproduced the Alphafold 2 work and they tried training Alphafold 2 on a tiny fraction of the available data, about 1% of the data. They could show that Alphafold 2 trained on 1% of the protein data bank was as accurate as Alphafold 1 trained on the entire protein data bank.  Smith: Wow.  Jumper: What that tells you is you can say that the kind of innovation methods that we had between Alphafold 1 and 2 was worth pretty close to 100 times more experimental data. That happened to be enough that took us to the threshold of solving the problem or making a really biologically useful system. What we do as machine learners is we’re always limited by the data in some sense. But then the more clever our machine learning, as we refine our methods as we come up with new ideas, it behaves as if we have some multiple of the existing data. I think data is always gonna be a limitation and the skill of machine learners will be pulling evermore knowledge out of it. For which problems in biology will this work is a very interesting question. There are problems, for example, like RNA structure prediction that we worked on in Alphafold 3 among other problems. I think it’s pretty likely that it’s going to be not impossible, but hard with the ideas and the data together that we have. But it’s a really good moment for twofold, fourfold, sixfold the data and that to probably make an enormous difference. We’re probably right on the cusp of doing really well on these problems. Data collection may be the easiest or cheapest way to get there, I think on some other problems we shall see. That’s the fun part, we talked earlier in the conversation, what do I do next? I try and figure out how to find the next problem where people say there isn’t enough data. In fact, you can read blog posts after Alphafold 1 that said it was a very fine engineering advance that the DeepMind team did to build Alphafold 1 (it wasn’t called Alphafold 1 at the time). It’s great to see modern engineering being used here. Talking down it as a scientific accomplishment, but data isn’t growing. They can’t exponentially scale in the data like they could for text or images. We won’t see another big advance going forward unless something really changes. That’s technically true, but it’s just something really changed. As we get better at machine learning things that were impossible in data before become possible and that’s why we go to work every day. That’s the value we bring to this enterprise, not just watching the computers run.  MUSIC  Smith: Something that people love to talk about all around the world is the interplay between the human and the AI in terms of scientific idea generation. People talk about that a great deal, but fewer in your position of being able to really understand where this interplay lies and how it’s develops. Do you see a time when AI will be setting the problems as well as coming to the solutions, identifying questions that scientists haven’t thought of?  Jumper: I remember being asked in one of the lectures after the official Nobel Prize lecture. I gave a lecture in Uppsala after the Nobel and someone asked me, “Will machines ever be creative?” And my response, and I think the response is similar here, that creativity or coming up with ideas or setting problems isn’t a binary, it isn’t a yes or no. If you asked five years ago, will machines ever be creative? People would say they’ll never write poetry. We clearly have machines today that write poems and now people say, these aren’t as good as the best human poems. I agree, I’m not an expert in poetry, but they’re certainly poetry, right? They’re better than some human poems. Are we going to put a stake and say yes but these poems are very derivative? Well, I’ve watched a lot of movies that are also very derivative. There’s a lot of plots of sitcoms that are very derivative. I think creativity is a continuum. Our culture is kind of constantly looking to its past to build its future. Similarly in ideation in science, we remix prior ideas. A lot of grant reviews will say, well this wasn’t very creative, it’s just taking this idea and that idea and putting them together. It’s not that interesting. Sometimes those people are right and sometimes they’re wrong. But I think all of our ideation, creativity is on a continuum and clearly these machines are getting better at it. The question will become twofold. When are they so good at it that a good percentage of the ideas we pursue are created by machines? Will they have taste in which ones they pursue? In what cases can we build on this work and go beyond kind of one step. We build ideas that we build on. We build entire kind of enterprises, disciplines, building on each other’s ideas, testing, refining, kind of the work of scientists. I don’t know how close or far we are from machines doing this kind of higher level, but in the sense of coming up with some idea that someone will find useful. There’s work at Deep Mind, there’s work elsewhere. Of course they will.  MUSIC  Smith: You mentioned that you have two young children.  Jumper: I now have three children.  Smith: Congratulations.  Jumper: Another false premise.  Smith: What a blessing. But balancing your work and your home life is something that everybody’s always interested in with Nobel Prize laureates. It’s just a truth that in order to get things done, you have to work incredibly hard. How do you make it all fit together?  Jumper: Balancing home life, one is I simply could not do it without my wife Carolyn. She’s both an incredible force for me in terms of my career and pushing me forward and helping me make the right decisions. But also helping to take care of the kids. I think the other thing that I found, my kind of secret superpowers is being an incredible night owl. What I would do, and actually I think Demis runs a similar schedule, is that I’d come home from work at a normalish time. I would play with the kids, I would have time with the family, and then when the kids go to bed, I’d open my laptop back up. For a lot of Alphafold, my third child was born three weeks before the CASP 13 conference. I will say I have yet to hear the end of my three weeks of paternity leave when I could have taken much more from Carolyn. But I remember having this tiny baby and trying to build what would get me a Nobel Prize. One of my secrets to this is realising that very young babies are very happy just to sleep in a warm spot. So I put my daughter Katie on my chest and she’d be happy and I’d reach around her with both arms and I could operate the laptop and everyone was getting what they want. So I think one of the things that helps is I really do also enjoy my work. Being at a company, I do have less of the kind of academic committees, I have been more time to focus on my work and the team’s work. I think that helps. But ultimately I think I do work long hours. I have been accused of being a workaholic, but I also enjoy it. In fact, my fun time is when I actually am writing personal code, when I’m doing machine learning myself. I would do that at night and then I just try and do it as a balance. Because ultimately though the kids come first. If I got a Nobel Prize but my kids didn’t get to see their father, that would not be worth it. The only way it works is if my kids are being raised the way they deserve. I brought them into this world, I didn’t ask them. I think it’s just so incredibly important, the duty and the joy of our families.  Smith: That’s lovely. It’s just play all the time. It’s play at work because it’s such fun and play with the kids.  Jumper: Sometimes there’s work at work, but most of the time it’s fun. Sometimes, especially your kids get older, but they’re really fun and they’re wonderful.  Smith: John, thank you very much indeed for taking the time.  Jumper: Thank you. It was a wonderful interview.  Svensson: You just heard Nobel Prize Conversations. If you’d like to learn more about John Jumper, you can go to nobelprize.org where you’ll find a wealth of information about the prizes and the people behind the discoveries. Nobel Prize Conversations is a podcast series with Adam Smith, a co-production of Filt and Nobel Prize Outreach. The producer for this episode was me, Karin Svensson. The editorial team also includes Andrew Hart and Olivia Lundqvist. Music by Epidemic Sound. If you’d like to hear from another laureate who knew early on that a PhD was definitely something special, check out our earlier episode with 2018 physics laureate [Donna Strickland](https://www.nobelprize.org/prizes/physics/2018/strickland/podcast/). You can find previous seasons and conversations on Acast or wherever you listen to podcasts. Thanks for listening. |
| **Telephone**  **interview** | [JJ]  Adam Smith: Hello, am I speaking with John Jumper?  John Jumper: Yes.  AS: This is Adam Smith calling from the website of the Nobel Prize. Many congratulations.  JJ: Oh, thank you.  AS: I detect in your voice some surprise. Can I just ask you how you feel about this?  JJ: Oh, it’s, it’s absolutely extraordinary. I think it’s, I think it’s a wonderful group. I’ve been a computational biologist a long time and I like to say in talks, we need this to work. You know, we need computation to solve the problems of biology. And I just love that it’s starting to work and I can’t believe we’re getting recognition this fast for it. And I think it’s, I don’t know. What I love about all this is that, I can draw this, you know, I used to be a physicist, that kind of made it amusing to me, the prize yesterday, right? The physics of AI. But, we could draw a straight line from what we do to people being healthy because of what we learn about biology in the cell and everything else. And it’s just extraordinary.  AS: And things are moving so fast.  JJ: They are, in the modern era, four years from paper to Nobel or maybe three, three or four.  AS: You know, you are the youngest. You’re the youngest chemistry laureate for over 70 years.  JJ: God. You know, I love this speech, I don’t know if you’ve ever seen it, You and Your Research, by Richard Hamming and he talks about after people get prizes or I guess there’s also Nobelitis, but people only work on important things, so they never work on the small things that become important. That’s a scary thing.  AS: Yeah, that gives something to think about, doesn’t it?  JJ: Let me see if I can get down. I apologize. We have some cleaners around. I was trying to avoid the vacuum sound. You get to do this once per year. It’s not even fair. My plan was to, I thought I had a 10% chance, so my plan was to sleep in and, my goal was actually to sleep in to the point that by the time I wake up, either way I know if I’ve received the Nobel. It didn’t quite work, because it’s hard to sleep in that much.  AS: It must be. With a 10% chance, or an estimated 10% chance, you must, yeah, you must be on a little bit on tenter hooks.  JJ: I couldn’t believe it. I was telling people, it made early October miserable. Because it felt like a 10% chance of winning the lottery.  AS: Well, yeah.  JJ: Right, objectively the best anyone ever gets is a 90% chance of disappointment.  AS: How nice. It’s come quickly. Future Octobers can be relaxed.  JJ: Exactly. Future Octobers can be relaxed! Anyway, it’s a great pleasure. If you don’t mind, I’m gonna go now. It takes me about an hour to get into the office.  AS: Okay well, have an exciting journey and they could at least send a car for you, perhaps.  JJ: I’m sure they would, but it’s actually slower, heading into London.  AS: Alright. Anyway, congratulations again. It’s been a pleasure speaking. Thank you.  JJ: Alright, thank you. |
| **Interview** |  |
| Q1 | How did your interest in science come about? |
|  |  |
| Q2 | Was there a particular person that influenced you? |
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| Q3 | How did you get interested in chemistry? |
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| Q4 | How important is interdisciplinarity in science? |
|  |  |
| Q5 | How did you get into AI? |
|  |  |
| Q6 | What advice would you give to a young researcher? |
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| Q7 | How important is failure in research? |
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| Q8 | Why do you think it is important to give others access to your research? |
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| Q9 | How important is it to use science to solve the challenges we face today? |
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| Q10 | Why do you think you are in the field you’re in? |
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| Q11 | What do you think are the greatest possibilities for AI? |
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| Q12 | How important has your family been to your work and career? |
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| **Podcast** | [Bawendi]  Moungi Bawendi: I think it’s so important to be well read, to understand history. Science is a part of history. To understand science’s role in our community and the world. You need to understand all these other things.  Adam Smith: The point that Moungi Bawendi is bringing up there is something that always fascinates me when I’m talking to Nobel Prize laureates. This idea that you have to be so focused on a question that you can go further with that question than anyone has been able to go before. And yet, keep an eye on the broader picture. Have the latitude to be both super focused and in Moungi Bawendi’s case, for sure, super broad. Certainly that breadth then informs what you focus on and how you focus on it. Bawendi in particular has so many outside interests. Sports, ice climbing, playing the violin reading, Zola, Nobel Prize laureates are all different. Do join me as we explore what it is that motivates and interests Moungi Bawendi.  Clare Brilliant: This is Nobel Prize conversations. Our guest is Moungi Bawendi the 2023 laureate in chemistry. He was awarded for the discovery and synthesis of quantum dots and shares the prize with [Aleksey Yekimov](https://www.nobelprize.org/prizes/chemistry/2023/yekimov/facts/) and [Louis Brus](https://www.nobelprize.org/prizes/chemistry/2023/brus/facts/). Your host is Adam Smith, Chief Scientific Officer at Nobel Prize Outreach. This podcast was produced in cooperation with Fundación Ramón Areces. Moungi Bawendi is the Leicester Wolf professor at the Massachusetts Institute of Technology. He talks to Adam about how as a 10-year-old he ploughed through the complete works of 19th century French author Èmile Zola, by what you don’t understand should excite you and how for him, rock climbing puts the balance in balance. But first techniques may advance at breakneck speed, but the scientific process remains the same.  Smith: I wanted to start by reflecting on the extraordinary pace of change in science. You are a relatively young chemistry laureate, but even in your career, there’s just been a staggering change in the field when you were an undergraduate studying chemistry and physics, quantum confinement, the idea that you could change the properties of tiny particles depending on their size, was something you read about in textbooks. It was theory. Now we’re surrounded by devices making use of technologies that have been developed by you and others that use the principle of quantum confinement. It’s just a wonder how fast things change really.  Bawendi: I couldn’t agree with you more. The pace has been incredible. When I look back on just the equipment that we were using when I was an undergraduate. We didn’t have computers set up to run experiments back then. Everything was manual, knobs and stuff like this, pens, we didn’t have screens to look at. Everything was analogue pretty much. The acquisition of data is so much faster today. Part of the change is really the ability to cycle through data so much faster than we used to. That’s for the acquisition and then the analysis. So much more powerful today. My students can sit at home, run the experiment from home, and then on their PC just run incredibly sophisticated software that you just couldn’t do in 15 minutes they can do something that would take months.  When I was starting out as an undergraduate on a big computer that you had to have special access to, it’s just amazing. Quantum confinement is certainly one thing, but in nanoscience there’s so many other materials that have popped up since then. All the carbon based materials like graphene and things like this and nanotubes and buckyballs that are part of the everyday world. In biology, we have seen incredible progress and it’s just a completely different world and it just keeps accelerating it seems.  Smith: I imagine that as a scientist, you don’t feel very different from how you felt when you first embarked.  Bawendi: Yes. In terms of the thinking, in terms of the questions that we ask, it’s the same process. You get excited by results that you don’t understand. The unexpected is what we as basic scientists, what we live for, trying to understand it and make sense of it and move on. But that cycle time is much faster. We’re able to ask much more sophisticated questions now than we were able to do before because of the availability of equipment that wasn’t there before. I would say the one thing that hasn’t changed in terms of slowing things down is our ability to make samples. Once we have samples, we can really run them through a gauntlet of really sophisticated tests.  Smith: That was the key thing that you worked on for so long, wanting to ask questions about the physics of quantum dots, but needing to be able to make things that were reproducible. But you could actually study.  Moungi Bawendi: Yes. That part is still really painfully slow.  Brilliant: It is so early in this conversation, Adam and I already have so many questions. You’ve mentioned quantum dots, Moungi Bawendi mentioned quantum confinement. Can you help us to understand what’s going on here?  Smith: Yes, it’s getting complicated quickly, isn’t it? Oh dear. Quantum dots are tiny particles that behave differently depending on their size. In Moungi Bawendi’s hands, they become particles which have a whole spectrum of different colours, which are becoming incredibly important in all sorts of different applications. They’re an example of quantum confinement, which is really quantum mechanics in action. When a particle becomes very small, the electrons in it can’t go anywhere. They’re confined within a particular space. It’s often described as the particle in a box situation. That constrains the energy levels that the particle can have and the transition of electrons between those energy levels creates different sorts of properties, including that they shine in different colours.  Brilliant: I love this idea of them shining in different colours. What sort of size does it have to go down to for that to happen?  Smith: Very good question. We’re talking very few nanometres, sort of the one to 10 nanometre range.  Brilliant: Amazing. That’s hard to sort of visualise.  Smith: 10 to the minus nine meters. Yes, it is hard to visualise. We’re above the atomic scale, but we are just a few molecules put together, a few atoms put together.  Brilliant: So I guess at that kind of scale, it must be very hard to make and work with samples like this.  Smith: Incredibly. One of Moungi Bawendi’s great contributions was to take the initial finding that his supervisor Bell Labs’ Louis Brus, who shared the prize with him had made, which was that properties were changing with the changing size of these semiconductor particles and get to the point of being able to reproducibly make particles of a certain size, which would then have dependable properties. That was a huge breakthrough being able to make that happen.  Brilliant: What are the applications of that? If you, once you can make those dependable size tiny particles, what can be done with them?  Smith: Then you can have things that have a particular colour and dependably have that colour. Then they’ve been put in, for instance, the quantum dot screens on our flat screen, TVs. They can be used for biomedical applications. They can also be used for all sorts of electronics applications. The world is just beginning to find out what we can do with quantum dots.  Brilliant: Were the applications evident early on?  Smith: I don’t think they were at all. I can’t say whether they had an inkling that things might come out of it as they did. But the initial discovery was made for completely different reasons. They were studying semiconductors. They made an observation that quantum mechanics was becoming real in front of their eyes, if you like. They got interested in that and they studied that because it was a fascinating question, what’s going on here? Certainly at that point there was no thought of, okay and what can we make out of this? It was just pure fundamental curiosity that was driving them. In our conversation, Bawendi himself makes that point very strongly.  Bawendi: If you look at technologies that we have today, they have roots 20, 30, 40 years ago in curiosity based research questions that people were asking because they saw something that they didn’t expect or because they were exploring a topic with no real idea of where to go. It’s not something you can write in a grant proposal. I’m going to do this, this, and this, and in three years I’m going to get this. That’s not how curiosity based research work. You start off with an idea and then you’ve got to switch. There’s always these bifurcations and you change path depending on what you see. You have no idea really where it’s going to go. You certainly don’t know what the applications are going to be. When we first started this quantum business, when I was at Bell Labs and when Louis Brus and his coworkers were studying the application initially that was in mind was to use these things as lasers. I remember when we made the little solutions of these quantum dots, initially the first thing we did was to put them in front of a high power short pulse pump laser to excite them in a cavity. Trying to get these things to laze and they just would not laze, one of my colleagues at the time said you can get blood to laze here. These just don’t laze.  Smith: Clearly.  Bawendi: That was the wrong application.  Smith: Indeed.  Bawendi: The motivation was basic science. The motivation was to understand this transition from atomic properties to bulk properties. They’re so different from one another and atom looks nothing like the bulk and the bulk looks nothing like the atom that it’s made from. Somewhere along the way you have to have a transition from the atomic to the bulk properties. How does that transition go about how big do you have to be? Are there any special things that happen between, that’s really the overarching curiosity question that drove this?  Smith: It’s such a beautiful question. How do you go from the atom to the bulk solid? What happens?  Bawendi: Right. It’s a question that was being asked at the time by a bunch of different communities. The closest community to us was largely physicists, but also some chemists studying clusters of metal atoms made in high vacuum in something called a molecular beam. Basically you have a furnace and you heat up a vapor of a metal. Then you have these atoms that are now in the gas phase and then in a normal pressure sort of chamber. Then you have a little hole, and then you have a stream of these atoms that now go into high vacuum chamber. As they go in that stream, they collide with each other and they begin to form clusters of 5, 6, 7, 8 atoms. Then you send these through a mass spectrometer to analyse how many atoms you have. The first thing you do is you ask a question, are there any special clusters that come out?  Bawendi: You know ones that are more stable than others, magic sizes. You find that yes indeed, there’s some numbers of atoms that are favoured, that seem to be more easily made than others. Then you go to the theorist and they calculate the structures of these 6, 7, 8 atom clusters and try to understand how they’re bonded together. It’s sort of like the reductionist view. I start one additive at a time and I begin to build the bulk. If you do it one additive at a time, going to be a really slow process to get to a million atoms. Those are very clean experiments. They’re beautiful experiments since I started in this field 30 years ago. Basically our interest was really focused on the small particles. The ones where quantum confined was really obvious. You see these transition of colours from the quantum dots, that’s really obvious. Your eyes see the quantum mechanics. It’s an incredible visual gratification.  Smith: That’s an amazing statement. Your eyes see the quantum mechanics. Would you have imagined as an undergraduate that you would be in that position of making that change happen before you on the bench  Bawendi: No. You could say that I see quantum mechanics all the time because quantum mechanics is at the root of everything that we see. Making up molecules from atoms, that’s quantum mechanics. But it’s not a simple quantum mechanics, it’s this bonding of atoms to make molecular bonds, etc. This is more complicated. But the particle in a box, one electron in a box, as the box gets bigger, this is something you teach in freshman chemistry or early physics. It’s a model system. It’s a toy system to begin to understand at a qualitative level and to have an actual material that shows this. To me, that’s just amazing. That’s beautiful. But more recently driven by quantum optics and quantum computing applications, we’ve been investigated much larger particles. Instead of the 5 to 10 nanometre range, we’re going into the 2030 nanometre range.  It turns out, even though they don’t have these visual properties, you don’t see the colour change anymore when you go to 15 to 20 to 30, it looks like by eye a piece of the bulk. But then we start doing these more sophisticated experiments and we find that we’re still not at the bulk yet. There’s still these really beautiful properties that were unexpected to us that are still changing. For the applications that we’re looking for, like these quantum optics applications or quantum computing applications, it turns out that there’s a sweet spot right there in the quantum mechanics evolution of the material that is really beautiful. Most of my lab now is going into that direction, at least the part of my lab that’s on quantum dots.  Smith: I’ve heard you describe this as creating a new periodic table.  Bawendi: Yes, at the beginning where we’re just making one material. Can you selenide? But now over the course of the last 30 years, people have used this methodology of not just making the particles but using electron microscopes, X fraction, all sorts of tools to put a picture together. Use that methodology and keep true to the idea that you want really great material system, really focus on size, distribution, crystal quality, understanding the surface. You’re not studying defects, but you’re really, truly studying the properties that come out of just changing the size itself. Now there’s so many materials that people have developed within this field. Not just optical materials, but magnetic materials, metallic materials, all sorts of semiconductors. Each one of them has unique properties. If they’re all well characterised and all have the same size within each material class, when you put them together, you can begin to build new constructs.  You can begin to build things that look like crystals, where the particles now are the equivalent of the atoms. They form cubic crystals and face centre cubic and the hexagonal crystals, etc. Depending on what you do with them. The challenge now is to get them to talk to each other just like Adams and a crystal talk to each other. That generates the new properties of the crystal. You get connectivity, etc. Now the challenge that people are beginning to solve is how do we get these things to talk to each other so that the properties, so the different components that you put in there, or even just the same component, when it starts talking to each other, you begin to see collective effects, effects that need multiple atoms to talk to each other. There have been reports of people for many years now, people making dimers. They take two particles and you connect them together with DNA or some other linker and change the difference in length between the two to try to get them to talk to each other. I would say that it’s a work in progress. Slowly we’re beginning to understand what it would take to create these new properties, but there’s a lot of progress.  Smith: It’s obvious that the possibilities are so extraordinarily large and must be increasing exponentially as you have different materials being created. And then within each of those materials, the size of the material makes a difference to its properties. Then you can combine these and people are producing new things all the time. The potential toolbox becomes bigger and bigger and bigger.  Bawendi: Yes. It can sound overwhelming. I suppose if we had an all powerful AI, we’d just ask the AI, okay, so what should I use? It would spit out the right answer. But we’re far from that. Now it has to be the creative mind that has to try to make educated guesses on what’s going to be interesting and important, and then try some things, see what happens, and use those results or the failures or the new understanding that comes to guide you into making it better. Combined with theory, I think theory has definitely a place to play in that exploration.  Smith: Absolutely. There are two strands I’d like to pick up on there. One is the theory aspect, because you came at this originally as a theorist, and indeed I suppose your father was a theorist, you graph in a very theoretical environment. He was a mathematician. Let’s combine them because there’s you as the theorist. Then I wanted to ask you about your own creative mind since you raised the idea. I don’t know if you ever have the time to stop and think about how you approach problems, but do you have any reflections on your own creativity?  Bawendi: From the very beginning in this particular field, theory was simple enough that you can get a lot of intuition out of it. It’s the intuition that you gain from this fairly simple theoretical, and it may not be perfect. I think people sometimes misunderstand the role of theory. They think that you have to have theory that exactly explains the data that matches all the numbers that come out. But really what we’re looking for is a theory that explains the trends. It doesn’t have to be perfect, but if it can catch the interesting parts of the trend where the trend begins to deviate from a linear line, for instance, or things like this, right? It may not be at exactly the right size, but it catches this evolution and simple theory, like if it’s simple enough, then an experimentalist like me can get intuition out of that to begin to ask new questions. Guided by this understanding.  Smith: When you say get intuition out of it, what do you mean? How does that work?  Bawendi: That’s actually a hard question.  Smith: Sorry.  Bawendi: It’s something that you try to teach graduate students how to get intuition. If you have enough background and you see something happening that can be explained by fairly simple theory, then you can use your background to add on top of that simple theory, or you can try to apply that simple theory to other materials. Or basically you try to extrapolate from what you think you understand to outside of the gram where that simple theory may be applicable. Intuition is hard to teach and hard to explain.  Smith: I completely understand. Of course it’s quite usual to hear scientists who have done great things talk about having scientific taste or intuition or some kind of feeling for where to go. I don’t think anybody’s been able to describe what that is. It’s obviously the combined experience of having thought about it and done it for year after year after year. Somehow the fruition is this intuition that you’re talking about. As you say, teaching it to the young is very challenging.  Bawendi: I’m going to go to that teaching a little bit. Because being a graduate student and even a postdoc is an apprenticeship, really that’s what it is. You work with somebody who has a lot more experience asking questions and maybe the person like me maybe have become completely incompetent in the lab because the equipment changes so fast and we just don’t have time to stay up to date on how to work the equipment. But we’ve learned to ask questions and we’ve learned to look at data that comes out. We know enough about the equipment that we can guide what should be done. That 30,000 foot view of the experiment, that’s what we try to teach through an apprenticeship by asking questions and having, so when a graduate student starts they have no idea about any of this, right? So we pair them up with more senior students, or we give them a project that’s to begin to cut their teeth on. There’s a lot of failure, but out of failure sometimes there’s gold nuggets, right? We have to teach them how to recognise these gold nuggets that they may not recognise and teach them how to ask questions.  Smith: In your Nobel Prize lecture, you referred to Louis Brus as the person who taught you how to be a scientist. I guess that many things contributed to you becoming a scientist, but was there something in particular that he showed you?  Bawendi: I think it’s that process of asking the questions that really clicked because it was a new field, right? The fields that I was working on before had ambassador literature behind them. Many groups and communities had worked on these for so many years. They were mature fields and the progress was evolutionary stepwise. And you could write a paper making a little step and making another little step, right? Which is certainly fine. But the big questions of the fields were hard. They were really hard. One person by themselves wouldn’t be able to begin to address them. It was a community effort. You have to put everything together. But this particular field, when I met Lewis and started to work with him, nobody else was working on this. Every question was a new question and guided by simple theory.  Because he’s the one who taught me how to really use simple theory to guide yourself again through this apprenticeship, right? Then when the theory doesn’t work so well, you add another layer, but you don’t want to add too many layers altogether because then you lose the intuition, you lose the ability to predict what you think should happen. You abandon that and you give it to the theorist to tell you what to do. As an experimentalist, you really need to be able to guide yourself to the next question. He taught me that. He taught me how to think like that, which for this field has been really important.  Smith: How has it been being in a field, which, as you say, when you started out, it was sort of yours for the taking, there was nobody else there, and now it’s so huge. You’ve witnessed that evolution, you’ve been part of it. How does it feel to travel that road from having it to yourself, to sharing it with so many?  Bawendi: At the beginning it’s a little disconcerting because there are a lot of really smart people out there. Then suddenly it becomes competitive and you realise that, my background was in physical chemistry, not really in synthetic chemistry. Then people with more intuition and chemistry come along and they can solve problems they had no idea how to solve before, which is great, but it makes you realise, you can’t do everything anymore. You got to pick things that you’re good at that really interest you at the beginning. Everything was wide open and you could follow a path that interests you and at the same time play in other directions. But unless I wanted to run a group of 500 people, I couldn’t cover everything. I really had to pick the directions that were particularly interesting to me and watch other people solve problems I wish I could solve, but I can’t.  Smith: But I suppose it’s about having the intuition and confidence to know where to head. Obviously you can’t do this 24/7 for a whole lifetime, although I imagine that there have been periods where it has been completely absorbing. What do you do other than concentrating on the work to kind of give yourself the space to reflect on what’s happening in the lab, which is so necessary, I suppose, to making good decisions when you get back in the lab?  Bawendi: I guess I have two parts to that. There’s my work life and my personal life on my work life. As I matured as a scientist, as a professor and became more interested in technologies, I get interested by many fields and really like to learn about other things. Maybe not at a very deep level, but at least know about them. Being in a place like MIT and being exposed to engineering and other scientific fields and medicine across the river and Harvard Medical School and a lot of startups around here, you really are exposed to so many things that are so interesting and I love that. Those things give me ideas of how to go back to the lab and take different directions, whether it be applications of the quantum dots in Bioimaging, which we did 20 years ago or so, that has been really fruitful.  Bawendi: You meet people, you meet different communities, different communities that then allow you to think about fundamental questions that you can ask in your lab, but also how to apply these things and basically touch other communities, whether that be through science or through entrepreneurship or just by learning. That feeds me intellectually. I think that’s really important. If I were just working with quantum dots or nanomaterials thinking about their properties all the time, that would be exhausting. I think it would get old after a while, but it’s the ability to then connect what you’re studying to this huge scientific endeavour. I’ve worked with people at NASA for instance, and from that I’ve learned about problems of sensing things in space that maybe quantum does have nothing to do with, but I love these questions that people ask.  Smith: How about home life? How does that contribute to the work?  Bawendi: I do take time to do things outside of the lab. I like to climb. I rock climbing in the gym and outside. I have a partner that showed me the beauty of ice climbing. I’ve been doing that for a number of years.  Smith: I should mention as an aside that we run these dialogues in Stockholm as part of Nobel Week, these meetings on the 9th of December. At one of those we had one on risk and we invited Alex Honnold to join this.  Bawendi: My goodness. That’s a different category entirely. His idea of risk is not my idea of risk. I like to travel and see new places. I like to cycle. I used to be able to run. I used to run quite a bit, so I like to be outside. My lab has, since I started, I’ve had a retreat for my lab every year in January, February, where I rent a house for a few days and the whole group goes up and we all ski together. Those who don’t ski, that’s fine. They can learn or they can stay in their chalet or whatever and enjoy the beautiful surroundings. Ee bond together. The students all cook together for a number of meals. This is a way for me to ski with a bunch of people.  Smith: Do you talk about work on these retreats?  Bawendi: We always work. We talk about all sorts of things, but it’s an informal way to really discuss work in a different setting where we can talk about these bigger ideas because when you’re in the lab, day in, day out, you’re so focused on the details of a particular project. These students can lose sight of the bigger picture. This is a setting where on the way up in the car, we start talking and we can just philosophise about science, where we’re going, the big pictures. I think it’s a wonderful way to get students to think about these things.  Smith: When you and your partner are ice climbing, does work pop into your head at those moments?  Bawendi: No, it doesn’t. There’s no room in there for anything but the surroundings and the activity that you’re doing. That’s a wonderful thing.  Smith: It sounds fairly perilous.  Bawendi: I think if you can keep yourself safe, let’s just say you can minimise your risk as much as you can. You look at the weather, you look at the quality of the ice, you look at all the variables, and you have to learn very quickly when to turn back.  Smith: What’s the attraction?  Bawendi: The attraction, it’s the intense physicality, the intellectual problem solving that goes along with it. That combination, to me, that’s the attraction. When you’re climbing, you solve the problem. How do you get from point A to point B? It’s a problem. You have to solve it.  Smith: Is that how you grew up? Were you were an outdoors sort of child doing not perilous things, but exciting outdoors things?  Bawendi: Absolutely not. My father was completely removed from any of that stuff. He was a mathematician who just loved math and was actually not very good at any of that stuff. He managed to break his toe skiing in the boots. How does that happen?  Smith: He’d found the right path for him behind a desk with his mouth.  Bawendi: Yes. When I was a child, I just loved to go out and just run or ride a bike. I didn’t really discover my taste for more active things than running and cycling until I was a professor. I met people who taught me, showed me this part of these activities. I loved them.  Smith: What about your taste for science? Was that obvious to you when you were growing up? Was it clear that that’s where you would end up?  Bawendi: I think so. I think that I was always thinking that I would go into science. Maybe there was a brief period when I thought I would go into medicine, but it was going to be science oriented from a very early age.  Smith: Do you think that’s necessary for people who want to go into it? Or do you think you can?  Bawendi: No, I don’t think so. I’ve seen people, some colleagues that were English majors and were interested in science on the side and then became scientists. I don’t think you need to be into science from a very early age. I think you can go into it later.  Smith: These day one of the refrains when he is constantly from young people around the world is that education systems, pressures of exams, selective education, it all makes people make decisions very young. Then it’s increasingly hard to switch gear and realise that actually maybe that wasn’t where you wanted to be or that you want to switch on later.  Bawendi: I think that’s the feeling for sure. I’m a really strong believer of a liberal arts education, the kind that we have in small colleges here, or some universities. I think that there’s a certainly a trend towards a more career oriented education that focuses too quickly on one subject, let’s say, or a couple subjects. I think it’s so important to be well read, to understand history. Science is a part of history to understand science’s role in our community and the world. You need to understand all these other things. You need to understand social dynamics. Those things are so important. I always liked to read when I was a kid, I would get into so many books and my parents moved around a lot and I was constantly in new schools and new communities.  I would just get lost in novels, old French novels or translations of old Russian novels. Really thick things. I remember one year when I was 10 years old, I think my parents rented a house and they had this collection of all the books of Èmile Zola. I started reading them one after the other. I think it’s super important for us as a community, as a society, not to lose this broad education. Because when you’re 20 years old, you may not know what you really want to do. That’s really perfectly fine. You can come to figure out what it is that interests you a little later, and you’ve lived a life that you can bring to that field and contribute things from a different direction. I think that’s really important.  Smith: I know you play the violin as well.  Bawendi: Yes.  Smith: Do you play with friends?  Bawendi: I don’t really play much anymore at all. Basically when I got to graduate school, my violin career kind of ended. I still play it every now and then, but not to the extent that I did when I was into my mid-twenties. There were too many things to do.  Smith: But it never leaves you.  Bawendi: It never leaves you. I learned a bit of piano. I like to pick up instruments and just learn how to do simple things on them. It never leaves you, it’s definitely part of you.  Smith: If the right three students join the lab, you could then form a quartet.  Bawendi: Yes. I love music.  Smith: It’s been an enormous pleasure speaking to you.  Bawendi: It’s my pleasure.  Brilliant: You just heard Nobel Prize Conversations. If you’d like to learn more about Moungi Bawendi, you can go to nobelprize.org where you’ll find a wealth of information about the prizes and the people behind the discoveries.  Nobel Prize Conversations is a podcast series with Adam Smith, a co-production of Filt and Nobel Prize Outreach. The producer for this episode was Karin Svensson. The editorial team also includes Andrew Hart, Olivia Lundqvist, and me, Claire Brilliant. Music by Epidemic sound. for another episode that mixes the quantum world with a touch of French literature. Check out our episode with 2022 physics laureate [Alain Aspect](https://www.nobelprize.org/prizes/physics/2022/aspect/podcast/). You can find previous seasons and conversations on Acast or wherever you listen to podcasts. Thanks for listening. |
| **Telephone**  **interview** | Moungi Bawendi: Hello?  Adam Smith: Hello, congratulations the award of the prize!  MB: Thank you, thank you.  AS: Did the news wake you this morning?  MB: Absolutely, I was sound asleep!  AS: [laughs] A nice way to be woken up.  MB: Definitely! Unexpected and very nice.  AS: What was your first action on hearing that you’ve been awarded?  MB: Yes, well I wasn’t sure it was true, and I was trying to wake up. And my wife was telling me “What’s going on, what’s going on?” And then I realised it’s true, and so I tried to figure out, you know, clear my thoughts, and yea, it’s quite an honour and quite a surprise.  AS: Of course, and one of your co-laureates was of course your post-doc supervisor, Louis Brus.  MB: Absolutely yes, Lou Brus, a giant in the field, yes.  AS: What was it like working together?  MB: He is an amazing mentor, he is a true scholar, he’s dedicated to science. I learned so much from him, really, he moulded me as a scientist. You know, I try to emulate his style of mentorship with my own students.  AS: And what is that style? What do you do?  MB: You know, you basically, you guide the students, you let them explore, and you provide feedback, but you have to teach them to become scientists through, gentle guidance.  AS: Discover what’s best about themselves I suppose is the key.  MB: Exactly, yes.  AS: It was thirty years ago that you perfected the synthesis of colloidal quantum nanoparticles, did you imagine then that that would be the kind of route for the rest of your career, up till now, that this would blossom so?  MB: No, absolutely not. It was with my students, Chris Murray and David Norris, that I did this at MIT when I first started out as an assistant professor. It was basically my first work there; it was built on work that I had started at Bell Labs with Brus. And at the time it was really to understand the physics of the material, we needed a really good samples to understand the physics, but I had no idea this would become what it is today. Over the years, you know, many of us in the field kept thinking, “When is this going to end?” But the field just keeps on giving, and it’s been really amazing to see that, the community is so large today, who knew it would be like that.  AS: There’s so much to be excited about in it, is there anything in particular that pops into your mind now, that you’d say was the most exciting thing at this moment.  MB: For me? No, it’s still a blur.  AS: [laughs] No, I meant in the field, rather than in the day.  MB: Oh, I mean, you know every few years something really exciting – when I go to conferences and I hear people talk about their work, I’m always amazed at the quality and new things that are coming out, so it’s an ongoing excitement I would say,  AS: I know it must be difficult to put into words what is going through your mind now about the day as it’s unfolding, but how do you see the prospect of today and the days to come as a new Nobel laureate?  MB: I think it’s going to be very chaotic today, and I’m supposed to teach at 9 this morning and I’m not sure what’s going to happen. I’m sure MIT has some events that they are going to plan and so I’m just going to let it ride.  AS: sounds very wise, and I think you’re going to have some very happy students at nine o’clock.  MB: Oh, I’m sure I will!  AS: Exciting for them, how lovely. Thank you very much indeed, once again congratulations.  MB: thank you so much.  AS: Bye bye.  MB: Bye bye. |
| **Interview** |  |
| Q3 | Where does your passion for science come from? |
|  | Moungi Bawendi: I was born in Paris and my father was a mathematician – became a professor in mathematics. My mother was a high school teacher in math. Eventually when we moved to the US she became a computer scientist. My maternal grandfather was a doctor. My maternal grandmother was a pharmacist, so you could say I was surrounded by people who had interest in sciences. As a child, my parents moved quite a bit, so I grew up in Paris, outside of Paris and in Tunisia for a few years, and in Nice in France. Then we moved to the United States when I was ten – West Lafayette, Indiana, which is a university town, and we moved back to Paris when I was 15, then back to the US and the same place. Through all these movements, you could say that one thing, which was a constant with science. The literature goes back and forth and everything else, but math and science is the same everywhere. I was pretty good at it, and I liked it, and so I kept on going with it. |
| Q2 | When did you decide science was the path for you? |
|  | Moungi Bawendi: I think I was a child when I decided that science was for me. I had a chemistry set and a physics set, which was really electricity and magnetism. I don’t remember when that was, but I was pretty young. I was maybe seven or eight when I started with these sets. I don’t think you could buy these sets today because I think they would be considered too dangerous for children, but I really liked them, they were great fun. I remember crystallising some solutions of some copper compound. In the electricity set there was a little piece of it that amplified the voltage and you could feel the voltage go up with your hands, complete the circuit. And you just learn a little bit of practical science this way. It was great fun. |
| Q3 | What do you enjoy about science? |
|  | Moungi Bawendi: But for me, the curiosity is really the fundamental aspects of it combined with the applications. I started into science because I was curious about answering really fundamental questions about how the world works. When you’re doing science at the beginning, you’re asking very particular questions. Not big questions about why is there life or big philosophical questions, but why is a molecule doing what it’s doing and how can I use math and experiments to understand it and explain it? That always is something that … It’s like solving puzzles, it’s basically very practical science puzzles, figuring out what experiments to do, and then data comes out. I find it always so exciting when you get data and you start trying to answer that puzzle, to figure out that puzzle, especially when the data isn’t exactly what you thought it was going to be, and then that increases the surprise. It gets you into thinking about new directions.  This process of asking some questions, developing an experiment or a thought process to answer it, and in the process of answering the question, discovering new questions, I think that’s really the exciting part of science for me. In the field that I’m in, because it was a new field, every question was a new question, every answer was a new answer. We created to the community, my community created a new material or set of new materials which had properties that didn’t really exist before. When that happens, then you start thinking about, okay, what are they good for? Can we use them for something? That aspect of it became also very interesting, so even though at the beginning I wasn’t thinking, as a young person, I wasn’t thinking about the applications, I was only thinking about why does the world work the way it does? After a while, I started thinking, what is it good for? What can I do with it? That process, to me is very exciting, because it allows you to learn a little bit about a lot of different kinds of fields. It allows you to see how your discoveries can touch fields that you may not have learned anything about before. In my case we were able to touch medicine, biology, electrical engineering – all sorts of fields that I really didn’t know very much about – but I found it very exciting to learn about them and how we could influence them. |
| Q2 | How do you cope with failure? |
|  | Moungi Bawendi: Sure, my science is often a process of failures. For instance, when I was at when I first came to MIT as an assistant professor and set up my lab, I tried t, in some ways recreate the atmosphere that I had been in at Bell Labs. I hired a student that was more synthetically inclined, and a student that was more inclined towards doing physics types of experiments, and another student that was going to do some magnetic work. These more ‘physicsy’ kind of students they needed samples, and the synthetic students was going to help provide samples. We tried to reproduce some of the things that I had done at Bell Labs, and it didn’t really work as well as I expected it to work. At the very beginning, I felt like things were not working, there was kind of a failure. The material wasn’t as good as I had hoped we could make it be. That process of having to overcome that difficulty of creating material that was good enough for my physics, more ‘physicsy’ sort of graduate students to be able to do experiments on, that’s what gave rise to the reinvention of making the material, making the quantum dots. Eventually that’s what gave rise to this work that was published in 1993, which eventually gave rise to the Nobel Prize. So that was a failure with a very good outcome, I would say. |
| Q2 | Do you have any other examples of failures? |
|  | Moungi Bawendi: My first chemistry exam at Harvard was a disaster. I chose chemistry because I was very good at it. In high school, I had a great high school teacher, and I came to Harvard, and I decided I was never going to be a physicist because it was too hard. Again, this idea that I was an outsider, this imposter syndrome, you had these students that came from these science high schools from all over the country that were so much better prepared than I was. At least I thought they were so much better prepared than I was. There was no way I was going to compete with these students, but chemistry I thought I could do.  When I came into this exam, and it was in a very large room, a place called Memorial Hall at Harvard, it’s an old church, a church-like building. Averness, there was a bird flying around, there was a proctor who was administering the test, we called him Mr Test. I didn’t know that, but that’s what he was called by the students. The environment immediately was very overwhelming. Then I saw the exam, and I knew what the questions were asking, but I couldn’t answer them. At least I couldn’t answer them fast enough, it seemed. I went to the first question, and I got paralysed. I wrote a few things down, and I panicked, and I went to the next question and panicked, the next question, I panicked and looked around and got completely paralysed. I got a 20 or 23 out of a hundred, and that was probably generous, and that was the lowest rate in the class. That was a clearly a failure, I would say. But I knew the material, I liked the questions and I thought I knew how to do it.  The problem is that I didn’t know how to study. I didn’t know how to study for an exam, a timed exam in college. I learned how to do that, and one of the things that’s important is to spend the time to do it. I developed a very systematic way of studying for exams, which was time consuming, but for me, it worked. After that, I didn’t have any problems with exams. It’s a skill, it’s really a skill that students need to learn. I was asked recently about whether it’s a necessary skill, because research is a creative process. It’s not the same as taking an exam. It’s very different. An exam does not test creativity, it tests the ability to use knowledge from a class and apply it under time pressure. I think you need both skills, that exams are not useless because the studying for them requires you to really understand material very well, because then you have to use it quickly. When you’re doing research, the creative process, you need to have all that information available to you. Even if you don’t remember it, you know that it’s there and you understood it at some point, and once you understand something, it’s somewhere deep in your mind and you can recover it. I think both skills are important for success in research. |
| Q2 | How important is teamwork in science? |
|  | Moungi Bawendi: One of the things that is really important, I think, for people to understand is that when you’re an academic scientist you rely on students. The students, your advisees that you mentor, are the ones that are spending the time in the lab solving very practical problems, and you’re giving them vision. You have a big picture of what you expect to happen, and you can help solve problems with them, but at the end of the day, they’re the ones that are every second trying to do the experiments that you’re hoping will work out. They’re the ones that come back to you and say, Oh, it’s not working. What should I do? Or when they become more advanced, in this case, Chris Murray became very advanced extremely quickly, within a few weeks, or a few months, of arriving at MIT. They solved problems that you might not have been able to imagine were problems because they solved the problems along the way – so it’s really a collaboration between the professor and the students. |
| Q5 | Have you had any scientific mentors? |
|  | Moungi Bawendi: Immediately before coming to MIT, that would be Lou Brus, the co-recipient of the Nobel Prize. I first met him when I was a graduate student, and I had gotten a fellowship from AT&T Bell Laboratories to spend a summer, which my graduate advisor Takeshi Oka had nominated me for. Louis chose me to be the person to be in his lab for that summer, summer of 1987. I had no idea what he did. I came at Bell Labs, and I was first introduced to quantum dots then and to a way of doing science at Bell Labs. The way that Louis does science, which is recently to surround himself with a few really smart people, and to have really deep discussions about fundamental issues of science and solving problems and going in a direction that really nobody else was going at the time. That really influenced me for the rest of my career. He was a really important mentor for me. For the rest of my life. |
| Q5 | What skills did your mentors teach you? |
|  | Moungi Bawendi: Patience and asking the deep questions and trying to get it right. Trying to get it right is more important than to do it quickly and get the wrong answer. To really get at the root of a question and to ask really broad, fundamental questions. And the patience also to get to the answer. |
| Q1 | What piece of advice do you have for young scientists? |
|  | Moungi Bawendi: I think that what is extremely important is to stay curious. What I see is that you can be very, very smart, but if you’re not curious, then that intelligence and that innate ability that you have is not going to get channelled. You can be very curious and that can overcome any other deficiencies you might have in your background because you’ll learn what you need to learn because you’re curious. The curiosity of trying to answer the right questions or how the world works around you, I think that’s the key, it’s really the key to success. By curiosity, I don’t mean just curiosity about some fundamental question, I really mean curiosity about how things work generally. For instance, when you set up an experiment, curiosity about how the experiment actually works, how does the equipment that you use to do the experiment work? That kind of curiosity is a very practical kind of curiosity. When things go wrong, then you know how to fix it, or you know why things might have gotten wrong in a certain way. I would say there are two levels of curiosity: this very practical curiosity of how the experiment actually runs, how it works, so that you can create new experiments, make it better, and then the curiosity of the questions themselves, why does the world work the way it is? Those are two very different, seemingly very different kinds of questions, the practical ones and the broad, more philosophical ones, but I think they reflect the same sort of innate curiosity that humans have. |
| Q6 | How has your international background influenced you? |
|  | Moungi Bawendi: Moving around has influenced me in a number of ways. It influenced me personally, in that as a child, I never really felt like I fit in anywhere. Starting as in France, having a French mother and a Tunisian father, and then moving to the Tunisia where my mother was French again, I wasn’t really Tunisian in the same way as somebody from Tunisia. Then moving to the US where nobody knew where Tunisia was in the US, I remember somebody telling me, Oh, Tunisia, they said, Oh, Tasmania, how interesting. They had no idea. And moving every couple of years as a child, you’re suddenly in a new school surrounded by new people that really don’t know you, I think that made me feel a little bit like an outsider.  I felt like that in science also, but it also made me more comfortable to be an outsider. In the field that we’re in, the quantum dot field, at the beginning there were nobody else. There was nobody else working in that area – it was really being an outsider. I was comfortable with that, but at the same time, I think that – and I don’t think I’m alone in this – but I think it’s true of many scientists and for myself with my background, having moved around and not always feeling like I belonged, people can develop a sort of an imposter syndrome where they feel like, Yes, this is working out, but they’re going to find out that I’m not the real thing, right? So, I developed a bit of an imposter syndrome which I think I’ve had to overcome. It’s this combination of being somewhat comfortable being an outsider because you become a little bit more self-contained, and things are okay even if you’re not part of the club. But at the same time, the club is going to find out you’re not part of them. I think that’s been a big part of my life, and my career as well. |
| Q1 | What advice do you have for those that feel like outsiders in science? |
|  | Moungi Bawendi: I think that, and I’ll go back to in terms of overcoming imposter syndrome, as in terms of advice for that, I’ll go back to thinking about curiosity, because really in the end when you’re doing science, fundamental science, fundamentally, you’re working for yourself to answer deep questions that you might have yourself, not to answer questions that other people have. As long as you’re true to that, true to yourself, and believe in yourself, I think you can overcome that, you can succeed. It all comes down to curiosity. |
| Q11 | Do you think diversity in science is important? |
|  | Moungi Bawendi: I think diversity in science is very important for many reasons. One of the reasons, for instance, is to inspire youth that may have no idea that that’s a possibility for them. I think that one of the most important reasons why you want to have diversity in science is to make sure that that path is one that is recognised to be a viable path for as many people as possible. I think it’s only by allowing these possibilities, to be very broad, that as humans, we can get and progress as fast as we can by letting as many minds as possible think about hard questions. I think that’s extremely important for that reason. I think science is international to begin with. Science, at least in the US, is one where there are many immigrants from all sorts of countries, so it already begins with a certain amount of diversity because of that, and we can further that diversity because there are people that are not well represented still in science for sure. Women are still underrepresented in science, in many fields of science, to a degree that is still to me shocking in some ways. We need to do better on that. I think we have a lot of work to do. I think there are positives because of the way that science is already in some countries – I’m thinking about the US – a way for people who may not really belong, say, in the business world or other places, to find a home. That’s been true for a long time. If we can take that idea and broaden it out, I think that would be a really good thing. |

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| **Chemistry\_2024-2000** | |
| **ID** | 0304 |
| **Biographical** | I was born in Cleveland, Ohio in 1943. My earliest memory is my father Victor John Brus coming home from World War II in 1946. He was an officer in charge of communications on a large US Navy troop transport and assault ship in the western Pacific and was returning home after an absence of more than two years. During his service, my mother Mary Alicia Megede and I lived with her parents in a rural Missouri town of southern culture, where her family of German origin had operated a jewelry store since the Civil War. My grandmother Megede ran the store while my mother took care of me.  My father took a job as an insurance administrator in downtown Chicago, and we moved into a small rowhouse in the South Shore area, perhaps 4 miles south of the University of Chicago. This neighborhood was somewhat dangerous then and much more violent now. In 1948, my brother John was born. I walked with my mother as she went to vote in the election that year; she voted for Truman and my Dad voted for Dewey. I remember them discussing the election at the dinner table.  Tragically, my mother became ill and was hospitalized for the rest of her life. In order to keep the family together, my father’s mother came to live with us. She was in her seventies and was born in 1876. She loved us, but she was frail and had decidedly old-fashioned ideas. My Dad and I did all the housework and shopping. I washed dishes and did the family laundry on an old wringer washer in the basement. We were busy just doing what had to be done, with little time for culture. We did have a few books, as my mother had been a high school teacher earlier in life. In her absence, my brother and I did not learn common social graces, such as how to entertain visitors who came to the house, or how to talk to girls.  I attended the local Chicago public school through the 8th grade. Typically, we had 42 students in a class, and the quality of teaching was uneven. In the fourth grade I had a teacher who lectured us on the evils of communism, rather than teaching us spelling. Just as I was to go into high school, my father was promoted to head the Kansas City, Missouri, office. We moved to a pleasant green suburb in Johnson County, Kansas, which was quite a contrast to our Chicago neighborhood. I attended a far better high school than I would have in Chicago with accelerated classes. For the most part, I did well academically without much effort. However, I remember struggling on my own to read the great books, such as *The Brothers Karamazov.*  My father had worked his way through university during the Great Depression, and he believed I should work during my “spare time” after school. He got me a job as a clerk in the local hardware store. I worked there 24 hours a week on top of attending high school. The hardware store was certainly a valuable experience for the introverted, shy, and bookish boy that I was. I learned something of how to deal with different people, and how to use tools and take apart machines with my hands.  In the 1950s, the United States greatly expanded science and engineering, partly in response to the cold war with the Soviet Union. A military draft existed, and most men were veterans of service in World War II or Korea. I liked science, but never imagined I could make a career out of it. While both my mother and father were college graduates, no one in our extended family had ever been an engineer, scientist, doctor, or lawyer. I planned to serve in the military and then be a businessman like my father. In 1961 I enrolled in Rice University with a Navy scholarship that obligated me to serve on active duty after graduation. **Education at Rice and Columbia** Rice was a rigorous school that challenged me and opened my eyes. When I graduated in 1965, I had begun to think like a scientist. At Rice, the undergraduate student body was 80% male with many engineering majors. Typically, students came from small towns in Texas, and a cowboy culture prevailed. Life in the residential colleges was chaotic, with systematic drinking. Although I did not realize it, Rice was racially segregated when I first arrived. In contrast as I write this now in 2024 Rice has a black President – Reginald DesRoches, a sign of the progress that both Rice and American culture has made over the years.  We took five classes a semester and had lectures six days a week. All freshmen were required to take American History, which has remained a strong interest all my life. I declared a chemical physics major, showing my interest in both fields as well as in theory, to the extent I could understand it. I took at least one class each in chemistry, physics, and mathematics every semester for four years. None of us thought about biology; for example, I did not learn about DNA and heredity until I became a graduate student at Columbia.  Zevi Salsburg taught physical chemistry and had a strong influence on me. He was a pioneer in large statistical mechanics calculations on computers at Los Alamos. I remember him saying that the machine made a mistake every 300,000 steps, and that he hoped this would not affect the result too much. [Bob Curl](https://www.nobelprize.org/prizes/chemistry/1996/curl/facts/) was a beginning assistant professor; I did not study with him but got to know him and [Rick Smalley](https://www.nobelprize.org/prizes/chemistry/1996/smalley/facts/) well later when I would come back to review the chemistry department and to give talks. B. Frank Jones was an excellent lecturer who taught junior level differential equations. I vividly remember the fall semester in his class. There were perhaps 75 students, essentially all engineering and hard science majors. He gave out only 3 As and 7 Bs in his final grades. When I tell this now to Columbia undergraduates, they are amazed.  The Navy sent me out into the fleet during my undergraduate summers to learn something of the real Navy. These summers had a major impact on me, as much as my academic education at Rice. I spent time on an old World War II destroyer in San Diego, with Naval Aviation in Corpus Christi, Texas, and on a modern aircraft carrier in the Mediterranean. Carrying a heavy pack and rifle, I assaulted a beach in California in a training exercise with the Marines. I had a flight on a jet trainer and watched flight operations day and night on the carrier. Carrier flight operations are intrinsically dangerous. Three pilots died during my seven weeks on the carrier. I toured the Navy’s second nuclear submarine – USS Seawolf. On my 80th birthday last summer, I gave a talk (now on Youtube) which describes some of these experiences.  At Rice I became increasingly interested in science. What would happen to me after graduation when I went on active duty? Perhaps, I thought, I could serve on a nuclear submarine. To my great luck, in my senior year the Navy established a new policy opening the possibility of going to graduate school before active duty. I jumped at the opportunity. I remember thinking that “quantum mechanics is so interesting that I would like to learn more of it before getting on with my life.” So, I joined the chemical physics graduate program at Columbia in the fall of 1965, just as many others my age were sent to Vietnam.  At Columbia, most of my graduate classes were in physics. However, most of my research interests and friends were in chemistry. Both departments were strong, with outstanding faculty. My classwork in electricity and magnetism, mathematical methods, and advanced quantum gave me the foundation to teach myself new things in later years. I attended colloquia given by the outstanding scientists of the day. My advisor was chemistry professor Richard Bersohn, who had been a PhD student with [John van Vleck](https://www.nobelprize.org/prizes/physics/1977/vleck/facts/) at Harvard, and a postdoc with [Willis Lamb](https://www.nobelprize.org/prizes/physics/1955/lamb/facts/). He was trained as a pencil and paper theorist. In the 1950s and 1960s, he realized he did not like computer modeling, which was beginning to dominate theory. At this point he turned to experiment. When I joined, he had sub-groups in gas phase small molecule kinetics and in biophysics. I did a thesis on the velocity dependence of the reaction of Na(2P) with I2.Excited sodium atoms of differing speeds were generated by photodissociation of diatomic NaI in the far ultraviolet. Bersohn and I discussed all sorts of science. He gave his students wide leeway. For example, in 1968 I abandoned my thesis work for a week to read [Jim Watson](https://www.nobelprize.org/prizes/medicine/1962/watson/facts/)’s just published *The Double Helix*, recounting the day-by-day discovery of DNA structure. Bersohn was a gentle soul who had a great influence on me, and people have told me I copy his mannerisms. **U.S. Naval Research Laboratory** I was lucky again when I finished my thesis in April 1969 and reported to the Navy as a Lieutenant. Through a series of chance occurrences, I was ordered to the Naval Research Laboratory (NRL) in Washington DC. as a “Scientific Staff Officer”. NRL, the most basic of the Navy’s various R&D facilities, had perhaps two thousand civil service scientists and engineers. I had a certain degree of freedom, as NRL had no assigned responsibilities for my position. I wore my uniform only one day per week. I had no budget or lab space but did have partial ability to choose which group I joined, and what to work on. The first year, I worked in an applied physics group on chemiluminescence during surface oxidation of silicon in high vacuum. On my own, I spent one hour a day studying Kittel’s textbook on solid state physics. This was really interesting: it discussed the same issues of structure and bonding that occur in molecules. Band structure was a natural outgrowth of molecular orbital theory. Yet, in the limit of large size there were new phenomena that had no direct counterpoint in chemistry.  I worked with Ming Chang Lin on exothermic gas phase reactions that might lead to product vibrational population inversions for infrared chemical lasers. One day, I managed to blow up a large glass vacuum line by co-condensing ozone and carbon suboxide in a liquid nitrogen cold trap. I was not injured but had to pick shards of glass out of my hair. Towards the end of my 4 years at NRL, I worked with Jimmy McDonald on tunable dye laser excitation of molecular fluorescence in the dilute gas phase. We were trying to understand dynamic irreversibility in isolated molecules. All in all, I published 14 papers during my time at NRL.  When I arrived at NRL, the Navy sent investigators to interview my colleagues at Columbia. I was given a high security clearance. About a year later, an FBI agent came to talk to me. He showed me pictures of staff members of the Soviet Embassy. As it turns out, a large group of Soviets lived in the same apartment building as I did in Arlington, Va. He wanted to know if they had made friends with me. Luckily, I did not realize they were in the same building or recognize them. The agent then spent an hour or so discussing how his job was made more difficult because J. Edgar Hoover would not allow him to tap the telephones of the Soviets.  In Washington, D.C., I met Marilyn Drennan in the fall of 1969, and we were married within a year. She was a violinist trained at the Eastman School of Music. Her father had been an FBI agent during World War II and was now a Methodist minister. She had a large extended family in the DC area, and I have many fond memories of family gatherings. As of 2024 we have been married 54 years with three children – Michael, Christina, and Elizabeth – and four grandchildren. For many years, we vacationed in the mountains out West each summer. Michael is now a psychiatrist and Christina a medical doctor. Elizabeth is a teacher and published writer of fiction. **Bell Telephone Laboratories** As my time in the Navy was coming to an end, I was fortunate that my mentor Rich Bersohn wrote to Bill Slichter, head of materials research at Bell Labs in Murray Hill, NJ. They had been graduate students together at Harvard in 1946 after returning from the war. I was invited to interview and was hired in the summer of 1973. Bell Labs was the research facility of the national telephone monopoly AT&T. As I remember, there were about 350 scientists in the materials division and about 300 in physics. There were also divisions for mathematics and for quantum electronics. Bell Labs was focused on long range research to support the communications and computer industry. Our goal was to discover new phenomena and materials, to quickly figure out what was going on, and to write pioneering patents.  I set up a spectroscopic laboratory. Bell Labs believed that in research, working scientists were best positioned to figure out where the real opportunities were. There was substantial leeway to define your own project. If I wanted to discuss something, I could almost always find an expert somewhere in the building. The culture strongly encouraged open discussion. There were no students, and very few postdocs. Many projects required collaboration to assemble the necessary expertise and equipment. Over time, the management tried to assess who was especially creative in defining projects and building teams to get them done. The strength of the Labs was that experienced scientists could focus full time on a difficult problem, typically too hard for a graduate student. Occasionally, as in the cases of optical communications around 1975 and organic electronics around 1990, management would assemble a larger team for a deep sustained effort. I never wrote a proposal or had a definite budget in the 23 years I was there.  in excited electronic states of molecules trapped in rare gas matrices at 4 degrees Kelvin, using nanosecond tunable dye lasers. This experiment built upon my experience in gas phase, small molecule spectroscopy. Rare gas [van der Waals](https://www.nobelprize.org/prizes/physics/1910/waals/facts/) hosts minimally perturb intrinsic molecular structure while providing an external heat bath to allow relaxation and flow of energy into the environment. We studied the host cage effect on diatomic ICl and perfluoroakyl iodide dissociation processes, and on the formation of a small host bubble around the lowest NO Rydberg state. We observed the internal structure of the weakly bound rare gas diatomics XeO and XeF. The internal electronic structure of the (O2)2 dimer proved to be especially interesting. We also showed that the vibrational relaxation of diatomic OH was controlled by pseudo-rotational local modes with hydrogen bonding to host atoms. I also observed internal processes in large organic species, such as proton tunneling in tropolone and methyl salicylate.  In 1981, I had been out of graduate school for 12 years. I resolved to try to find problems that were more in the mainstream of chemistry. I developed pulsed transient resonance [Raman](https://www.nobelprize.org/prizes/physics/1930/raman/facts/) spectroscopy as a technique for observing vibrational structure of short-lived intermediate species in chemical reactions: one laser pulse to initiate a reaction and a second delayed pulse at a different wavelength to generate Raman spectra. Postdoc Steven Beck and I applied this technique to solution phase organic reactions at room temperature, particularly in aqueous inverse micelle solutions because the water Raman background signal is weak. I began to read the aqueous metallic and semiconducting colloid literature. We observed surface photochemistry of adsorbates on semiconductor colloids. In 1983, we first observed the band gap shift of small CdS colloids.  I decided to focus on colloids. The basic motivation for studying semiconductor colloids (quantum dots) was to understand the progression from molecule-like behavior at small size (perhaps 1–3 nm) up to semiconducting behavior at large size, and to make macroscopic amounts of intermediate size quantum dots by colloidal synthesis. Synthetic chemist Michael Steigerwald and I formed a close collaboration. This was a radical shift in my research. No academic research group in the US was interested in this problem. In the 1980s, I traveled around the country giving colloquia explaining why this should be considered a branch of chemistry. Inside Bell Labs, this subject was of long-term interest as transistors became smaller and smaller each year. I have described this work in reviews,1234 and in an autobiography written for the Kavli Foundation in 2008.5 Significant progress occurred with postdocs Paul Alivisatos who arrived in 1986, and Moungi Bawendi who arrived in 1988. Quantum Dot science spread widely as both Alivisatos and Bawendi went on to establish large academic groups. Bawendi and I shared the Nobel Prize for chemical quantum dots in 2023.  Bell Labs was entirely supported by a small tax on AT&T revenues, which were steady in good times and bad. This may sound idyllic, but as time went on, I lived under a cloud. The Federal Government sued to break up the AT&T monopoly. If this were to happen, our financial support would fade away. Each day I would come to work saying to myself, “This cannot last, I must get something significant done today.” My style of research fit very well into the Labs, and management (John Tully, Mark Cardillo, Bob Laudise, and Kumar Patel among others) supported me. I did not want to leave. Nevertheless, as AT&T was progressively dismembered and conditions deteriorated, I knew I had to leave. I returned to Columbia as a professor of chemistry in 1996. **Return to Columbia** In retrospect, moving back to Columbia was a good decision, leading to new ideas and collaborators, and to personal renewal. However, it was a difficult transition. I knew almost nothing of what it takes to be a professor. I had never balanced a budget, written a proposal or taught a class, never trained a beginning graduate student, or mentored a large group, keeping track of many different projects. The chemistry chairman George Flynn tutored me on university life and convinced the administration to build new labs for me. From Bell Labs, I brought my nitrogen dry box and Schlenk line for sample preparation. As my group grew, we built apparatus for [Rayleigh](https://www.nobelprize.org/prizes/physics/1904/strutt/facts/), Raman, fluorescence, optical reflectivity, and AFM images of nanostructures.  Common facilities for materials characterization and nanoscience were essentially non-existent. About this time, Tony Heinz was also recruited from IBM and [Horst Störmer](https://www.nobelprize.org/prizes/physics/1998/stormer/facts/) from Bell Labs. Together, with Rick Osgood, Irving Heman, Ron Breslow, Jim Yardley and George Flynn, we wrote and won NSF, DOE and Keck grants, enabling us to acquire modern equipment and to begin building a culture of collaboration, especially between synthetic and physical groups. Collaboration grew with the arrival of younger faculty, including Philip Kim, Jim Hone, David Reichman, and Colin Nuckolls. Almost every paper had multiple authors as students freely went from one group to another, making measurements and teaching each other. For example, over a period of 14 years I published 27 papers with Tony Heinz, almost all of them with additional co-authors. Working with Tony has been deeply satisfying.  The first semester at Columbia I taught graduate statistical mechanics. I had to spend much of August re-learning material I had not thought about since my time at Rice. Subsequently, I occasionally taught physical chemistry and graduate quantum mechanics. Almost every year I volunteered to teach introductory chemistry-bonding, thermodynamics, and kinetics. In this course, I often included lectures on climate change and possible life in the universe. I must have written more than 100 letters of recommendation for medical school. I enjoy teaching the basic ideas of science to smart Columbia College freshmen who go on to major in all sorts of subjects.  At Bell Labs, I had worked on single quantum dot luminescence, and now at Columbia, we began to try to understand single molecule Rhodamine 6G Raman scattering in aggregated Ag colloids. We found that intense Raman signals came from single molecules at the junction between two large Ag nanocrystals, in agreement with electromagnetic field enhancement theory. Both systems exhibited the blinking characteristic of single molecules under continuous irradiation.  This research was part of a continuing effort to understand field enhancement and photochemistry resulting from optical excitation of metal particles, initially in collaboration with Abraham Nitzan.6 We found that we could use surface plasmon enhanced photoreduction of adsorbed Ag+ ions to grow colloidal Ag nanodisks in a controlled fashion. The mechanism involves surface citrate ligands capturing “hot holes” from metal excitation, thus creating an increase in the double layer potential. This is a sort of light-induced Ostwalt ripening. Even in pure water in the dark, Ag particles on conductive substrates showed Ostwalt ripening. The mechanism involves electrons moving through the substrate to larger particles, followed by Ag atoms on smaller particles oxidizing to Ag+ ions, diffusing to larger particles which have a more negative potential, and reducing back to atoms.  Using electric force microscopy, we studied the photoionization of CdSe/CdS core/shell quantum dots as a function of the underlying substrate. Doped Si surfaces with a higher affinity for electrons due to surface band bending showed a higher quantum dot photoionization yield. We also studied the progressive self-organization of nanocrystal solutions on graphite as hexane solvent evaporated. The van der Waals attraction between nanocrystals increases by a factor of about 4 due to decreased screening in the absence of solvent. This triggers organization via spinodal phase separation in the nanocrystal 2D van der Waals phase diagram.  Rayleigh scattering is a coherent process whose intensity grows as a high power of the number of atoms in an object. The Rayleigh excitation spectrum mimics the electronic absorption spectrum and can be a sensitive spectroscopic tool for larger samples that do not fluoresce. I had been fascinated by the family of single wall carbon nanotubes (SWNTs) ever since hearing Sumio Iijima describe them in the early 1990s. Their crystal structures dictate that some are metals and others are semiconductors. The metallic tubes are unique, far different than normal bulk metals. Similar to chemical quantum dots, they show hybrid molecular and solid state properties. In 2000, we began to study SWNT electronic structure and reversible oxidation, using Rayleigh and Raman scattering. Under ambient conditions, SWNTs are sensitive to hole doping from adsorbed oxygen species, such as endoperoxides. From a comparison of two photon and one photon fluorescence excitation spectra of individual semiconductor tubes, we showed that the peaks in the SWNT absorption spectra were strongly bound excitons, and not van Hove singularities. The exciton binding energies were on the order of 400 meV. These high values result from strong electron correlation created by the 1D structure of SWNTs and from decreased screening compared with bulk 3D semiconductors.7 By growing single SWNT across an open slit in a substrate, we were able to obtain the Rayleigh and Raman spectra of non-fluorescent SWNT, which were subsequently identified by high resolution TEM at Brookhaven National Laboratory.  Our interest in SWNTs naturally grew into an interest in the chemistry of single and few layer graphenes. Like metallic SWNT, Graphene is a metal with a density of states that is so low that the Fermi level is easily shifted over electron volt ranges by charge transfer from adsorbed species. Graphene electronic structure is strongly coupled to the C=C double bond stretch mode. As such, it shows resonance Raman spectra that provide a measure the extent of charge transfer from adsorbed and intercalated species. We studied hole doping from electronegative Br2 and NO2. , As the metallic electrons are pulled out of graphene, it becomes more transparent. The local dielectric constant has a strong effect on the extent of charge transfer. Transfer is higher for internal intercalated species and lower for surface adsorbed and edge species. This is especially clear when alkali atoms are adsorbed.  Graphene is also an excellent substate for Raman scattering. Being a metal, it quenches the interfering background of fluorescence from species directly on the surface. Adsorbed R6G shows especially strong Raman as it shows molecular resonance Raman for visible lasers. **Final Thoughts** In my scientific and personal odyssey over the past seven decades, I have worked on an unusually wide range of problems. Good fortune led me from one institution to another, from one scientific community to another, and from one interesting problem to another. A common theme has been electronic structure: trying to understand what the electrons are doing. My experience in the Navy and Bell Labs has been important in shaping my approach to the rest of my life. Finally, throughout my career, I have been blessed with a stable and supportive home life. This family support allowed my career to flourish. |
| **Autobiographical** |  |
| **Podcast** | [Brus]  Louis Brus: If you studied engineering or science, it was seen as patriotic science and engineering helped us win World War ii. There was a period of time in the 1960s where many corporations thought that PhDs could do anything.  Adam Smith: It’s fascinating to listen to Louis Brus speak about what was really a different time in science, and I think a sense of duty sort of pervaded his career. But these days, I don’t think that concept comes into the equation when talking to young people about going into STEM subjects. And maybe they should, and perhaps it’s not a patriotic duty. Maybe it’s a global duty, given that the humanity and the planet are faced with so many seemingly insurmountable challenges. It’s also interesting to hear him reflect on the idea of being encouraged to do anything with a PhD. His own training exposed him to so many different spheres of science, and that’s obviously stood him in terribly good stead as one will hear. So do stay with me to explore Louis Brus.  Clare Brilliant: This is Nobel Prize conversations. Our guest is Louis Brus, the 2023 laureate in chemistry. He was awarded the prize for the discovery and synthesis of quantum dots. He shared the prize with [Moungi Bawendi](https://www.nobelprize.org/prizes/chemistry/2023/bawendi/facts/) and [Aleksey Yekimov](https://www.nobelprize.org/prizes/chemistry/2023/yekimov/facts/). Your host is Adam Smith, Chief Scientific Officer at Nobel Prize Outreach. This podcast was produced in cooperation with Fundación Ramón Areces. Brus is the Samuel Latham Mitchell professor Emeritus of Chemistry at Columbia University in New York City. In this conversation, he talks about how he found his way into science by serving in the Navy, and about the moment he realized he wasn’t cut out to command a battleship. But first, let’s hear about some of the perks of being a senior scientist.  Brus: It’s hard to think about new things when you have a big group and you have contracts that obligate you to do certain kind of research, and you have to monitor the progress of everything that’s like a business and you don’t have much time to think about things coming out of the field or things that may have been invented since you were a student.  Smith: That’s such an important point that you need time for reflection.  Brus: Yes, I’ve been studying things now that I was always too busy to actually work on mostly biological issues and genetics and so forth, just trying to understand the state of the art.  Smith: Your curiosity leads you. It’s the perfect way to approach research.  Brus: Yes, that’s right.  Smith: People complain a lot that nowadays nobody has the time to reflect, especially young people. Their phone is constantly delivering information. It’s just a 24/7 environment. But actually, when you were a child at school, I don’t think you had all that much time to reflect. Your father made you work as well as going to high school. It was a busy life.  Brus: It was a busy life, but it did not strike me as a bad thing, let’s put it that way. I was very good at academic subjects and homework and all of that didn’t take much effort on my part. Most homework could be done during the free time in school itself. I was able to work in the hardware store and actually I had a second business cutting lawns in the local neighborhood. It just seemed like the way humans normally operate. It’s very different now in some wealthier suburbs of New York and in the United States. These students, they have all these extracurricular activities. They’re being tutored for college exams and working in a store is not on the radar.  Smith: But apart from the money it brought, which I’m sure was handy, the experience of working in a different environment was helpful.  Brus: Yes, for sure. The guy who ran this hardware store was a Russian Jew. His father had come over from Russia and he was a very tough character. He had been a Marine in World War II and he was really mad at Truman because when the Korean War came, Truman sent the Marines into Korea and he called up the reserves. This guy, Alex Por, he was called back into the active duty of Marines. That was the last thing he wanted because he was running the hardware store and he had a very abrupt and abusive way of dealing with the salesman who came by from the wholesale hardware companies. They were trying to get him to buy things. He worked hard and you could see he had to deal with customers and the customers would also say stupid things, but he had to grin and bear it and not get mad.  All of this tended to have a short temper, but I learned how to do all this stuff. My father was not adept with tools and didn’t repair things in the house and all of that. I learned that in the hardware store. That’s good for an experimentalist because I was always theoretically inclined. I went into science because of the ideas, not because of the machine I was going to build, but just experience in the hardware store just gave me the fundamental foundation to deal with the apparatus that we had to build as time went on.  Smith: Yes. It sounds like it gave you the ability to deal with apparatus and also with people to a certain extent.  Brus: Yes. There are all kinds of crazy people come in as customers and you have to work with each of them.  Smith: Because something that turns out a scientific career is also about socialisation. It’s getting on with people and filming collaborations and that’s another skill you have to develop.  Brus: Basic research. It’s less important than in other walks of life, but still it’s important. You need to be able to work with students, you need to be able to work with colleagues, make collaborations and so forth.  Smith: It sounds like you had happy schooling days and then a happy time at Rice when you went to college as well.  Brus: Yeah, Rice was tough. It was a heavy course load and it is true. We had lectures six days a week. We went for lectures on Saturday morning, and I tell these stories now to my undergraduates and they just are amazed. But I liked it very much because I was well fit for the course load down there and so forth.  Smith: Was it clear to you even at that stage that you wanted to make a life in arts because you had gone to Rice as a Navy scholar, you were also in the Navy at the same time?  Brus: No, it was not clear. It wasn’t really, in my mind, it wasn’t possible for me to be a scientist as a boy in high school or as an undergraduate at Rice. In fact, in those days there weren’t that many scientists after the war. There were more coming up all the time, but it was only towards the end of my time at Rice at this in my mind, became a real possibility. But it was linked to the fact that I had to go on active duty with the Navy. There was always this complication.  Smith: Complication, but also how amazing to have the experience of stepping from the academic world of a high pressure engineering school to being out in real life and serving on destroyers and aircraft carriers.  Brus: Yes. That was a much better experience for me than working in someone’s lab for the summer, basically.  Smith: It must have been amazing.  Brus: Yes. I was in a midshipman program that was supposed to produce career naval officers after college. Because of that they rotated us through all these different aspects of the Navy during the summers, three weeks here, three weeks there, seven weeks on the aircraft carrier and all of that. Extremely vivid memories of all of that.  Smith: Were you tempted by the career?  Brus: Not really, because I recognised that I wasn’t sufficiently a leader and I had introverted personality and I would be good for technical things, but not for leading 300 men on a destroyer or something like that. Some people have a natural gift for leadership. When I was in training in the Navy, I saw two or three of these captains who were just marvelous people. The morale on their ship was a lot higher than it was on other ships. The way of organising, and it’s the same thing in business. There are some people in business who are very charismatic leaders and get more out of the operation than others. Politicians are like that. Politicians have to know when to be at the right place at the right time and to pursue an idea not too early when people won’t accept it. Anyway, there’s all these calculations going on.  Basically I had a leave of absence from the Navy for four years in order to earn a doctorate before I went on active duty. I was in the Navy, commissioned to the Navy, but I was put in the reserves for the four years so that I could attend graduate school full time. Then I looked around the country and I applied to Columbia because it had a chemical physics program, which was more to my liking. Very lucky there. Lucky that that opportunity came at the right time for me. Otherwise I would’ve probably ended up as an officer on a nuclear submarine, or I would’ve been an instructor in the nuclear power school or something like that. At the end of my time at Columbia, I was also very lucky because it just worked out through circumstance that I was able to be assigned to the Naval Research Lab rather than assigned on board ship.  That’s because I had a PhD at that point, a new PhD. They didn’t know what to do with me at the Naval Research Lab because they had not had officers coming in with PhDs before, scientific staff officers. I was like an extra person floating around and they maybe paid my salary, but I didn’t have a lab or I didn’t have research money, but I was able to join basically different groups in different divisions to work on things that were of interest to me. So I finished at Columbia and then I went to the Naval Research Lab and I realised I was very lucky to be there. It was also an opportunity at the same time in the sense that I could learn these new things, take part in the research without actually having to write a contract and build a group and so forth. Just sort of like being a postdoc. My training was in molecular chemistry, but the Naval Research lab was far broader than that and had all these engineering aspects and I attended some classified seminars and many seminars in physics and material science. That was good.  Smith: Were they happy for you to be basically asking fundamental questions?  Brus: The NRL was the most basic of the various. Navy had many different facilities across the country, but the Navy had a substantial basic research effort in the Naval Research Lab in this one location. They were supposed to basically keep track of science and look for things that happened that might impact the Navy discovery made somewhere and maybe this could be used for solve a problem the Navy faced. They had bigger efforts in certain areas, obviously had a huge section on radar, fundamental principles of radar and electromagnetic radiation, had a big section on the surface science and fundamentals of how to protect the steel ship in the ocean. Big section on the engineering of on a nuclear submarine, you have to process the atmosphere. This carbon dioxide is building up, you have to take it out and it has to be.  They had a very big section on the basic science of how to deal with gases in the atmosphere. They tried to build up first class efforts in the areas that were particularly relevant to the Navy. Obviously Navy is the most technical of the various services. Everything is a complicated machine on onboard ship. As time goes on, there are fewer and fewer jobs that involve manual labor and more and more jobs on board the ship that involve, you have to be technically trained, operate this complicated apparatus, months of training before you can go on onboard ship. There was huge technical operation.  Smith: That sounds like you made absolutely the right decision to have been part of the Navy as you went for your undergraduate course.  Brus: Yes, I don’t know that I had it in mind when I was in high school like that, but anyway, that’s the way it worked out.  Smith: Why did you choose the Navy? Do you remember why?  Brus: It was mainly because my father had been in the Navy in World War II, so I had to choose one of them. I’ll choose the Navy.  Smith: How much influence do you think it had on you growing up at that particular time, the Cold War going on technological developments like Sputnik happening around you and garnering a lot of excitement?  Brus: Similar to now, basically, so now the government very strongly encourages STEM education. It’s good for the country and good for the economy. At that time, if you studied engineering or science, it was seen as patriotic. People would always say the Soviet Union has more engineers than we do. It has more medical doctors than we do. We need to build up this strength. There had been all these improvements in society and in due to science and engineering, science and engineering helped us win World War II. This was very important for the economy. There was a period of time in the 1960s where many corporations thought that PhDs could do anything. They had no experience with research, they just were ordinary businesses. But they thought if they hired two or three PhDs and let them loose, they would make one marvelous invention after another help the company, you know, that failed, obviously. But we went through a period where that happened basically.  Smith: I can imagine people try to tempt your away, but you found your way to Bell Labs, and that’s a legendary place, which people talk about a great deal, and many have tried to emulate the research environment there. It must have been such an extraordinary environment because you had no particular directive there. Just a bit like at the Naval Research Labs, you were free.  Brus: They wanted you to create your own program, but it had to be in the context of the subjects, again, that were important to the telephone system. They did not have a big program in biology. As time went on, they developed one department, but that was like one department out of 40 departments or something like that worked on biology. You worked in a certain area and you were supposed to invent new things, just like the Naval Research Lab, invent new things. The main thing that would come out, that would be a very valuable patent if you’d figured out something in advance. It was a very valuable patent. That gave some economic leverage to it. But it was a curious situation in the sense that because it was more like a federal laboratory than it was a corporate laboratory, because it was a regulated monopoly. Part of the regulation was that at and t could write these valuable patents, but they were also forced to license the patents to companies in the US who wanted to use them because the patent had been developed using money from their regulated monopoly. Everyone had to use the telephone system. It was a great research operation and it made for a very strong telephone system. But it was not a great money making operation. No one got rich from it, let’s put it that way.  Smith: No, but an awful lot of discoveries poured out.  Brus: That’s right. Great place to do physics.  Brilliant: Here we are again, Adam, with another Nobel Prize. What did Louis Brus discover?  Smith: He discovered quantum dots, which have become a very big deal. Back then what he found was that some particles he was studying, some particles of semiconductors seemed to change their properties depending on their size. That was truly remarkable because physical properties aren’t supposed to change his size. If you’ve got a lump of something and it’s the one size or another size should behave the same. But in this case, when you get down to very small sizes, things begin to behave differently. He recognised that that was very interesting. Something was going on.  Brilliant: He must have been really surprised and excited. In what way did the properties change?  Smith: He was studying a semiconductor called cadmium sulfide, and he was studying it in a colloid.  Brilliant: What is a colloid? I sort of vaguely recognise that term from school chemistry lessons, but I’d love a reminder.  Smith: A colloid is just a suspension of tiny materials in liquid. Most common example we encounter on a daily basis perhaps is milk. Milk isn’t a solution. It’s a colloid where little bits of protein or fat or phosphates are suspended in this material, which makes it opaque. He was studying a colloid of cadmium sulfide in a car liquid. When he shone light on that, he found that the particles absorb light differently depending on how long that colloid had been standing. He worked out that what was going on was that the particles were aggregating over time and getting bigger. Depending on their size, they absorbed light differently. That shouldn’t be happening if things behave the same at different sizes. But it was, and he studied it.  Brilliant: If different sizes were absorbing light in different ways, how did this present itself? How did he observe that?  Smith: He observed it in the absorption spectra of the particles. But what he worked out was that these dots, these little particles were behaving as described by quantum mechanics. Quantum mechanics predicts that very small sizes, there’ll be discreet sets of energy levels in particles that are governed by their size, and they would result in different sorts of absorption spectra. With much refinement and study that’s gone on to produce a whole world of different quantum dots of different colors. But back then it was just a first observation.  Brilliant: What made him decide to sort of follow through on that observation and take it further?  Smith: He saw that he was seeing quantum mechanics in action, if you like. That’s what he was interested in. He was interested in the physical manifestation of principles that are all there in the textbooks. That’s what first attracted his attention. Then I think quickly he realised that this could be applied. The remarkable thing is that he took notice and followed it up. It’s very interesting to hear him talk about that.  Brus: Often there’s an element of luck in that, that’s his famous quote, luck favors a prepared mind. There’s certainly truth in that. Most discoveries are made by people doing research in a more or less straightforward fashion, but then they stumble into something unexpected in the lab and they can either ignore that and continue on the original line of research or they can take a risk and try and work on this unexpected thing, which you don’t know what’s going to come out of it and whether you’ll make much progress and whether you could get it funded. It takes a lot of courage to go into new areas. Some people have the natural personality for that and others don’t.  Smith: But obviously your particular question, which I think it’s fair to say, has defined all your work of just asking what the electrons are doing.  Brus: There were lots and lots of scientists who were basically doing that. Everyone in solid state physics and everyone in chemistry at some level is you have to deal with the electrons either in molecules or in solid state. That was my original training. I spent all this time studying quantum mechanics of molecules in graduate school and spectroscopy. That’s evolutionary. I was like 12, 14 years out of graduate school before I started to work on the quantum dots. There’s a long evolutionary pathway from finishing graduate school to the point where I began to work on quantum dots. When I got down to the working on quantum dots, nobody understood what I was doing to begin with bcause I was a member of this community of people who were doing ultra fast laser spectroscopy on molecules or doin and trying to use fancy spectroscopy to study chemical reactions. Nobody in the world was working on colloids. This was a completely dead subject. It had been popular in the early part of the last century.  Smith: I wanted to ask why you made that switch to colloids at about 12 years out of graduate school?  Brus: Part of it for sure was I recognised that this was important for Bell Labs. I had the opportunity, so the management supported me. I didn’t have to go to the NSF and convince them or convince reviewers that college were important. I just needed to convince the management of Bell Labs. They understood that these small particles represented the future of microelectronics in some sense, it might be 20 years out, but the driving force in the whole business was the fact that transistors were getting to be smaller and smaller every year. That was the driving force for the entire industry for the last 50 years or ever since 1970. At some point they’d get to be so small, they would behave more like molecules and they would not behave like bulk transistors. Then the industry would have to adapt to the fact that this silicon was behaving differently at small size than big size.  This was not necessary yet when I started in the 1980s. But any intelligent person could see that it was coming down the horizon. It might be 40 years away, it might be 15 years away. But anyway, this was recognised as long range research relevant to the computer and communications industry. It was just one person. Me. It’s a question of how important is it versus how much money do you have to invest? So if Bell Labs make a development effort, they might be 15 or 25 scientists. That’s a big expense, you know. But if it’s just a research project carried out by one guy with his own hands, let him go and see what happens.  Smith: They got their award for backing you. It does sound like an absolutely perfect environment to be with people making decisions above you based on your track record and also with an extraordinary timeline in in mind, not thinking about any benefit.  Brus: A lot of the people, most of the people in South State physics were thinking of very long timelines in superconductivity and a correlated electron behavior. None of that was relevant to the present transistor design and so forth. There was just new areas of solid state physics they weren’t uncovering. Again, it wasn’t clear that any of this could be made into devices. The idea was you would discover something brand new that people didn’t realise and then you would sit and think a little bit about where it might be relevant or if it might be relevant. Then if there was some obvious relevance, the management might want to make a development effort out of it, but maybe not. Anyway, come up with new ideas. It had worked, the laser was such an invention, basically took a long time to figure out what the laser was actually good for once it was invented. A different thing was the transistor. The transistor had been a real effort by the telephone system to make better equipment. They put a team together to make solid state switches rather than continue with using vacuum tubes like they had for the first half of the century. But again, that takes money. You don’t know that it’s going to work and we have to fund all this.  Smith: But that’s more of a moonshot program where you put the resource in.  Brus: Moonshot required many hundreds of people to build a rocket. But this initial research on transistors was like three people and they didn’t know quite what they were doing. Nobody knew how to do this, how it was possible. They didn’t understand the principles of semiconductor physics. They stumbled around for a while and then finally made a device that worked a little bit. The managers of the corporation could understand that this might be very important because they were struggling with the present equipment. They were struggling with the fact that the system used vacuum tubes and microwaves for long distance transmission. They’re looking for the system we have now using fiber optics and light propagation carry all kinds of communications that’s far better than what we had when I was just starting out in Bell Labs. Completely changed the world. All of that comes from basic research that people think about and then decide how to use it in the present day. It’s entrepreneurs who start new companies in order to make money.  Smith: I really like the phrase you used that they didn’t quite know what they were doing, because that’s such an important point to get across to everybody about trust in science, that it’s not as if you can fund people to get to a definite end. You have to fund people who don’t quite know what they’re doing. But on the other hand, you have to trust them that they’re sort of heading in the right direction.  Brus: No, you make a judgment that they are creative and this happens based on what they’ve done when they were younger. You make a judgment that they’re ambitious and so they would like to make a great discovery. They’re kind of always looking for, it’s not just a job, it’s their entire life, basically. Some great projects, for example, there is this infrared telescope that’s in outer space, won the Nobel Prize. That’s a great achievement, but that’s not an accidental discovery. That’s a great big engineering project involving hundreds of people. That $10 billion budget that everyone knew that if it worked, it would revolutionise the data you got on the universe in chemistry and in biology and in material science. It’s not like that. It’s one or two people working on a project that stumbled into something unexpected. This CRISPR business for the editing of DNA, that’s an unexpected. After working on it for six months or a year, they realised they might be able to actually monitor change the DNA and all of that.  Smith: When you came across colloids and you dedicated your research to that, and you came up with the first quantum dots simultaneously with those in Russia, but you didn’t know that that was happening, do you remember the feeling of particular excitement that you’d managed to make quantum mechanics visible in this way?  Brus: It was an accidental discovery when we first saw the spectrum beginning to change because of small size, make particles smaller and smaller. Spectrum looks the same all those time, and then all of a sudden when you reach a certain size it against a change. New peaks appear that I realised was important, but I was more focused on the fact that to make progress, we had to make better particles. I’m a spectroscopist interested in quantum mechanics, but to make progress we had to focus on synthesis. That was a long struggle. My mind kept thinking all the time about how lousy these particles are. I just wish I could find a way to make them better in all of this. At the same time, my position in the labs was stable. They’re quite happy, as I said, for me to one or two people just to work on this project. I come from the academic chemistry community of research, basic research, and I wanted to convince them that this was an interesting project. What I had to do was go around the country and give colloquial different schools over time telling them what I was doing and then trying to explain why this was interesting to be part of chemistry. Chemical research takes time for people to accept the ideas.  Smith: Sure. If you’re sitting on something that’s so novel, how do you balance the desire to tell people about it and to get everybody excited with the possibility that then people will run off and do the same thing and suddenly you’ll increase competition? Or is that not an issue?  Brus: If people begin to copy you? But it’s the old cliche that’s the most sincere form of flattery. I would be happy with that. My whole life I worked on subjects and then when the field got to be too crowded, if there’s a well-recognised problem in science and strong academic groups all across the world are working on this project different ways, everyone recognises this as an important project, then it’s hard to make progress. That’s not a good field for a young scientist to go into because the competition is so stiff, much better to find a project that nobody else is working on that somehow is important and you’re in the right place at the right time in the right institution where you have the resources or the opportunity to actually pursue this curious project. But you can’t really invent this from scratch. It typically comes from unexpected observation in the laboratory that causes you to sit down and think about things.  Smith: When you first produced quantum dots, when you then learned that there was similar work going on in Russia, you tried to reach out across to the Soviet Union to make contact. But that was hard, wasn’t it?  Brus: I sent a paper, I found these papers in the Russian literature, eventually translated into English, and I realised they were working on the same thing, the different high temperature glass and the different materials and so forth. I wanted to make contact, particularly with the theorist in Soviet Union Afros. This is common among scientists. You make contact with other groups around the world that might be interested in the same thing that you are in time. I sent a letter and I think plus one of my publications, just a reprint of a paper that I had written into the Soviet Union, just to show him what we were doing. That worked out fine. It took another five or eight years before Afros could come out from behind the Iron Curtain. The Soviet Union was beginning to collapse, and the strongest scientists in the Soviet Union were leaving one by one and trying to find some kind of position in the West Europe or in the United States to continue research. Russian science today is the weak shadow of what it was when I was young, because the Russian government put so much money into basic research because it was relevant to the weapons program. But now it’s collapsed, basically.  Smith: It’s tragic, isn’t it? They’ve disbanded the National Academy of Sciences there and everything.  Brus: It’s taken up by the Chinese. The Chinese have just done the reverse. Chinese have gone from complete poverty to being very strong. They recognise all these arguments you and I have been discussing here. China is a country that has no natural resources. They have intellectual resources and manufacturing, basic science and all of that.  Smith: I know you read a lot of history. Do you find historical parallels in what you do, figures in history, who you relate to?  Brus: If you read the details of the famous people of history, Lincoln and [Churchill](https://www.nobelprize.org/prizes/literature/1953/churchill/facts/) and Eisenhower, things like that, what was always striking to me is that they made a lot of mistakes as well as doing some good things. Maybe 25% or 40% of the things they tried were stupid. They were not that much smarter than everyone else. They were just driven to find something that worked, basically.  Smith: It’s a nice idea to feel that somebody like Lincoln is approachable.  Brus: I kept telling people that he did not control events, but events controlled him. That was true for the entire length of the Civil War. He was this country lawyer who all of a sudden became president and a very ambitious man, but still country lawyer, a politician in Illinois. But he was good with dealing with people because he’d spent his whole life on the law circuit in court trials and things like this. He had a very good understanding of the range of human people and how to build an organization and so forth. He was in a place where he had to act when he became president. He had no idea that he was going to be in this long, hard war, that 600,000 people would die and almost destroy the country. Nevertheless, he had to deal with it. Churchill got into power just when everything was going to hell. Any rational man would have tried to negotiate with the Germans, rather than continue the war. But he was steeped in British history. He’d been in the army as a young man, and he wasn’t going to give up easily. He was of a mind that he would rather fight and die than negotiate with the Germans and live under their control like that. Even if it meant that a lot of people would die.  Smith: I suppose the lesson one learns from them is that it’s necessary to rise to the occasion when it presents itself.  Brus: Almost every great person is like that. You recognise opportunity and then you have to take advantage of it. Seize the opportunity basically. It takes some struggle.  Smith: It takes struggle and strength and the good fortune to be in the right position that you can devote yourself to it. That’s a wonderful point to end on. Thank you very much.  Brus: Yes. Thank you for calling me.  Brilliant: You just heard Nobel Prize Conversations. If you’d like to learn more about Louis Brus, you can go to nobelprize.org where you’ll find a wealth of information about the prizes and the people behind the discoveries.  Nobel Prize Conversations is a podcast series with Adam Smith, a co-production of Filt and Nobel Prize Outreach. The producer for this episode was Karin Svensson. The editorial team also includes Andrew Hart, Olivia Lundqvist, and me, Claire Brilliant. Music by Epidemic sound. If you’d like to hear from another laureate who relishes the challenge of the unknown, then check out our episode with 2022 chemistry laureate [Barry Sharpless](https://www.nobelprize.org/prizes/chemistry/2022/sharpless/podcast/). You can find previous seasons and conversations on Acast or wherever you listen to podcasts. Thanks for listening. |
| **Telephone**  **interview** | [LB]  Louis Brus: Hello?  Adam Smith: Hello. Am I speaking to Louis Brus?  LB: Yes, that’s correct.  AS: Good morning. Sorry to call so early. First of all, congratulations on the award of the Nobel Prize.  LB: Thank you. It’s… I was dead asleep when the phone calls came. I did not answer them, and it’s a surprise at this point, you know, at this point after all these years.  AS: Indeed. How did the news actually reach you then?  LB: Well, the phone kept ringing and I was trying to sleep and normally that doesn’t happen. And so I finally got up and returned one of the phone calls. And it was from some kind of television station, I think, in Miami or something like that. You know, and they wanted to get my reaction and they told me, you know, they were the first people to tell me that I had won this prize. So that’s how I got it, basically. And then I just looked on the internet to make sure it was real, you know.  AS: And there it was, yes. Your first reaction to realizing it was the case?  LB: Well, first reaction is thinking about the whole field and people who did not get it, you know. This is a collaborative effort, you know, it’s partly physics, partly chemistry and partly material science. Synthetic laboratory, synthetic work, you know, organo-metallic chemistry. And so it’s basically done by collaboration rather than one person making a discovery. And I’ve had some very strong collaborators who participated strongly in this, you know, that should be recognized as well. One is Paul Alivisatos of the University of Chicago. Another is Mike Steigerwald, who’s here at Columbia as well, besides the people who actually won it. The third one is Sasha Efros. That’s what went through my head, you know. This is a team effort.  AS: To you personally, what does it mean to be awarded the prize?  LB: It’s a great honour and it’s recognition for the field. It’s recognition, you know, that I have worked very hard on this subject for a long time, but at the same time, there are many scientists all over the world who have worked very hard on their subjects for their lifetime. And so I’m just lucky, I guess, is the right word, you know, that the Nobel Prize has chosen to honour this particular area of science at this time, you know.  AS: Nicely put. It was a long time ago, it was 40 years ago that you first produced colloidal nanoparticles.  LB: Yes, I began to work on this in the early 1980s. And it was for me, it was an accidental discovery. I wasn’t intending to work on it. I was using semiconductor particles for chemistry purposes, for spectroscopic purposes, studying chemical reactions on the surfaces of semiconductor particles. And we made smaller and smaller particles just empirically, you know, by using recipes. And I began to notice that the spectra of the particles began to change and I didn’t understand that and I don’t think anyone did at that point. And so I slowly, rather than studying the chemistry that occurs on the surface of the particles, I shifted into studying the basic physics and chemistry of the particles themselves, trying to understand this science evolution. What goes on here is this evolution from molecules to bulk solids or bulk semiconductors as a particle becomes larger. Smaller ones, really small ones, behave just as simple molecules in chemistry. And as they get bigger, they take on more and more solid-state characteristics. So that’s half of what we did, basically, this kind of fundamental knowledge or trying to understand this evolution with size. And the other half is that you actually make the particles, you know, and that allows them to be used in the televisions, you know, for quantum dots and televisions and things of that sort.  AS: But the important point there is taking notice of the questions as they reveal themselves to you.  LB: That’s right. It was accidental, you know, and so then we just realized that it would be important. You know, at that time, I was working at the Bell Telephone Laboratories in New Jersey. And, you know, that was, the laboratories were part of the electronics industry, the semiconductor chip industry. And I knew for sure that as the particles, you know, the semiconductors, they were trying always to make smaller and smaller transistors. And when they succeeded, if they succeeded, you know, they would reach this size regime where the properties began to change to become more molecule like rather than semiconductor like. And so for that reason, I knew that this research, you know, would be valuable in that context.  AS: Yes. Of course, the environment of Bell Labs was legendary for promoting enquiry.  LB: Yes, that’s what I was trying to make the point in the beginning, you know, that it’s a collaborative effort. And so I was able to talk. I mean, basically, the culture of the laboratory was, well, you know, I’m a physical chemist and a chemist and I, there were experts in all different subjects, mostly physics inside of Bell Laboratories. And I was able to talk to all of these people. The culture was such that their doors were open. And when I had a question, you know, I wanted to learn something quickly, I could just go to find somebody who was an expert on the subject and knock on his door and go in and discuss it with him. So that was an excellent, you know, unique way to make progress in an area which is not traditional.  AS: So many people have tried to recapture that spirit of the Bell Labs. It’s hard somehow.  LB: Yes, it is hard. I mean, you know, the basic research is not really a good fit for industry, you know, in the sense that the results of basic research are just so unpredictable, you know, you can’t really tell it’s going to help one in business or one product line in one company over another. It’s best to try and do it in the university, you know, the context or research institution context.  AS: Hmm.  LB: You know Janelia Farms in… There’s a biophysics institute in Virginia, the Howard Hughes Medical Institute. And that captures some of the flavour of the old Bell Labs.  AS: That’s right. [Eric Betzig](https://www.nobelprize.org/prizes/chemistry/2014/betzig/facts/), another chemistry laureate, he worked there, didn’t he, for a while? Yes.  LB: That’s right. Betzig was a collaborator of mine in Bell Labs before he left, you know, he was out of science for a period of time and then he came back in, working at the Janelia Farms. I published a couple of papers with him in the early days.  AS: Again, this inquiring mind and wide-ranging interest and somehow knowing to focus on what matters. There’s an art to it. But who knows what that art is?  LB: Yes, you have to give the credit to the management of Bell Labs as well. Basically, because they allowed me to continue to work on the subject once they understood, you know, that it was important. And that was before the outside world understood it was important, you know, it was not something that was worked on in academic life in universities or in other companies. That was always the strength of Bell Labs. We tried to work on things that… It’s always best to try to do research on something that is an empty field and other people don’t really think about and there is opportunity to make progress.  AS: This is a fascinating discussion. And I can’t keep you on the phone for too long. I just… I noticed on your website, you summarize all your life’s work as being ‘trying to understand what electrons are doing’. And I love that.  LB: Yes, so I used to work many… when I was very young, I was coming out of school, I worked on small molecules. You know, three and five and seven atoms and things like that. But it’s… There, the question is the same. What are the electrons doing in that, in those small molecules? And how to understand it? And it’s the same question in solid state chemistry. You know, it’s just a larger, larger piece of matter.  AS: And the question just keeps on expanding. The more you look, the more you have to ask. How does the prospect of the days ahead with some extra interest in you and your work strike you?  LB: What I will do in the coming weeks and so forth is just try and discuss all of this with people who are interested. Just to promote the chemistry and this area of basic science. You know, it’s become important now, but it was not important years ago and so forth.  AS: It’s been such a pleasure to speak to you. Thank you.  LB: Thank you for calling.  AS: Thank you, and congratulations.  LB: Yes, bye.  AS: Bye-bye. |
| **Interview** |  |
| Q2 | When did you first become interested in science? |
|  | Louis Brus: I was a small boy in the 1950s in the United States, and at that time, there was a strong effort to encourage people to do science and engineering. That was so-called Sputnik generation, in response to the Russian satellites that were launched before the American ones. I was always interested in science, and my father certainly encouraged me to do that. He was in insurance sales, not a salesman, but he ran an office of insurance. I can’t remember a time when I was not interested in science and engineering. There certainly were teachers that encouraged me in one way or another. I had a very good chemistry teacher in high school, and if I’d had a very good physics teacher, I might’ve gone that way. Almost every scientist tells a story, some story like this, where a chance occurrence had a big influence on their career. Certainly, I had good undergraduate teachers at Rice in science. |
| Q6 | What was your first job and how did it help you? |
|  | Louis Brus: My father felt that everybody should work, it was not good to have free time. It’s very different than the experience now for high school students in the United States. He went actually out and got me this job with the man next door who owned the hardware store. I was a clerk making 65 cents an hour, that was my salary, but it was very good because at school I was more theoretically inclined, and I didn’t have much experience with mechanical things, for example, I didn’t take cars apart, put them back together again. This time in the hardware store was quite good on two, learning about tools, but also learning about people. Everybody comes into the hardware store, you have to deal with the customers in any kind of sales job, so that was good. I worked, basically it’s hard to imagine, I worked – let’s see if I get this straight – 24 hours a week. Either two or three hours after school on every school day, and then eight hours on Saturday, and then two hours on Sunday. It’s a lot of working, there was not much time for anything else. It’s amazing that I could work halftime, and still do well in high school. |
| Q6 | Were there any other experiences that influenced your work as a scientist? |
|  | Louis Brus: My time in the Navy was quite important. It helped open my eyes to the real world. Not many scientists in the US have any experience out of universities. They’ve been in the university their entire life. But I was 19, I think, and I finished my freshman year in Rice studying physics, chemistry, math, and then went off in the summer to train with the US Navy and the fleet, and in an old destroyer out of San Diego. All those experiences were extremely vivid in the real navy. I learned about electromechanical computers. During World War II they didn’t have digital computers. There was no software, but they had machines where this mathematical function was encoded in the shapes of cams. These were hardwired computers to solve one problem. The problem was how to aim the guns on the destroyer. This kind of experience, I went on an aircraft carrier one summer in the Mediterranean. I found out later the aircraft carrier was carrying many nuclear weapons, preparing for war with Soviet Union. Anyway, they said these summer training cruises had a big effect on me. When I went on to get my PhD and then began to serve on active duty in the Navy, but I was lucky to be able, I was assigned to the Naval Research Lab, which is in suburban DC and I was able to do more or less basic research there for the four years that I was on active duty. I got to learn a lot of things outside of academic chemistry, just the kinds of technical issues which are important in a mostly engineering laboratory. All of that was good. In those days there was a draft in the US so I was expecting to go into the service in any event. My father had been in the Navy in World War II, so that predisposed me. I went to Rice on Navy Scholarship, that was part of it. I never expected to be a scientist, I thought I would be a businessman like my father, and I thought I would serve in the military before getting serious about business, and that’s how I was thinking about all of this in high school. |
| Q3 | What made you change your plan and pursue science? |
|  | Louis Brus: It was my experience, undergraduate experience. I became more and more interested in science, and in particular I was interested in quantum mechanics. I remember my reasoning as a senior, I was thinking, quantum mechanics is so interesting. I’d like to study it some more just to learn more about it, even though I’m going to go off and be a businessman and not really use it. I was lucky that the opportunity came. The Navy gave me first a leave of absence to go to grad school, and then the Navy assigned me to work in the laboratory research at the Naval Research Lab. All of that contributed to my career, made it possible to be a scientist. |
| Q3 | What do you particularly enjoy about science? |
|  | Louis Brus: It’s the old-fashioned way of doing science. I like to understand how and why things work, and I don’t really love machines. There’re some experimentalists who really like to build machines, and they’re not particularly interested in the problem that they solve with the machines, to measure something. I’m just the reverse. We build machines in order to solve a problem that I’m really interested in, basically. |
| Q5 | Why did you decide to teach? |
|  | Louis Brus: I didn’t teach for a long time because I went to Bell Labs. That’s an industrial private enterprise, not the school, there are no students there, so I did not teach, but I was certainly missing teaching and missing being around younger students. That’s one of the reasons I came back to Columbia. I enjoyed teaching freshman chemistry at Columbia for many years. There are a lot of smart students at the undergraduate level at Columbia, and very few of them are going to become professional chemists or scientists. They all go off into med school or lawyers and all these things that people do going into business in New York City. But I’m teaching them the principles of physical science, probably the last time they’ll see them in their major, you know, and I enjoy that because the US does not need more PhD scientists. What it needs is every citizen to be somewhat scientifically literate so that decisions can be made. The science is not black magic – for many people it’s just completely black magic – and that’s not good for society. |
| Q5 | How does it feel to be a mentor to many scientists? |
|  | Louis Brus: I think many people have the experience that it’s a fun and a delight to have a student of high scientific ability, that’s not hard to teach and picks up very quickly. Certainly that was my relationship with the Bawendi and with the previous postdoc in that program, which was Paul Alivisatos. Bawendi had started off graduate school as a theorist, and yet when he came to work with us, he was doing experimental work, mostly synthesis, and he didn’t know anything about it, but he had great enthusiasm, and he was highly intelligent, so he picked up pretty quickly. He had other people to mentor him around Bell Labs as well. The strength of Bell Labs was that there was always an expert nearby that you could talk to, so if there was a field I didn’t know anything about or that Moungi didn’t know anything about, we try to find the guy in the building who was the expert in that area, or at least knew more about it than we did, and then go and ask his advice. The culture was such that he was obligated to talk to us, not obligated to work on our problem, to abandon his own research, but to advise us. It’s a very quick way to learn, and you could turn on a dime, essentially, if you found a better problem. You could quickly switch your own research into this better problem without any prior obligations to the previous work, so it was great delight. It was a great fun to work with Moungi, that’s for sure. |
| Q7 | What qualities do good scientists need? |
|  | Louis Brus: A lot of times in research, perseverance is important. Very often your initial ideas are wrong, and you try to do something – it doesn’t work – and then you have to reconsider. You may start in an experiment thinking that you’re going to show one thing, and it doesn’t come out that way, it points in another direction. You have to sit down and rethink. There are very few accidental discoveries which are immediately important to the entire scientific community. Someone told me this morning that the average time delay between a discovery in chemistry and Nobel Prize for that discovery is 30 years. That shows that it wasn’t considered revolutionary when it was first made. People were still struggling with it to figure out, is this good for anything or? It only becomes apparent over time that it has a real value. Any new result, any really unexpected result takes time to sink into people’s minds, so that they can think through the consequences of it. Most of science is not really conducted on this Eureka principle. I’m [Albert Einstein](https://www.nobelprize.org/prizes/physics/1921/einstein/facts/), I sit down and I think through this, and I come up with a great theory which changes the world – that almost never happens, has not happened since the early days of quantum mechanics in world science. I mean, it happens. Structure of DNA was a case where they were able to … They were at the right place at the right time and worked hard on this structure and fell into it, the initial ideas failed. And they had help from the real chemists in Cambridge. So there are a few things like that, but not many. |
| Q2 | How important is collaboration? |
|  | Louis Brus: When I was in Bell Labs, collaboration was the basis of almost everything. You had a certain expertise in your own laboratory. I was a laser spectroscopist, I could do laser spectroscopy on many different samples. But to work on a given problem, you needed people who do electron microscopy of the sample, and people who understood separation science in analytical chemistry. You could talk to them and they would agree to collaborate with you because they thought it was an important problem and they could make a contribution that you could not make. It’s not necessarily true in academic life. In fact, there are many schools that pride themselves on the fact that they don’t really have strong collaboration among the faculty. Each faculty has its own self-contained universe, basically. But I always like collaboration better because to make progress you have to deal with the weakest parts of the experiment. We have to work on the weakest parts of the experiment even if nothing in our background qualifies ourselves to do that. At Columbia, we tried to institute a similar system to what we had in Bell Labs, and what existed at IBM before, a much more collaborative effort among the junior faculty who were part of the material science effort. The science is going in that direction, basically. My whole life, the institutions in the US have stressed interdisciplinary collaboration, people from different backgrounds forming a team to work on a specific problem and to get money from the federal government to work on that problem, because they are a team. In industry, industry will always form a … If there’s a problem in the industry, it works the same way, they’ll form a team. If there’s something wrong with the manufacturing or they’re trying to make an improvement to the manufacturing, they’ll form a team of maybe 8–10 people that have wildly different backgrounds scientifically so that each person might see the problem from a different perspective and can contribute to the overall success or failure of the team to solve that problem. |
| Q4 | Were you aware of your co-laureate Aleksey Yekimov’s research? |
|  | Louis Brus: This was the height of the Cold War, and the Russians were our enemy, and we tried to keep contact with the Soviet research effort, basic research effort, but it was hard. Yekimov was not allowed to travel to the West to talk about his research, His research was published in Russian, not English, and in obscure journals. In the beginning I ask around a lot of people what kind of research had been done on small particles. Nobody knew of any research, they was all zero. That’s the situation. I found Yekimov’s paper after a couple of years. I found his paper in translation in the American Physical Society, I guess American Institute of Physics used to do translations of some of the Russian journals, and I found an abstract, I don’t think it was the entire paper, it was just the abstract that was translated into English. That was a surprise. Then I wrote to them in the Soviet Union, just in surface mail, there was no email in those days. Just a handwritten letter to the one of Yekimov’s collaborators, Sasha Efros. I think I sent them a preprint of my work along with his handwritten letter. This was, as I said, in the depth of the Cold War. |
| Q2 | Does openness and collaboration aid science? |
|  | Louis Brus: Yes, for sure. You still have to have centers which are experts at doing specific things, like understanding the human genome and things like that. But taking the tools, those centers will much more open now about adapting tools from other areas that may give some progress on understanding the human genome. It’s certainly a big advance over what it was when I was a small boy and when I was a young student. |
| Q1 | What is your advice for young scientists? |
|  | Louis Brus: It’s mostly having to do with the choice of the problem. You have to choose what to work on. If you’re doing basic research, then you have to start off on one problem, and you don’t work on all the other’s possibilities. You don’t know in the beginning what the heck is going to work out better than anything else. It’s always have an open mind for, and a broad interpretation of what your goal is. In engineering, what people prize is the ability to make something cheap enough, which works well enough that people will buy it. You don’t have to be first, but you have to have a product which works well and is cheap, relatively cheap. But science is different. Science values very much the people who first think through the issues in a field which is completely unknown to the rest of the scientific community. If you start experimental work on something and maybe five years before anyone else picks up on it and realises it’s actually important. All kinds of examples in Nobel Prizes of people who invented effectively a new field that was not really … Their colleagues didn’t understand why they were working on it because it was so different than the experience in the cultural situation in their community. Therefore, they had five years to work on it, and work out the basic ideas without competition, so to speak. What science prizes is new ideas, and I guess the measure of a new idea is it affects the work of other scientists somehow. Either intellectually it affects the work, or they shift their fields in response to some paper that you published, or you invented a technique or a machine that could be useful in their work, even though that was not what you did, you just invented the machine. They decided how to use it for a really good problem. But anyway, all these different ways you influence their work, you influence the work of the community, and that’s what science prizes, that it goes forward because of these individual contributions. |
| Q2 | How do you deal with failure? |
|  | Louis Brus: In your own research you have constant failure. It’s rare that something works out well, and you have to sit back and reconsider and find a different way to do the same thing. In that sense failure occurs all the time. Drug industry, the huge amount of money spent in the drug industry on research and development, and almost none of it actually leads to new drugs because we just don’t understand the principles, what’s going on inside the body. You may have some idea about how this drug will interact with certain proteins, but the body is so complex that only God knows how it’s going to work once you put the drug in there, things like that. You can consider failures, I guess if you find trouble with somebody else’s work most scientists will step around it, not really devote their own time to confront the other person, unless it’s really a super critical issue or something like that. Because you’d much rather work on your own ideas and to make them, you’d much rather spend available time and mental energy working on your own ideas than spending your time and mental energy to dis disapprove what others have done is wrong, which it may be wrong. Anything really important will be picked up pretty quickly and reproduced in the lab. Many scientists will wait until something has been reproduced somewhere else in the world before they get serious about thinking about what this first paper has said. Because there are only so many hours in a day, you have to somehow maximize your chances, that you’ll do something important. |
| Q8 | What are your hobbies and do they help you in your work? |
|  | Louis Brus: I had a very good history teacher in my first year at Rice, and he opened up my ideas about history. History is really interesting, study of the people who have changed the world. I began at that point to study history, mostly American history. I became interested in investing at one point. My father left me a little bit of money, I never spent any time thinking about that, but then I figured I should spend a little time under trying to understand this investing so that we don’t make huge mistakes. I do enjoy gardening. My mother and my grandmother and my maternal grandmother were very strong gardeners, and I very much liked that. I wish I would’ve done more with that over time. If we lived in a house that had more sunshine, I would’ve been a better gardener, you know. |

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| **Telephone**  **interview** | [AY]  Alexei Yekimov: Hello?  Adam Smith: Hello, may I speak to Aleksey Yekimov please?  AE: That’s me.  AS: Hello, my name is Adam Smith, I’m calling from the website of the Nobel Prize, nobelprize.org. Congratulations on the award of the Nobel Prize.  AE: Ok, thank you very much.  AS: Would you mind speaking just very, very briefly?  AE: Ok, it’s the middle of night here.  AS: I know, and how did you receive the news of the award?  AE: Very positive!  AS: Very positive! That’s nice. [laughs] And when the call from the academy came, were you sleeping?  AE: Yes, I practically was sleeping, now yes.  AS: And what did you do as the first thing when you heard the news?  AE: I waked up, just! What could I do. It has taken some time, because it was something about 5 o’clock or even before in the morning, here.  AS: What does it mean to you to be awarded the prize for work that was done, gosh, 40 years ago in St Petersburg?  AE: No, ok, in some sense the satisfaction, you know, that this process is very, very long, and it was mentioned about 40 years ago I think it was 1980 or ‘81…  AS: ‘81.  AE: ‘81, my first publication, it’s about 40 years, so we are just happy.  AS: Do you remember the feeling of excitement when you realized that you were being able to change the properties of these particles in your doped glass by changing their size.  AE: No, in some sense it was a surprise even for us at the beginning. It actually will take almost one year when we confirm it for ourselves, that it is true, I mean experimentally and theoretically. I think it will be worth to emphasize that it was not, you know, surprising at that time, because it was a phenomena of quantum confinement that was discussed and described theoretically. And in Russia it was, at that time, it was the main handbook for the students, it was five volumes handbook for physics and quantum confinement. I still remember that picture where there is a quantum well and the levels of electrons confined in the quantum well. So, we treated for ourselves that experimental confirmation of theory, solid theory which was made maybe 20 years in advance of the experimental observation.  AS: Right.  AE: It was not very surprising, because that’s what we hoped, just to make experimental confirmation.  AS: Right, exactly, it’s not just a surprise happening, its based on textbook quantum chemistry, on established chemical protocols bringing together previous knowledge in new ways, yes, there’s an important lesson in that. Wonderful! It’s been such a pleasure speaking to you, thank you very much indeed.  AE: Thank you very much for calling, actually you’ve been the first one, gave me this news, so thank you.  AS: Again, congratulations.  AE: Bye.  AS: Bye, bye. |
| **Interview** |  |
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| **Podcast** | [Bertozzi]  Carolyn Bertozzi: I tell my students that the best armament that you can have as a scientist to navigate these realities is really great innovative ideas that put you, at least for a time being, in a kind of place of your own, so that you have your turf on the playing field, and it came from you, and it’s unique to you, and it’s personal to you.  Adam Smith: I wish I had been supervised by Carolyn Bertozzi. She says with such clarity the things that are so important. Don’t worry about all the extraneous stuff, but just focus on what you yourself can bring in terms of ideas. If you have good ideas, they will serve you well and protect you from the inevitable difficult things that you have to deal with as a scientist. She made it sound quite uncomplicated. I like that. I like the idea that this is open to everybody. She made that clear. There are lots of people with good ideas out there, good brains, and I suppose if you listen carefully and follow her advice, you can do this too. Let’s listen to my conversation with Carolyn Bertozzi.  Clare Brilliant: This is Nobel Prize Conversations. Our guest is Carolyn Bertozzi, the 2022 chemistry laureate. She was awarded the prize for extraordinary achievements in bio-orthogonal chemistry – a field she herself named – creating safe chemical reactions within living organisms. She shared the prize with Barry Sharpless and Morten Meldal.  Your host is Adam Smith, Chief Scientific Officer at Nobel Prize Outreach. This podcast was produced in cooperation with Fundación Ramón Areces.  Carolyn Bertozzi is the Anne T and Robert M Bass professor in the School of Humanities and Sciences at Stanford University in Palo Alto, California. She is also an Investigator at the Howard Hughes Medical Institute.  She speaks to Adam about how different molecules have different personalities, why she became her own PhD supervisor, and her musical claim to fame: playing in a college band with a future superstar.  But we begin – with romance.  Smith: I wanted to start with a love affair, a love affair between you and organic chemistry. Tell me about your first encounter with serious organic chemistry.  Bertozzi: For me, it began with the class that I took as a sophomore in college, which at the outset I was looking forward to as my last ever chemistry class. I took that class because it was required as a pre-med student, not because I had any inclination that I would enjoy it. Again, I thought it would be the last chemistry class I would ever have to take and that would be a good thing. Then much to my surprise, a week or two into the class, I found myself really engaged with the subject and I felt like it had this beauty and elegance and it just made perfect sense to me and I just couldn’t get enough of it. It turned out to be far from the last chemistry class I would ever take.  Smith: For those not familiar with organic chemistry, it’s the combining together of carbon-based molecules in all sorts of wonderful ways. But for many people, it’s extremely daunting. You’ve got lots of structures that are kind of hard to decipher if you don’t know what you’re doing and so many different ways of joining them together and that’s terribly confusing until you really get into it. A lot of people find it quite off-putting and just bewildering. Why didn’t you?  Bertozzi: I’m aware of that reputation because I had heard that before I took the class. I found it to be very different from that description. I did not find it overwhelming and bewildering. I found it to be like logic, especially since you can break the molecules down into their individual components that have recognisable reactivities. We call them functional groups. Smaller collections of atoms can behave in predictable ways regardless of their surrounding. If you understand really just a handful of core principles, then you can predict how two molecules will engage with one another. Then you can also start to apply that logic to creating roadmaps to build larger, more complex molecules from simple building blocks. I guess my brain just is built in the right way to understand the deconstructions and to do the pattern recognition. It’s also about looking at a molecule and having intuition about its behaviors and being able to predict the personalities of molecules so that you can predict the outcomes of chemical reactions. It’s very visual and I’m a visually minded person. It’s all about seeing these molecules in three dimensions and imagining in your mind’s eye what happens when two molecules encounter each other and then understanding some core principles of chemical reactivity. People told me in advance, oh, you’re going to hate that class. You have to memorise so much stuff. I didn’t think you had to memorise much at all. It was just understanding some core principles.  Smith: It’s extraordinary. You make it seem so vivid. And the idea of personalities of molecules is absolutely beautiful. I’ve never heard that before. I love it.  Bertozzi: Oh, really? People who are practitioners of organic chemistry think this way. Every molecule has its own personality, right? Some are really chill, and others are aggressive and unpredictable and sort of particular and delicate. For every personality on earth, you can find a molecule that kind of matches up with that personality.  Smith: Then the vision of all these molecules dancing around, making connections, as you say, it must take a particular sort of visual way of looking at the world. I don’t know what it is, a visual imagination to put it together.  Bertozzi: Yes, it is very visual and very imaginative. I found it was unlike any other science or math class that I had ever taken. Whereas general chemistry as it’s taught, at least as it was taught when I was a freshman, was really centered around physical chemistry, which is more quantitative and for me a little bit more abstract. I had difficulty with that subject. I had difficulty with physics, especially as physics became more and more into complex mathematics. I hung in there through linear algebra, but I started to lose it in quantum mechanics and differential equations. It was just too abstract for my brain. I struggled through those kinds of classes. But when it came to organic chemistry, it was a totally different part of the brain that was engaged. For me, it was a stronger part.  Smith: The other thing about organic chemistry is that synthetic organic chemistry did have, I don’t know if it still does have a sort of slightly macho reputation, because when you get in the lab and you build these molecules and you do 35 step synthesis, it’s kind of yeah, it’s a slog. Do you recognise that picture of it?  Bertozzi: Yes, you’re right that the field of organic chemistry through, I’m sure there’s some idiosyncratic origin story to how this culture evolved, but it did have a macho culture, certainly in the 1980s when I discovered the subject and it probably still does now in certain areas. I don’t know that that has to do with anything inherent to the subject. I actually don’t think there’s anything about organic chemistry, which requires a macho culture in order to execute or to succeed. There’s really no connection between the intrinsic properties of the science and that culture. I think instead, you know, like most cultural, historical, evolutions, there were probably a handful of practitioners in the very early days of the field, and their particular personalities have an outsized influence on how the field unfolds. That’s true in academia in general, right? Because we know that in academia, one professor can influence hundreds of, or thousands even, of students. So if a handful of people have a certain personality type, and they happen to be the leaders of a field when the field is young, they will have an outsized influence on the culture for generations and generations, because their trainees inherit some of their philosophies. A culture evolves from that. I think it’s interesting, you can look through other branches of chemistry, other subdisciplines, and you’ll find different cultures within each subdiscipline, having nothing to do with any inherent difference in those subdisciplines. I think it really is something you trace back to individuals. Science is practiced by people, people have their personalities and their idiosyncrasies and their prejudices and all of their failings as human beings. Those are manifest in the way that we practice the science.  Smith: What a fantastic opportunity then, if you are a practitioner of science, and you have the potential to influence generations of people coming after you to set things on a good path, to start a more palatable way of viewing a particular field, if you like. Let me play you a clip of you speaking at the Nobel banquet in December.  Bertozzi: Okay.  *CLIP with Bertozzi speaking:* We are indebted to our students, students, postdoctoral fellows, and staff for their contributions that are embodied in this prize.  Smith: That was a beautiful moment. It’s not so usual for people to mention their students and lab in the banquet speech. Obviously, the lab is incredibly important to you and the culture of the lab, as we’ve just been discussing. How do you create that sort of desirable culture in a lab?  Bertozzi: I can only speak for my own lab, I guess. For me, it’s important that my lab is a place where people can do the best science most effectively. Then the next question is, what’s the culture that promotes the best science? What I mean by that is the most creative science, the most innovative science, productivity in science, integrity, quality. In my experience, those attributes come from a lab in which people feel like they belong there. They feel supported. They can make friends and collaborators within the lab and feel comfortable being transparent about their science and generous with their time. That’s the culture I try to create. It has to start with me demonstrating those values in the way that I treat my coworkers and in the way that I expect them to treat each other. I lay this out pretty clearly in presentations to my lab that I give every year so that new people who have just arrived can understand what I value and how I expect people to behave in my lab. I think mutual respect and giving people the freedom to exercise their own creativity and to make their own choices and bringing in diversity so that people can come in with different ideas and feel free to share those ideas and with different mindsets. You never know where the next big insight will come from. It usually comes from an unexpected place. So I try to create a diverse environment where the unexpected ideas can come up and thrive.  Smith: As we go around the world talking to students, their concerns are always rather similar wherever they are. How do I make my mark? How do I negotiate the terrible publishing environment? How do I pick the right place to be? All of that is about me getting on. It’s about I’ve got to kind of drive through my own career. How do those things come together in your lab?  Bertozzi: You’re right. All of those pressures exist. As a group, the best I can do is acknowledge the reality of the ecosystem that we live in. We’re not cut off from the rest of science and society. We have to navigate those tensions, sometimes indirectly. My students worry about the world and all of these pressures and so on, and sometimes directly. Sometimes we find ourselves in competitive situations with other labs, or sometimes we might have a collaborator with whom we have a different philosophy or a different set of values, and we have to kind of negotiate around that. This is reality. The best I can do is try to create an environment where we can talk about it honestly and acknowledge the things we don’t like and can’t change, and the things that we don’t like and can change. I tell my students that the best armament that you can have as a scientist to navigate these realities is really great innovative ideas that put you, at least for a time being, in a kind of place of your own, so that you have your turf on the playing field, and it came from you, and it’s unique to you, and it’s personal to you. To the extent that you can have really innovative, cutting-edge ideas, there’ll be less competition to worry about. When the competition starts to pile up, that’s great. That means you’ve had an impact, and it’s time to think about the next big new innovative idea and keep moving forward. There’s that philosophy. Then the other philosophy is that you can’t control how other people behave. You can only control how you behave. At the end of the day, you have to look in the mirror and look at yourself and feel good about your behaviour and feel good about your contributions. Your purpose as a scientist is not to achieve fame or money. That’s not your purpose. Those might be side effects, and good for you. That could be wonderful for you, but it’s a side effect. It’s not the main goal. The main goal is to make discoveries and gift them to humanity. Those discoveries and that knowledge stays with humanity long after you are gone. You’re gone before you know it in this world, in the scheme of life on Earth. Your discoveries will have a much longer-lasting impact than you and your physical being. Keep that in mind, that regardless of your frustrations, because as a human being, you’re subject to feelings of anxiety, jealousy. There’s negative experiences all human beings have to deal with. But at the end of the day, it’s the discoveries you make and the contribution to humanity that long outlasts any of that.  Smith: I can just imagine a whole bunch of students leaving the room after you’ve just said that to them, feeling really buoyed up and fantastic.  Bertozzi: I hope.  Smith: At least it should last for a while before the next disaster hits. But yes, I love the thought that, yes, the best defense is having ideas. Those ideas will give you confidence to negotiate everything else.  Bertozzi: Try not to pile on to what everyone else is doing. Look for those areas where it’s just a wilderness with missing knowledge that needs to be filled in. For us, we work in biomedicine. We’re interested in discoveries that benefit human health. There’s so much we don’t understand about human biology. We’ve just scratched the surface as a field. After hundreds of years of knowledge, there’s so much we still don’t know, because there’s just so much there. If it takes hundreds of millions of years to evolve this being, one should expect it’s going to take a while to understand it all. There’s no reason to go out there and work on things that other people are already working on when there’s so much to do that no one is doing. That’s the mentality. Then again, at the end of the day, you just have to sort of take the high road, do the right thing, and focus on the science and not on the peripherals. I think that’s a mechanism that helps people to be happy and to minimize the stress about all those other things you mentioned. But having said that, you mentioned the publishing system, the pressures and the dysfunction of scientific publishing. That’s something that I would challenge my trainees to try to do something about. That is a changeable system. It was invented by humans. It can be changed by humans. To the extent that some of my trainees might end up working in the publishing industry or being in a position to affect change in publishing, maybe through policy, for example, I would encourage them to do that, to exercise that power.  Smith: Yes. It’s going to take a generational shift.  Bertozzi: Or more.  Smith: It’s such a massive problem. Of course, people try at the edges to change things, but somehow it’s got to come from within, as you say.  Bertozzi: That’s true. But again, I’ve lived long enough now to see what I thought were just immutable institutions actually change. I think things can change and online publishing was a huge disruption. You saw a big change in the publishing industry in the late 1990s, 2000s around that. I think we can change things and we should change them to the extent that they actually undermine scientific progress. That’s the ultimate litmus test. If some institution is actually impeding the progress of science and depriving humanity from discoveries that might otherwise have been made, that’s how you know it’s time to disrupt it.  Smith: Keeps coming back to the central message. It’s all about the discovery. That’s what matters.  Bertozzi: Right. Yes.  Smith: Yes. You mentioned your upbringing, a very scientific upbringing, surrounded by science. Was there ever any question in your mind that you would be a scientist?  Bertozzi: Oh, I mostly thought I wouldn’t be a scientist. Honestly, the closest I came before I discovered organic chemistry was declaring myself a pre-med. That’s somebody who wants to be a doctor, right? That’s the closest I really came to thinking of myself as a scientist before the age of 19, let’s say. And you’re right, I did grow up with a father who’s a physicist, and an older sister who was a mathematician and was kind of a declared mathematician starting around age six.  Smith: Right.  Bertozzi: She her whole life knew what her passion was and what she would be doing, but I did not. It was a surprise to me when I discovered my passion for organic chemistry. At that time, I really committed myself to the field. I knew that this was what I loved and what I wanted to do. Before that, no, I didn’t think of myself that way at all.  Smith: It’s hard enough figuring out maths as a kid. It must be even harder if your older sister is a maths genius.  Bertozzi: Yes, she was a super genius. She was the kid who outpaced all of her teachers in elementary school and middle school and had special math classes created just for her with older kids and stuff. When she was in college, she would help my father debug his quantum mechanics midterms for his students. That’s who she was. I tried keeping up with her when I was younger. She was just one year older than me. What that means is that every teacher who had her in school would have me a year later and they’d have these expectations that were I couldn’t meet. I think maybe that might have driven me to focus on other things besides science and math, because there was no hope of competing with her. I was more into sports and music and just not really academics so much.  Smith: I’d like to speak about both sports and music. Sports first. You’re pretty good at sports, I gather.  Bertozzi: I was when I was younger and that was a long time ago.  Smith: What was it that you liked about it?  Bertozzi: Anything with a ball is fun for me. I was decent. I don’t think I was anything close to being like a world class athlete or anything like that. But I was pretty good soccer player and I actually was recruited to Harvard to play on their team. That probably helped me get admitted to Harvard. Then what happened was when you play soccer at the college level, at least back then, this was in the mid 1980s. It was really hard back then. It probably still is difficult, but it was really hard to be on a team like that and also be a science major because the science classes like chemistry and biology and physics, they have labs in the afternoons. There’s also a lot of problem sets you have to work on every day and lab reports and midterms. There’s just a lot of work. You’re busy in the afternoons and evenings. It’s really hard to play on a team that practices in the afternoons. You can’t do it. Then also the teams travel for games that are away games. So you end up missing a lot of class. If you’re a science major, you’re missing labs. Those two things were totally incompatible. I quickly figured out that I probably couldn’t be on the pre-med track and also play on the soccer team. Freshman year, first semester, I gave it up and I ended up going out for the crew team instead because they would practice on the water in the morning, very early morning.  Smith: That’s the rowing thing, isn’t it?  Bertozzi: That’s the rowing thing. You get on the water at 5am in the dark and the cold in Massachusetts. Then by 7.30, you were done and you could go to your eight o’clock class, right? Your afternoons were free. I tried that. But I was so tired. The schedule was grueling. I really wasn’t very good at it. That doesn’t help. That lasted a few months. That was the end of my little college sporting career.  Smith: I think a few months of early mornings on the Charles, especially in winter, is surely enough for anybody.  Bertozzi: Yes.  Smith: OK, the other passion from childhood then you mentioned did take over at Harvard, music. You were in a band. You were a pretty successful band as far as it went.  Bertozzi: By college standards, yes, we were a successful band. So that’s true. I played the piano and the keyboards. When I was younger, I played a lot of music in school, like school performing arts groups, the choirs and the jazz singing groups. I played in a jazz combo. I spent a lot of time on the piano in middle school and high school. When I went to college, I was trying to figure out how to keep that up. I found some guys who were forming a band and needed a keyboard player. I played with them for a while. That was the band led by now famous Tom Morello, which is my claim to fame from college. He was our lead guitar player. He formed the band. He also composed music that we played. Then we also played cover music from the 80s at college parties. That was kind of our gigging music. That was really a lot of fun. He was such a phenomenal musician. He was the best musician I’ve ever played with. It was such a privilege to just see how he played and how he created music and how and his leadership of the band and so on. I really learned a lot from working with him. Then he graduated and went off to be a musician. The rest of us kind of drifted into the background and ended up going our own separate ways after college.  Smith: He went on to form successful bands such as Rage Against The Machine and Audioslave.  Bertozzi: He really had a unique style even then. That just carried right into Rage. He is also a very politically minded artist. Even the music he wrote for us in college when he was maybe 20 years old or something, was very politically minded. That still is one of his kind of signatures on a song. Most of his music is purposeful and thoughtful and deals with sort of difficult issues of the moment.  Smith: Is there something that carries over into the way you practice science from the way you practiced music together?  Bertozzi: Probably. It’s probably unconscious types of things. But I definitely took a liking of all the different forms of music that I was exposed to as a kid. Jazz and funk were the two that I really resonated with the most, no pun intended. What I like about them, those forms of music is the free form, the fact that there is a structure in the background, but then you have all of this latitude around that to express yourself. Sports are like that too, right? It takes a lot of rigorous and rote practice in order to develop the muscle memory so that you can be creative and in the moment do things that are almost subconscious. I would like to think that there’s some of that that goes into the scientific creativity, right? You have a structure of knowledge and you have to have command over that knowledge. You have to understand the literature deeply and you have to be rigorous and understanding experimental strengths and weaknesses and so on. But then within that structure, you can exercise a lot of creativity and push the boundaries. I also really like technology development. I like invention, especially if the invention flies in the face of dogma. I really like that. There’s something really appealing about that. Then at the end of the day, my favourite types of research projects are the type where maybe you invent something and it solves a problem or allows the creation of a new kind of medicine. Then when people see that, they say, oh, how come nobody thought of that? It seems so obvious, right? Those are my favourite types of things, things that in retrospect seem so obvious and so simple and so straightforward. But in the moment, they’re actually quite disruptive.  Smith: I suppose it’s one place it’s easy to be disruptive is at the interface between things, whether it’s in music or in science. In your case, you built up a solid grounding in biology and chemistry, and then were able to work at the interface between the two. I guess that served you very well indeed.  Bertozzi: It did. Actually, I think you’re right. It’s very insightful, that comment you just made about how disruption occurs at interfaces. It’s true in music. Bring a new instrument into an old genre, and that’s a disruption. In science, it’s the same way. For me, it was quite natural for me to develop knowledge both in chemistry and biology because I took an interest in the field of glycoscience. I learned about that field in my PhD through the window of chemistry. Then I did a postdoctoral fellowship where I studied glycobiology that was related to the immune system. So that was my biology training. Both my PhD and my postdoc shared the common thread of complex carbohydrates and glycobiology. That’s a field that I think quite naturally requires the convergence of chemical approaches and biological approaches. Glycoscience really brought all of those things together for me.  Smith: We’ll talk about glycoscience in a second because it is something that most people don’t think about. As you put it, it’s the sugar coating on our cells. Such a beautiful phrase of yours. But your move into that field also was accompanied by a physical move from the east coast of America to the west coast of America. You’ve done your undergraduate at Harvard, a male-dominated chemistry department, as you’ve spoken about before. You then found yourself in California at Berkeley. Was that an important transition apart from just being in a different place? Was there some kind of change in the air as you went from east to west?  Bertozzi: There was. I had really never been anywhere. I didn’t travel much as a kid. We were on a pretty modest budget as a family, so we didn’t take extravagant trips. When I went to visit graduate schools in 1988, when I was figuring out where to do my PhD, it was my second plane ride ever, and it was my first plane ride out of the east coast and to California. When I landed in California, and I’m 21 years old at this point, I’d never seen anything like it. It was just eye candy. I remember coming out in February to visit some PhD programs, and there was no snow, and with this nice temperate weather and people walking around with T-shirts. Even though in my head, intellectually, I knew that there were places on earth that weren’t buried in snow in February, I had actually never seen one. California was like a different planet for me. It was like I had just stepped off the plane and landed on Venus or something. It took me a little while to get used to it, because everything was really different to me. But it turned out to be a really good fit for me in my personality and the way I like to do science really works well on the west coast, maybe better than the east coast. I think, yes, I think I found it liberating and stimulating. Then really what happened was I was recruited to join the lab of a brand new assistant professor named Mark Bednarski. I was one of like three students that joined his lab in that very first class of students. He was brand new and enthusiastic with lots of energy. He just gave me the pitch on how sugars were so interesting and important and difficult to synthesize chemically and difficult to study biologically. I just was so intrigued by that. I really have to credit Mark with introducing me to the field and recruiting me to his lab. I’ve kind of stuck with it ever since then.  Smith: Your experience with Mark not only exposed you to the field, but it also exposed you to yourself, if you like, because he got ill and then had to step away from the lab. You found yourself having to really supervise yourself, which is a very unusual position to be in. You grew into it easily.  Bertozzi: Yes, you’re right. The story of Mark Bednarski was he started his lab with full throttle and recruited a bunch of students. We were off and running. Three years into it, he was diagnosed with colon cancer. He must have been 33 or 34 years old at the time. That’s a very unexpected diagnosis for a person that age. This changed his life. He took a leave of absence while he was having treatment. He had surgery and chemotherapy and so on. During that time, he had an epiphany about his own career. He made the decision that he wanted to be a doctor and he wanted to work with cancer patients. He quit his job at Berkeley and went to medical school at Stanford, of all places. There we were, a handful of students who were the senior students in the lab. We were just beginning our fourth year of graduate school or so. We found ourselves without a boss. There were a few students younger than myself who had to basically switch labs and start all over again. I was just far enough along that I could convince the department chair that I could just ride out the next two years knowing exactly what I needed to do and just doing it. It’s amazing.  Smith: He or she must have been so relieved to hear that. Good, I don’t have to worry about Carolyn. She can just take care of herself.  Bertozzi: In retrospect, you’re probably right that it was a problem that didn’t need to be solved as long as I acted confident in my ability to supervise myself and two other students with me. I think today in the year 2023, this probably wouldn’t go down the same way. I think there’s much more attention to, first of all, safety, right? You can’t have students working in labs with no safety oversight. There’s liability issues that we didn’t care so much about back in the late 1980s and early 90s. But now that wouldn’t fly and also just mentorship. Now I think there’s a lot more attention paid to the infrastructure for student mentorship and for student experiences, where when I was a student, once you joined a lab, nobody cared about you anymore except for your advisor. If your advisor stopped caring about you, you’re kind of on your own, right? For good and bad right? The good news for me is that I was able to continue working on my research and I didn’t have to start all over again in a different lab, which meant that I got to stay in the field of carbohydrate chemistry and glycobiology, which I otherwise would have been pulled out of that field, right? That was the good thing. It was difficult and frustrating because there are things that are hard to do without a graduate advisor, right? So getting papers published was a bit of a struggle, but we managed but it was probably harder than it would have been otherwise. But in retrospect, even though at the time I complained a lot about the situation, I’m sure now in hindsight, I do see how valuable that was as a training experience for me to take ownership of my research, my publications, my future, my postdoc applications at the end of the day, if I had to do it and if I didn’t do it, it wouldn’t happen.  Smith: I guess again, it’s that confidence. It’s developing so much self-confidence early on stands you in very good stead for all the rough and tumble to come.  Bertozzi: That’s right. And it also, honestly, liberated me from having to follow in a channel in my career. I think if I had been in a large lab with a professor who was there every day and with a kind of an infrastructure in which everyone was sort of standing in line and following the same path, then I probably would have done something different. Because I was on my own, left to my own devices, it gave me the latitude to figure out what do I really want to do next in the absence of having too many people whispering in my ear, right? That’s when I decided to leave chemistry and do this postdoctoral fellowship in an immunology lab. Some other senior professors who were my kind of backup advisors at the time, they counseled me against this. They told me it was not a good idea. It was too far astray from the path that was familiar to them. Again, if I had been in one of their labs as their student, I would have taken this advice to heart and probably chosen a more conservative path. Because I really didn’t have someone steering me, this kind of negative advice was in the distant. It was once removed. I didn’t really take it to heart. I just decided I should do what I want to do.  Smith: You’ll have legions of graduate students listening to this and thinking, oh, right, the thing to do is to dump my supervisor, go off and be so…  Bertozzi: They’ve become very good at ignoring my advice. I think that’s some metric of success, I think.  Smith: Yes, the sidestep into immunology and then staying with glycobiology all proved very successful. Can you tell me what is it that is so exciting about, to reuse your lovely phrase, the sugars that coat our cells?  Bertozzi: To start with, I get really excited about the field. That excitement has not waned in 30 years now because there’s so much we don’t know. Those sugars are on every cell in every living organism on Earth. Different organisms have different structures of their sugars, but even within our own bodies, different cell types have different patterns of sugars. There’s many diseases that have been described where there are changes in the sugars that are central to the disease, but we don’t really understand at the molecular level, like how the sugars contribute to both healthy biology and disease biology for the most part. In my career, there have been a couple of big breakthroughs where some clarity has been achieved. Every time there is a breakthrough in understanding, it has a huge impact. People make new medicines, come up with new diagnostic strategies, and there’s so much you can do with the knowledge. Yet there’s so much still to be learned that I feel like it’s just a great place to work because again, every discovery you make has a big impact because there’s just so much we don’t know. I love glycoscience. It’s a wonderful field.  Brilliant: Carolyn Bertozzi was awarded the Nobel Prize for developing bio-orthogonal chemistry. What is bio-orthogonal chemistry, Adam?  Smith: Bio-orthogonal chemistry is any chemical reaction that can go on in the body without interfering in the biochemistry that’s already happening in the body, and in turn also not being interfered with by that biochemistry. It’s happening completely independently to everything else that’s going on.  Brilliant: Where does the name bio-orthogonal come from?  Smith: The ‘bio’ piece is from the fact that it’s happening in a biological system, and the word orthogonal means something that is at 90 degrees to something else, and so this is describing chemistry that’s happening in, if you like, a different dimension to the dimension of normal body biochemistry.  Brilliant: This sounds quite tricky. How has Carolyn Bertozzi enabled this to happen inside a living organism?  Smith: Utilising these amazing click chemistry reactions, which are rather rare reactions where two functional groups just want to get together. They just click together without interfering with anything else going on around them, and without being interfered with. Because you’ve got these new reactions, they’ve only been around for about 20 years, you can make use of them and make click chemistry happen inside the body.  Brilliant: This is probably a silly question, but how do you get these functional groups into the living organism?  Smith: It’s not a silly question at all. That is absolutely the challenge, that for any click chemistry to happen, you need two functional groups because you need two things to snap together. You’re using this chemistry to do things like label protein molecules inside the body. One of those groups has to be stuck onto the protein you want to label, and the other of the groups has to be on the label that you want to stick onto the protein. The first thing to do is you need to get the functional group, that little chemical entity onto your protein. That’s part one. Part two is you need to introduce your label with the other chemical entity into the body so that they meet and snap together. That requires some sophisticated chemistry and biology to make happen. Carolyn Bertozzi and others have been able to develop this amazing technology.  Brilliant: It’s interesting because it sounds both sophisticated and simple at the same time, the fact that you can snap these molecules together.  Smith: I think that’s a lovely observation. The name click chemistry does imply that it’s all lovely and simple. If you look at the chemical functionalities that are involved, they look rather scary sometimes like an azide group, two nitrogens joined by three bonds. Not the sort of thing that you possibly encountered if you did a little bit of chemistry at school. There’s some sophisticated chemistry going on, acting in what in the end turns out to be a rather beautifully simple way.  Brilliant: How is this science beneficial to humankind?  Smith: Basically, it allows us to understand more of what’s happening in living systems. Because of this bio-orthogonal chemistry, you can label things in ways that you never could before, track their progress, see what’s going on. You can also change the function of molecules in the body. If you put the right sorts of labelled attachment onto these molecules in the body, you can turn them into, for instance killer molecules that will go around and potentially target a cancer cell and get rid of it. There are enormous numbers of potential benefits, and many of them are being actively developed now. It’s interesting to reflect on the fact that, of course, there’s a huge literature and history of the development of synthetic organic chemistry. Almost all of that happens on the lab bench. This is very rare in that it happens in living systems. It fits into this history of the development of synthetic organic chemistry, and it’s quite interesting to listen to her reflect on how she sees her own place in that history.  Smith: We began by talking about the importance of organic chemistry to you and you gave your chemistry textbook to the Nobel Prize Museum. That organic chemistry textbook is full of named reactions after famous chemists of the past. Kleisen condensation, [Diels-Alder](https://www.nobelprize.org/prizes/chemistry/1950/summary/). Indeed one of your fellow laureates, the Sharpless epoxidation, all these reactions named after people. Your bio-orthogonal chemistry isn’t named the Bertozzi reaction, but it could be. How does it feel to be part of that kind of pantheon of chemists?  Bertozzi: It’s funny that you mentioned that because the very first bio-orthogonal reaction that we invented, we called it the [Staudinger](https://www.nobelprize.org/prizes/chemistry/1953/staudinger/facts/) ligation. We named it because it was an adaptation of one of those old reactions from the textbook called the Staudinger reaction from the, like 1920, it was a hundred-year-old chemistry. Then the community at large, not myself, but other people started to rename it the Staudinger-Bertozzi ligation. Now I think I technically have a named reaction. That does put me in a kind of a pantheon, I guess. The naming of reactions after people who first invented them was quite fashionable in the previous century. Nowadays there’s less of that, I think people are a little bit more shy maybe about the grandiose, statement of naming chemistry after yourself. It doesn’t happen as much. I guess I should be fortunate that somebody out there decided to tack my name onto my own reaction.  Smith: I guess also, since you could only have one named reaction after you, it kind of discourages further discovery, which is exactly the opposite of what one wants to achieve.  Bertozzi: Maybe the hyphenated Staudinger-Bertozzi ligation is a solution to that problem, right?  Smith: Yes, exactly. That is a way to go. It’s been an enormous pleasure speaking to you. Thank you very much indeed for giving us your time.  Bertozzi: Thank you for everything. I appreciate it.  Brilliant: You just heard Nobel Prize Conversations. If you’d like to learn more about Carolyn Bertozzi, you can go to nobel prize.org, where you’ll find a wealth of information about the prizes and the people behind the discoveries.  Nobel Prize Conversations is a podcast series with Adam Smith, a co-production of Filt and Nobel Prize Outreach. The producer for this episode was Karin Svensson. The editorial team also includes Andrew Hart, Olivia Lundqvist, and me, Clare Brilliant. Music by Epidemic Sound  For another listen from the crossroads of medicine and chemistry, listen to our episode with Emmanuelle Charpentier.  You can find previous seasons and conversations on Acast, or wherever you listen to podcasts.  Thanks for listening. |
| **Telephone**  **interview** | [CB]  Carolyn Bertozzi: This is Carolyn.  Adam Smith: Oh hello. This is Adam Smith, calling from Nobelprize.org.  CB: Hello, how are you doing?  AS: I’m doing fine.  CB: I was told you would call, which is great because my phone has been like ringing, ringing, ringing, ringing with I think Swedish media people.  AS: I think the world’s media will be on to that phone pretty soon.  CB: I guess so, yes.  AS: How’s the morning been so far?  CB: I mean, it’s insane, you know. I was probably asleep for not even two hours, and all of a sudden, you know, the phone is jarring me awake, and I’m thinking ‘are you kidding me?’.  AS: Are you still in relative isolation, or has the house been bombarded by the press already?  CB: Nope, it’s all quiet here. Dark and quiet and hopefully they don’t find me too soon.  AS: That would be good. Maybe you should hide because the next few days is going to be …  CB: Okay.  AS: It’s exciting company to be in as well.  CB: Yes.  AS: How do you feel about having the prize?  CB: I’m still I think in shock, but it’s really exciting for me to be there, on the same list as Barry Sharpless and Morten Meldal. The two of them are among my chemistry heroes. Barry Sharpless’s work has been kind of mesmerising me since I was a graduate student, and I heard him speak at Berkeley back in … somewhere in the late 1980s or early ‘90s, and Morten Meldal’s work I studied while I was in graduate school because he did a lot of work on glycopeptide synthesis, before his epic publication of click chemistry. So these are people that I’ve been learning from for many years. Decades even. And to be among them is just a huge honour for me.  AS: You’re such a serially inventive person. You know, introducing biorthogonal chemistry in 2003, and you’ve started many companies, and you seem to have such energy for new directions. What drives you through all this?  CB: I love organic chemistry, I’m fascinated by biology. Like all of us, you know, I’ve had family members and close friends who’ve suffered from ailments that were so untreatable. It was always my hope that as a scientist I could make some contributions that might benefit human health, either in the near term or the long term, or not even necessarily in my lifetime, but that was always my goal. And I like teaching, and working with people who share my passion, and who I can help with the wisdom of my age, I guess.  AS: What about chemistry? It gets a bad press sometimes.  CB: It ought not to. Chemistry is the central science, as we call it. And it’s such an exciting area of science for people who want to have an impact in biology and medicine and materials and climate and sustainability, right? Chemistry is so central to all of it, really, when the world is in trouble, chemistry comes to the rescue, right. Covid-19 is a great example of that, so I think maybe, maybe I can contribute to making our public image more exciting and positive.  AS: It’s a wonderful image of chemistry the superhero coming to the rescue. I like that.  CB: Yes, that’s right.  AS: Of course people will focus on the fact that you’re only the eighth woman to have been awarded the chemistry prize. How does that sit with you?  CB: That definitely adds a layer of gravity to the occasion. You know, I’ve been in environments where a woman wins a prize and she’s the first woman to win a prize, or there’s very few, and I can’t help but think about all the women who came before me, who did spectacularly important work, every bit as important as anything I’ve done, but didn’t have the opportunity to be recognised. I love that the numbers tick up. I wish that they ticked up more broadly. I think the fact that they are ticking up is very positive, and I know some of the other women who’ve been recognised with Nobel Prizes, and again to sort of be among company like that is just incredibly humbling. I’m sure there’ll be many more in the future. I mean, there’s so many amazing women scientists, and I think we’ll see them coming up more and more.  AS: But progress is a bit slow. I mean, you yourself have found yourself, as you already mentioned, in all male environments. Have you any advice for those who want to, for want of a better phrase, break through?  CB: I’m very optimistic about how science and the culture of science is trending. Hold on, someone has just come to my front door. Someone is ringing the doorbell. I think things are looking so much better, and there are so many visible women now. I think there’s just every reason to be optimistic. Hi, are you the press people?  Press: Yes.  CB: Come in. I’m on the phone with one of the gentlemen from the Nobel Foundation here. Come on in, my place is your place, make yourself comfortable. Sorry, I’ve got the Stanford Press here.  AS: I’m sure, and I think I was lucky to catch you before they arrived.  CB: The phone is ringing off the hook. Just help yourself to whatever. Grab a soda from the fridge if you’re thirsty. This is the middle of the night for you too, so I understand. Okay. So Adam, is there anything to add? Action items here? Because I’m probably not going to remember anything you say.  AS: You can relax, and just enjoy the, the show that is going to unfold in front of you.  CB: It’s unfolding I know, my emails are, the box is already filled up.  AS: But it’s fun actually, listening to the press people arrive it’s quite nice to get an insight into what happens in the middle of the night in California. Enjoy your amazing day to unfold.  CB: Thank you so much, alright.  AS: Nice to talk to you.  CB: Talk to you soon.  AS: Bye now.  CB: Bye. |
| **Interview** |  |
| Q3 | Where does your passion for science come from? |
|  | Carolyn Bertozzi: I was born in Boston, Massachusetts in the United States, and I grew up in a household where science was very much a centerpiece. That’s because my father was a professor of physics at MIT. He had three daughters, and it was important to him that we would be exposed to science and that we paid attention to our science classes when we were children. At no point do I remember being told that I must be a scientist, but it was absolutely encouraged in our house. As for my choice of chemistry as a specialty, that did not really come to me until I was in college. Before that, I wasn’t really fixed on science. I think I paid attention to the science courses because again, in my family there was an emphasis on that, but I had a lot of different interests, and I thought I might be a musician as a career at some point.  It wasn’t really until I was in college when I thought about biology as a major, and I thought about being a pre-med student, and go to medical school after graduation and so on. But I didn’t give much thought to chemistry until I took a course in organic chemistry, and that was in my sophomore year of college. Chemistry just changed my life, and I just fell in love with the subject. I’ll just never forget what it felt like to find a subject that I felt very passionate about. I wanted to learn more, and I wanted to study, not because I cared about my grades at all, it was just because I really loved the subject. |
| Q5 | Was there a particular person who influenced you? |
|  | Carolyn Bertozzi: I have had a few influential teachers and mentors over the years. I would say the first important science role model I had was my high school biology teacher, and her name was Margaret Schwartz. She’s no longer with us. But she really turned me on to the field of biology. And then I would say the second important mentor was my organic chemistry professor that was David Evans at Harvard University, who just passed away about less than two years ago, I think. Those two people really brought the subjects of biology and chemistry to life for me. And it’s probably no accident that my own research career has been marked by the interface of chemistry and biology. |
| Q3 | What do you enjoy about science? |
|  | Carolyn Bertozzi: One of the elements of organic chemistry that hooked me on that subject was how visual the subject is. So understanding organic chemistry is all about understanding the structures of molecules, their shapes how they interact with each other. I’m a visual thinker, so for me, being able to understand a science discipline through vision was, I think, quite profound. It’s not hard to stay interested and curious in a field like organic chemistry, especially in the way that it intersects with biology, because there’s so much we don’t know about biology, about the natural world, including our own human bodies that we occupy every day.  There’s so much we don’t understand about how our bodies work and when things go wrong in our bodies. Like what is wrong at the molecular scale? So we walk around every day in one of the great mysteries of life on the planet earth. So there’s always unanswered questions and puzzles to solve, and chemistry is a very powerful tool for doing that. |
| Q2 | How do you cope with failure? |
|  | Carolyn Bertozzi: I think a career in science inevitably teaches someone how to cope with failure. Science is, it’s like all of the regular problems of life get amplified in science because you’re inherently trying to understand the unknown, and you have hypotheses that often turn out incorrect. And the only way that you can find the truth is to do experiments and try and understand the data, and sometimes the data are not what you anticipated. So failure is a funny term because we use failure to describe events in life, which sometimes it’s not really a failure if you think about it at a higher level. For example, when my students come to me and they say, “oh, I tried this experiment and it failed.” And I’ll say, “well, why do you think it failed? Did you do a bad experiment?” “No, it was a thoughtful, good experiment.” “So why did it fail?” And they’ll say, well, because I wanted this to happen, but instead this happened, and then I’ll remind them, that’s not really a failure, that’s just an unexpected outcome from an experiment. That means you, you thought you understood what the outcome should be, but in fact it was different. That means that you have to rethink your hypothesis and you’ve learned something from that “failure”.  With that backdrop, I’ve certainly had events in my life that at the time I felt were obstacles, even failures, but in retrospect, they were learning experiences. One of those was during my PhD years as a graduate student, when my thesis advisor, who was a young assistant professor at Berkeley at the time, unexpectedly was diagnosed with colon cancer. When I say unexpectedly, it’s because he was only 33 years old. It’s just the last thing a person expects at that age. To deal with this illness, he ended up leaving his position and his graduate students such as myself and a few other folks were on our own to finish our graduate work unsupervised. In the moment, this felt like a pretty big challenge and also quite risky in retrospect. I learned how to run my own research project. I learned how to serve as a mentor to the other students in the lab who are younger than I was. I just learned how to basically manage a research lab. This turned out to be wonderful experience later when I started my own lab as a professor, but at the time I was a graduate student, it did not really feel like an opportunity, it just felt like a crisis. |
| Q1 | As a woman in science and a member of the LGBTQ+ community, what barriers have you faced? |
|  | Carolyn Bertozzi: People often ask me if as a woman in science or as an LGBTQ person in science whether I’ve faced adversity specific to those categories. It’s hard to know as an individual what types of adversarial events I might have encountered. Because you never can really do the control experiment, right? So I don’t know what my experience would’ve been had I been male or had I not been a queer person. I can say that being a minoritised person in science has its challenges regardless of the minority group. When I was a student, there were people who were actively hostile to women in chemistry in particular, organic chemistry also has a historical culture that was not particularly welcoming of women. And when I was a PhD student women were a minority. Maybe one out of ten graduate students in my program was female.  I was the only woman in my lab. Most women were the only women in their labs. And I noticed actually that it was challenging for these women because the men in our labs often looked at the women as dating prospects. The interesting thing is the men did not look at me as a dating prospect because I’m a gay person. I found actually that that was of benefit to me because the men didn’t really know how to talk to me and think about me. And so without any better idea, they just interacted with me like a chemist or like a scientist. So in fact, I think that was a benefit, whereas the women that they might have thought of as a dating prospect was less likely to be thought of as a scientist, first and foremost. So it might have actually been an advantage for me since I was already minoritised as a woman to actually be a gay woman. I don’t know for sure. It’s just a hypothesis. |
| Q11 | Why is diversity of all kinds important in science? |
|  | Carolyn Bertozzi: Diversity is important in any setting where people need to solve complex problems and where people need to think creatively. So chemistry is a very creative endeavour. It’s very important that we have diverse voices, mindsets, people with different ways of approaching problems around the table when we’re trying to solve these important scientific problems. There’s social science that’s been done to quantify these benefits, and so that’s wonderful, but it really seems common sense that you would want to have as many different voices and as many different opinions as possible when you’re trying to solve a problem. So I’ve benefitted in my own research from having a diverse lab of coworkers right from the outset of my independent career. I’ve had very good gender balance in my lab, and I’ve worked to recruit people from other underrepresented groups people who might have historically been excluded from the sciences in the United States.  This might be people of colour, also people who are gay identifying or queer identifying. My lab has always been known as a welcoming place for folks who might think of themselves as being kind of minoritised. I always thought that this was my not so hidden superpower. People have asked me many times over the years: what was the recipe for success for you in your lab? It was very simple. It was diversity. Now I think being recognised with a Nobel Prize is the best validation I could ever have to reflect on the power of that diversity. |
| Q10 | How can you create an open and accepting work environment? |
|  | Carolyn Bertozzi: It’s actually not hard to create a work environment that’s welcoming to a diverse group of people. It takes attention and it takes good listening skills and communication is very important because you’re bringing people together who might not have had experience communicating with one another before. So just making it clear from the outset that this is a guiding philosophy of my lab. People who work in my lab have to understand that these are my values and these are the values of our lab. Then when friction arises, which inevitably it does, when you have different people working together, there will always be some friction, but that friction can be translated into creative energy. It’s a matter of fostering open communication, being a very open person myself, making it clear to people in my lab that it’s a safe environment for them to communicate with me, even if they’re communicating things that are difficult for me to hear.  Being willing to accept criticism in a constructive way. These are skills that I think people should develop anyways just to be successful, productive people in the world and impactful people. It can start in my lab, but it’s been a process for me opening up my lab in a way that makes people feel welcome to come in, even if no one else looks like them. I think there’s always room for improvement. And I’ve gotten better at it over the years, and I’m sure I’ll continue to improve, but it’s been very worthwhile and rewarding. |
| Q11 | How can we encourage more diversity in science? |
|  | Carolyn Bertozzi: I don’t know that I’m more qualified than anyone else to give this kind of advice when it comes to promoting participation in science. But I do think it’s wonderful for younger children, school children, for example, to be able to see scientists who look like them. I think representation is very important in how we envision the possibilities for ourselves. So for a young person to see women who are successful scientists, for a person who is coming into their own gender identity or identity around their sexual orientation, I think it’s also very helpful to be able to see role models, especially since those people are stigmatised in many geographies, less so in the United States than when I was born 56 years ago. But still that’s an identity that comes with a lot of risk in different geographies.  Just to be able to see a person who’s comfortable in their own skin and has found a way to lead a successful and fulfilling life, I think this could be really profound. And then just existing as a scientist is not enough for me. I think it’s also important to be able to reach out and to communicate with people who are younger and thinking about their future. And then to demystify what it means to be a scientist. I think if you look at the public images of scientists, whether it’s in Hollywood films or television, scientists are often painted as extreme personalities and usually male personalities who are just different from the rest of us, either smarter than the rest of us, or weirder than the rest of us, or both. The truth of course is that scientists are the rest of us. There’s nothing really different about a scientist from a non-scientist other than a choice they made about their career.  But otherwise I think it’s great if regular scientists that are not in the movies, not characters on tv, but real people can take the time to get to know people who might have a misconception about a scientist. I’ve noticed that things that I say seem now to have more gravity, even though they haven’t changed at all. I’ve always said the same things, but for example, the day after the Nobel Prize announcement, my university had an event and they wanted me to get up and say a few words about the prize. And so I did, it was very spontaneous. I didn’t script this at all. And someone had a cell phone video recording and they posted a clip on Twitter, and it was about a one minute clip where I talked about the diversity of my lab and how that diversity created a culture in which we felt liberated to think outside the box and try crazy things. That tweet just went viral. There were thousands and thousands of likes and retweets and so on, comments. I realised when I read the comments on that tweet, and it wasn’t my tweet, it was a tweet from the person who took the video. I was reading through the comments and I realised that there was an appetite out there for someone to say these words. Lots of people have said words just like this. I have said words like this myself, for decades I’ve been saying the same thing, but now I’m a Nobel laureate. So it just gave so much more credibility to the idea. Watching that tweet and watching the comments from that tweet, it really sunk in that it’s a platform when you have a Nobel Prize. |
| Q1 | What advice would you give to young women or people of minority backgrounds? |
|  | Carolyn Bertozzi: For people who don’t see themselves represented in mainstream science, and so that would be women and also people from underrepresented minority backgrounds. For those folks, first of all, I will say when I was young, I did not see myself represented. I did not see women, successful women scientists who were decades older than me. There just weren’t enough for me to find them. And I certainly had no view of openly gay people as scientists or in any career, really, because I came of age at a time when there was so much risk involved and being out that people stayed in the closet. So I know what it feels like to feel like you could never belong in a place. And then what happened was a few people here and there opened the doors for me, and I had the great benefit of being born into a family where science was encouraged.  I didn’t grow up thinking I couldn’t be a scientist. It was only later that I worried about whether I would find my way. So, for a young person who’s trying to figure out how they would pursue this career path, even though not many people look like them, I will say, first of all, now that we live in a globally connected world where people can get on the internet and find information they couldn’t have found in their backyard, you can find the role models you’re looking for. They’re out there. You just might have to look a little harder than the room you walk into. So take the time to look online and do your research and find out who are the scientists that remind you of yourself. They’re definitely there. First of all. Second of all, find your advocates. So somewhere along the way, all of us had a handful of people who stood up for us. If you can find a few of those people, they might be family members, they might be school teachers, maybe a neighbour even or maybe someone they meet at an event sponsored by the Nobel Foundation, right? If you can find just a few people that can really help your confidence, I think. And then finally, as hard as it might feel to break into an environment where you feel you don’t belong, there will be a chance for you to pay it forward. You might not find a lot of people in your own generation, but if you pay it forward, there’ll be a next generation that follows you that will be larger, more robust, and more energised. And it’s worth it, I think, to stick to your dream, even if it means you’re more paying it forward than paying it back. |
| Q1 | What advice would you give to a student or young researcher? |
|  | Carolyn Bertozzi: The one piece of advice I would prioritise for a young up-and-coming researcher would be… I would want to share with them how a life in science is incredibly rewarding. It’s rewarding because it’s creative. So you’re discovering knowledge and gifting that to humanity for all of posterity, because once you learn something, no one can take that away, right? It’s not an object. It’s an intellectual currency that will be shared throughout the generations, and you created that, right? And it has a permanence that ironically, a physical object doesn’t have. Or you can paint a painting, eventually it will fade, right? But knowledge doesn’t fade. Knowledge stays with us forever, and it becomes the foundation for the next generation. So that’s really exciting. That alone, I think, makes it worth it to become a scientist. But then on top of that, you have a lot of autonomy, and that’s something I have always valued, just the idea that I can govern my own activities, that I can pursue my own ideas and my own interests. There’s boundary conditions around it, of course, because someone has to pay for it and I have to convince them to pay for it and so on. But I have so much autonomy in what I do with science. Very few professions offer that kind of autonomy. That’s another great benefit of science. |
| Q7 | What qualities do you need to be a successful scientist? |
|  | Carolyn Bertozzi: The most important quality of a successful scientist, based on the people I’ve known, is resilience. So that’s the quality where you might be frustrated, you might feel like you just lost the game, but you dust yourself off, you get back up there and you go out the next day and try again. And science requires a lot of trial and error, and there’s a lot of confusion and frustration. But then you win a few. And when you actually have clarity on the science that you’re studying, when you feel you understand it, and it works as you had anticipated, nothing is more rewarding than that. |
| Q3 | Do you enjoy teaching? |
|  | Carolyn Bertozzi: I’ve always had a strong affinity for teaching. I discovered that actually during my undergraduate days when as a senior, I served as a teaching assistant for the introductory organic chemistry class. What was so fun about that was I got to teach the students who were basically the equivalent of myself when I discovered my passion for the subject. I remember how it felt when I took the class and how I fell in love with it. When I taught that class a few years later, I wanted to create that magic for my students. And every once in a while, a student that I was teaching would have the same experience that I remember having, and they would come up to me after class and say “I’m a pre-med or a biology major, but I had no idea organic chemistry was so fascinating. I want to switch my major. I want to become an organic chemist.”  I thought, yeah, I recognise that feeling. Even now, and I’ve been teaching for 30 years or so, but I still teach that introductory organic chemistry class from time to time. And every time I teach that class, I try to bring back the magic that I remember when I took the class from Professor Evans at Harvard. So that’s part of the fun of teaching, is just reliving the magic, you know? Then, of course the students, even the students that don’t embrace the subject as a calling the way I did, I know in my heart that I have given them a foundation that will help them with whatever they try to do next, whether it’s medicine or science or something totally outside. I still think having taken on the challenge of organic chemistry and having learned what many people feel is a difficult subject I think is really enhancing for them intellectually.  When you teach a class, you always learn something, even if it’s a very rudimentary class, a very introductory level class. I always learn something new when I’m teaching. I’m preparing the lectures and I’m trying to find real world examples of, of that topic. Then I’m reading the news and learning some interesting recent story that I wouldn’t have necessarily bothered to pay attention to otherwise. But I actually have a very specific story about teaching, which relates to the Nobel Prize, which is at the time that we were trying to develop a new bioorthogonal reaction, and we were trying to figure out how to get azides and alkynes to react with each other, with very fast kinetics. The other Nobel laureates who share the prize with me were able to accomplish that with a copper catalyst. But for our applications, for bioorthogonal chemistry, that was not going to be useful because the copper catalyst was toxic to cells.  We were trying to do chemistry in cells and in animals, so we needed an alternative. I was teaching organic chemistry that semester, and I was working on a lecture for the next day, which was on the subject of ring strain. Ring strain is a very foundational concept in organic chemistry that I had taught about every year for decades. But until that moment, it had not occurred to me that ring strain was a concept we could use to get this bio orthogonal reaction to work. It all kind of came together when I was writing that lecture. The next day I taught my class, I gave that lecture, and then I talked to my grad students and said, go see if ring strain will solve this problem. And it did. |
| Q6 | What are your interests outside of science? |
|  | Carolyn Bertozzi: I’ve always loved music. My parents, my mother signed myself and my sisters up for piano lessons when we were six years old or something. So I played the piano all through childhood. Then in high school, I had an amazing music teacher named Sandy Peasley in Lexington High School, and she introduced me to jazz, which was amazing because that’s a very creative form of music. So I played in jazz bands throughout high school and on the side I would play rock and roll and pop music just for fun by myself. But when I went to college I got involved in a freshman band. I met a drummer who lived in the same dorm, and we started this band and we weren’t very good. But one of our gigs was at a local college party and another Harvard student was there, and he heard our band play, and he was starting his own band. He was an amazing musician. This person is Tom Morello, and Tom was two years ahead of me in college, and he recruited me to join his band. The name of our band was Bored of Education, B-O-R-E-D. We thought that was quite clever at the time.  We played that year in this band, and we won the Battle of the Bands and we played some of his original compositions. People will recognise Tom Morello’s name because he went on to become a very famous rock musician. He formed a band called Rage Against the Machine, which was an award-winning heavy metal band. Later he formed a second band called Audioslave. And right now he still performs with Rage. I think they’re back together touring. He also does solo unplugged recordings and he plays with other bands. He’s very famous, very well known. At the time, I think you could have predicted it because he was a phenomenal musician, even when he was just 19 years old.  I still play the piano by myself with my headset on late at night as a relaxation activity. From time to time I wonder whether I could convince some other professors to get together and form a band with me, because there’s actually a lot of musical talent in the academic science world and in my own department at Stanford we have a drummer and a bass player and a guitar player. So nothing stops us other than time. |
| Q8 | How else do you like to spend your free time? |
|  | Carolyn Bertozzi: I don’t have a lot of free time, but I do try to make an effort to go to the gym. I’m an avid weightlifter and I’ve taught myself basketball during covid because that was an outdoor sport when all the fitness centers were closed. So I try to shoot hoops a couple times a week if I can. But any sport with a ball, I’ll try and probably have fun doing. |
| Q9 | How did you find out about the Nobel Prize? |
|  | Carolyn Bertozzi: The chair of the chemistry committee called me and woke me up. And so I found out, at 01:43 AM… I took a screenshot from my cell phone because I couldn’t believe it. I said, I’m gonna take a screenshot and then I’m going to wait 10 minutes and then see if it’s still there. So I found out the way that everybody finds out with crazy phone calls in the middle of the night. Then there was the live stream, which I watched online and was on standby on the phone. Then the doorbell rang, and it was the media relations people from Stanford University, who were just ready to go, came into my place and set up shop and arranged interviews for the next 12 straight hours, pretty much. So that was a pretty crazy few days. |
| Q15 | What do you believe is the greatest benefit to humankind of your research? |
|  | Carolyn Bertozzi: My research as recognized by the Nobel Prize, was the invention of a field of chemistry that we call bioorthogonal chemistry. We developed that chemistry so that a person could do a chemical reaction inside a biological system. By that I mean chemical reactions in living cells or living animals, or even living humans. Right now, the most obvious benefit to humanity is in the form of new medicines and new ways of treating cancer. And so bioorthogonal chemistry has allowed people to build new kinds of pharmacological agents, new kinds of drugs that would be hard to build otherwise. And right now there is a human clinical trial in which bioorthogonal chemistry is being performed inside the body of cancer patients in order to deliver a medicine to the cancer and spare the healthy tissues. So I think in the field of medicine is where the biggest impact is right now being felt. |
| Q15 | How does it feel to see your work having an impact? |
|  | Carolyn Bertozzi: I am delighted to see the work that came from my lab making the translation into new treatments for human disease. This was the dream of mine from my early days as a new professor, was to do something, using my skills in organic chemistry that might benefit human health at some point. I didn’t know whether that benefit would ever occur in my lifetime. A scientist rarely knows that. But now I’ve been working in this field long enough that I can see the possible new medicines that are coming from bio orthogonal chemistry, and I’m just delighted. |

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| **Biographical** | I was born in a small suburb of Copenhagen, Denmark, on 16th January 1954. I was the first of three children born to my parents, Hanne and Thorkil Meldal. My mother was from the Danish island of Bornholm in the Baltic Sea and was the daughter of Niels Anker Koefoed, who was a farmer and worked with the Danish resistance during the second world war. In my younger years, my mother worked as a schoolteacher and was a very creative artist. I remember spending time with her foraging in nature looking for objects that she would incorporate into her paintings. One of her more “creative” works was one incorporating three dead frogs, which I still vividly remember today. My mother was a very curious and open person who could easily forge relationships with anyone. Looking back now, I can see that the creativity and curiosity that she awoke in me early on, had an impact on my choice of career as a scientist.  If my mother exemplified creativity and a free spirit, my father was the opposite. He was a businessman who eventually worked his way up to become the head of Philips in Denmark. My father was very structured and disciplined, particularly when it concerned fiscal matters. From the time I turned 10 until I left home my father required my siblings and me to keep track of how we spent our weekly allowance to get the next. If we were unable to document how the money was spent, then we would not get an allowance the following week. I, of course, greatly resented this strictness and only did the minimum to secure the money that I needed and in my late teenage years, I rebelled against my father’s strictness.  We lived in a small two-family house near a beautiful lake and natural reserve. I spent my young days roaming around and exploring nature with my friends. I would sometimes leave home to explore without informing my parents and return home much later, very proud that I managed to get around the neighborhood all on my own. I found out much later that family and friends in the neighborhood would call my parents to let them know my whereabouts and that I was safe. Being able to explore in a safe and supportive environment is a key element to success.  During every vacation my siblings and I were shipped off to our grandparents, who had the most beautiful farm on Bornholm. My grandmother, Ady, was a strong and noble woman who never remarried and ran the farm for 5 years after my grandfather passed away. On the farm, I spent my days romping through the forests, meadows, and beaches. When playing hide and seek, I would lay down amongst the barley fields and look up at the blue skies. I would wonder about the universe, about life, about humanity. I discovered my love for nature that has been with me ever since, and a burning desire to understand the mysteries of life and the universe. I guess you could say that I was a scientist in the making, although I did not know that at the time. One of the memories of that time that have stuck with me was the overseer who helped my grandparents manage the farm spanking his children on a weekly basis (it was allowed in those days). The rationale was that they would do naughty things anyway, some of which the overseer would not even know about. Hence, they would be punished for what they had done, and what they could have done. I never quite understand that and was even more grateful for the freedoms that my grandparents and parents allowed me. Fear is not a good motivator and a certain way to kill creativity. However, I must agree that they were really naughty at every chance they got.  As my father rose through the corporate ranks at Philips, so did our income and standing in society. We then moved from Lyngby, first to Hørsholm, and from there to the affluent town of Rungsted, where I attended Rungsted Gymnasium (high school). During high school, I started to rebel against the firmness of my father and the expectations that I should follow in his footsteps and enter the world of business. I was not too attentive to my studies and did not get the best grades. My parents did not know how to handle the situation and their response was that what I needed was more discipline and structure. At 15, I was strongly encouraged by my parents to get a part-time job – which I did. I spent the afternoons stacking heavy bricks at a brick factory. I am convinced that my extraordinarily long arms are a result of adapting to carrying this heavy load of up to 12 tons a day. High school was a time of forging our identity and what seemed to be of major importance was that we lived up to the trend-defined expectations of classmate networks. Only a few of us spent the required time on solving homework exercises, and most of our time was dedicated to sports and friendly get-togethers.  One of the best things that came out of Rungsted Gymnasium is my friendship with the painter and artist Henrik Schutze. Our life-long friendship included sharing and developing as artists (painters) and musicians and is a common bond between us to this day. Henrik, Klaus Mortensen, and I spent many hours playing the guitar or the clarinet. I learned to play the guitar in elementary school and played throughout high school. I took a break from playing during my Master’s degree. Since my PhD studies, I have regularly played a 12-string guitar or a 6-string electric guitar in the evenings, just before bed, as a way of unwinding and preparing my mind for innovative solutions. Being able to develop within the creative arts, through the influence of my mother and my friend Henrik has impacted my way of thinking and approaching scientific problems. I am more creative in my solutions and I am convinced that great scientists may also often be fantastic artists and cooks. **The University Years** After high school years of playing around with chemicals to make rockets, fireworks and gunpowder I started engineering studies at the Technical University of Denmark (DTU). Most of my friends started studies in architecture at Royal Danish Academy, but something drove me towards science and particularly applied sciences i.e., engineering, which at the time was one of the best educations in Denmark.  I completed my master’s degree in chemical engineering in 1981 with a project supervised by Dr. Jørgen Øgaard Madsen on synthesis of indoles. However, during the studies, it became clear to me that I did not want to work as a production engineer and I rather wanted to study and answer fundamental, basic questions within science, since this was far more interesting. I then decided to do a PhD in Chemistry at DTU and approached Dr. Klaus Bock, who was known to be a demanding supervisor but also had access to one of the first superconducting NMR instruments in Denmark. I found NMR was a fascinating technology for understanding the structure, dynamics, and interactions of molecules. Klaus Bock had all the required expertise to study complex synthetic products. My thesis was on the synthesis of complex carbohydrate O-antigens of Salmonella Typhimurium rich in deoxy sugars. We managed in collaboration with the Canadian research group of David Bundle to produce many papers on the structure and function of these O-antigens, including their interaction with an antibody by crystal structure. Carbohydrates became a major part of my research interests in the first half of my career.  Choosing a career in science was just one part of me claiming my identity and breaking away from the expectations from my family. In my early years at DTU, I became involved in a group of Marxist-based students and had many intense discussions at home with my parents who were more on the right side of the political spectrum. The discussions became so dominant in the daily family time that my parents invited me to find another place to live to keep the peace and prevent bad influence on my younger siblings. I moved several times in the first years of studying, starting with a dormitory, then a student community and after two years an apartment in Copenhagen, shared with my friend Mick Ammentorp and his 120-pound Newfooundland dog, I moved into a collective in a small village of Asserbo (a 2-hour train ride from DTU).  It was there that I met my first wife, an Italian ceramist, Sandra Davolio. Sandra and I fell in love and got married. In 1982, my daughter Anna was born, and we moved out of the collective, first to an apartment and then to a larger home, a house in Måløv, 20 km from Copenhagen. We spent a lot of time refurbishing the old house so that it could accommodate Sandra’s workshop, where she could create her ceramics, and a home laboratory where I could test out ideas and do experiments in the evenings and on weekends. That way I would be physically present and not miles away in the lab at DTU and later at Copenhagen University and Carlsberg. I enjoyed renovating our home myself. I have always been skilled with my hands. It probably stems from my father, who had a workshop at home and who taught me carpentry and other home repair skills. He was self-taught and from his example, I also taught myself a lot of the skills needed to repair my home as well as to build and repair equipment and instruments needed for my research.  These were very productive days, when I developed combinatorial chemistry and Sandra her incredible and unique ceramic workstyle. Our home served as a hub for get-togethers with many colleagues, friends, and students over the years.  Our summers were spent travelling in our orange Volkswagen van to different Italian cities where Sandra held workshops on ceramics. Alternatively, we drove north to Sweden to my parent’s summer house where we detached from the world and immersed ourselves in nature, talking and simple living. As a scientist, I could never fully detach from the burning questions I wanted to answer. But these breaks in a creative or quiet environment often triggered ideas that I could later pursue upon returning to the lab.  Upon completion of my PhD in 1983 at DTU, I obtained a 3-year postdoctoral fellowship to work on peptides at DTU. The study was to establish peptide chemistry and synthesize peptide antigens from bacterial fimbriae from *E. coli* K-88 for collaboration on their immunology with Dr. Per Klemm. We established peptide assembly, managed to produce an effective immune response and could characterize the origin of immunogenicity. At that time, I also knew that I wanted to do more research with the most abundant building blocks of nature: carbohydrates and peptides. To augment my experience in peptides, I wanted to work more within synthetic peptides as that would provide the tools to enable combinatorial synthesis. During this postdoctoral period, I convinced Dr. Robert Sheppard at MRC in Cambridge that I should spent six months in his laboratory. This was an exciting and productive period of fundamental research into the technology, methods, and chemistry of peptide synthesis. I was involved in development of the emerging automated Fmoc peptide synthesis, which has since become the main technology used. We were able to establish the first monitoring technology based on amine-driven color change using 3-N-hydroxybenzo-1,2,3-triazin-4-one as a coloring agent. We also prepared all the Fmoc-amino acid active esters of this *N*-hydroxylated catalyst for use in direct couplings. **Copenhagen University 1.0 to Carlsberg Laboratory** Upon returning to Denmark, I worked as a postdoctoral fellow at the H.C. Ørsted Institute at the University of Copenhagen. Armed with this experience in peptide synthesis, I combined this new knowledge with my expertise in carbohydrates to develop glycopeptides to interrogate various biological phenomena. For example, glycosylated proteins are critical to the modulation of the way the immune system functions, and I needed multiple (lycol)peptides to explore their immunological behavior. I then began research in this field. However, at that time, there were no elegant and efficient methods for quickly synthesizing the myriad of peptides and glycopeptides needed for such research. Solid phase peptide synthesis was the starting point in developing these methods. However, the carboxyl activating groups used at that time were unsuitable and lacked the stability needed when carrying out glycosylations of amino acids, under acidic conditions. During this time, I developed the use of pentafluorophenyl Pfp-esters for simultaneous temporary protection and activation amino acid carboxylate groups. Pfp esters were stable under acidic conditions and allowed us to carry out acidic glycosylations to create glycosylated building blocks for subsequent use in peptide synthesis.  Once I had established the chemistry, I still needed to overcome the challenge of how to rapidly synthesize and cleave multiple peptides at the same time. Solution phase chemistry did not promote speed and solid phase synthesis was the way to go. At that time, the available peptide synthesis instruments allowed one to synthesize one peptide at a time, at that time a quite slow process. Parallel continuous flow synthesis of peptides was not yet established as an alternative to single compound synthesis. I then proceeded to design a multiple column peptide synthesizer that would synthesize in a manual fashion, 20 peptides at a time. My engineering background gave me a good understanding of how to design the equipment with the right flow and pressure differentials and which was made of an inert material (Teflon) that could withstand the acidic and basic conditions used during SPPS. I used a slight overpressure on the bottom of the 20 wells to keep the reagents and solvents inside the wells during the coupling and washing steps. The use of an overpressure simplified the design of the instrument and avoided the use of an outlet and valve for each of the 20 reactors. Therefore, the unique design featured a single stopper for all the 20 wells. The bottom of each reaction well was fitted with a sintered Teflon filter. I was fortunate that my neighbor in Måløv had the right tools such as a lathe and a milling machine that I would use to craft the system of reaction wells in a solid Teflon block.  I tested and optimized multiple column peptide synthesis (MCPS) using synthetic PEGA resin that I developed around the same time. The polystyrene resins that were available at the time did not swell efficiently in the solvents used for peptide synthesis and particularly for on-bead assays. I then developed a series of resins based on polyethylene glycyl (PEG) that enabled the resin to swell in non-polar organic solvents as well as water-based solvents. This enabled synthesis of difficult sequences and later, facilitated using one-bead-two-compound combinatorial library approach that I used to identify enzyme inhibitors. My very first MCPS paved the way for future commercial multiple peptide synthesizers once the patent lapsed. The first MCPS instrument can now be seen at the Nobel Prize Museum, and the PEG-based resins were critical milestones to my future research within solid phase combinatorial chemistry and my search for quantitative chemical transformations (QCTs).  In 1988 Professor Klaus Bock was appointed head of the Chemistry Department at the Carlsberg Laboratory and invited me to join the institute and be responsible for building a strong synthesis unit for biomacromolecules based on my work within peptides and glycopeptides in a combinatorial approach. Klaus has been a great advocate and sponsor through my career, and I am very grateful for his support. I must admit that administration and navigating office politics are not on the list of my best skills, and I was very happy that Klaus provided great support to enable me to navigate these. I could focus on the science. We secured funding from two EU programs. The first was a research award from the EU science program in 1992. The award supported research within the development of methods in glycopeptide synthesis program in collaboration with the group of Professor Hans Paulsen at the University of Hamburg.  Later, in 1995 we were awarded an INCO-EU-DC program grant to develop cysteine protease inhibitors for parasitic proteases. It was a global collaboration including laboratories of Dr Graham Coombs (Glasgow, Scotland), Dr Med Luis Juliano (Sao Paolo, Brazil), Dr Med Julio Sharfstein (Rio de Janiero, Brazil) and Dr Jorge Arevalo (Lima, Peru). During that program, we further developed the concept of one-bead-two-compound libraries and their use in screening for enzyme inhibitors in a fluorescence-quenched on-bead assay. The program very nicely integrated the discoveries developed earlier: SPPS using stable Pfp esters, MCPS now using a modified version suitable for combinatorial library synthesis, PEG-based resins that were suitable for synthesis and biological assays in water. It was also at that time that the work we did began to be recognized by the scientific community and some of the notable awards I received were the Mitzutani Foundation Award (1995), the Danish Society of Chemistry (NKT) Award (1996), the Leonidas Zervas Award from the European Peptide Society (1996), the Danish Ellen and Niels Bjerrum Gold Medal in Chemistry and the Bjerrum-Brønsted-Lang Award from the Danish Royal Society of Science and Letters (1997). While I do not believe that the motivation for doing research should be to get accolades and awards (e.g., the Nobel Prize), it was highly rewarding and appreciated to receive these recognitions of my work. The recognition facilitated acquisition of funding and research grants from various funding agencies. In 1996, I was appointed Adjunct Professor at DTU and at the University of Pharmaceutical Sciences, Copenhagen (now part of Copenhagen University). By these appointments, I was able to teach chemistry to university students, something that I missed doing as a professor at Carlsberg Laboratory.  In 1997, I received a grant from the Danish Cancer Society to study glycopeptides as vaccines for treatment of cancer. And in 1997 I was awarded a large 5-year grant by the Danish National Research Foundation to establish a Solid Phase Organic Chemistry Center (SPOCC) at Carlsberg Laboratory. The purpose of the center was to develop quantitative organic reactions for solid phase combinatorial chemistry. As mentioned earlier, there was a need for new types of quantitative chemical transformations that could be performed orthogonally and on solid phase. Particularly within the context of on-bead screening, which required that the compounds attached to the solid support were pure. The SPOCC center grew rapidly and at the time of the CuAAC discovery we were around 25 PhD’s and Postdoc’s from all over the world. The SPOCC center and Carlsberg Laboratory was a great place to do fundamental scientific research. There was close collaboration with the Danish NMR center, a facility that included 800, 600 and 500 MHz NMR spectrometers and which was established by Professors Klaus Bock and Flemming Poulsen. This center and a Micromass HR-Mass spectrometer provided core technologies vital for the results obtained in the SPOCC center. We are grateful to Dr. Charlotte Gotfredsen, Bent Ole Petersen and Professor Jens Duus for supervision and maintenance of the NMR facilities and their scientific contributions, in particular, towards NMR analysis of complex resin-bound compounds.  The period between 1988 and 1998 was extremely busy and I focused most of my attention and energies on building a career and finding fundamental questions to answer through research. Throughout my career, I have always spent time a lot in the fume hood doing experiments myself and keenly observing what happened. Maybe as a consequence of this single-minded focus (who knows?), in 1998, my wife Sandra and I sadly decided to part ways and end our marriage.  In the period following the divorce, I continued to focus on my fundamental research at the SPOCC center and also looked into ways of commercializing some of the inventions that came out of my research over the years. In 2000, I founded a biotech start-up, Combio, together with my long-time collaborator and friend, Søren Mouritzen and with the backing of Carlsberg Brewery. Combio’s core technology was based on use of our new PEG-based resins in combinatorial synthesis and on-bead screening of protease inhibitors. The purpose was to discover drug candidates primarily within infectious diseases. Combio also provided an opportunity for employment of the PhDs and Post Docs from my lab. After three years Combio was successfully sold to the company Arpida. However, in the process, the technology and target focus was unfortunately changed towards small molecules.  At the turn of the millennium in 2000, the year of the CuAAC discovery, I got married again to Dr. Phaedria Marie St.Hilaire, a Dominican-born scientist and strong advocate for women’s rights and diversity and inclusion (www.prowoc.org). We met when Phaedria worked at Carlsberg Laboratory, where she had very successfully developed methods for the synthesis, screening, and analysis of glycopeptide libraries. We developed a great friendship, which eventually led to marriage. One day in 2001, on a bike ride near Copenhagen we stumbled upon a small, old house in a beautiful nature reserve and decided to make it our home. We spent more than a year renovating it – the second home I had to rebuild. In 2003, we were very happy to welcome our son Ajani to the family. We enjoy adventures and traveling around the world. Phaedria has been and is a treasured confidant and sparring partner – someone from whom I seek advice on all matters, big and small, personal, scientific, and professional. I am deeply grateful to have someone with whom I can share many of my interests, and who challenges me to improve my personality.  In 2003, inspired by the success of Combio, Carlsberg Brewery established a special unit at the Carlsberg Research Center called Carlsberg Biosector. The purpose of the center was to commercialize the inventions that came out of the basic research of the institute. The Biosector served as an incubator for various ideas from the entire research center. Three ideas from the SPOCC center were part of the Carlsberg Biosector: 1) Affinyx – a rapid and differential way of screening for selective receptors, 2) VersaMatrix, which specialized in the manufacture and application of encoded PEG-based resins in combinatorial science and affinity ligand development for chromatographic applications and 3) 2cureX which utilized combinatorial, fluorescence-based screening of primary cellular cancer targets. 2cureX still exists today and VersaMatrix was bought up by the company Novo Nordisk. My wife, Phaedria, was instrumental in establishing the technology of the Biosector as a group leader and eventually became Director of Research and Development at VersaMatrix. When the company was acquired by Novo Nordisk she moved with the company towards new challenges. **The return to Copenhagen University** The years 2000 to 2004 were a very happy period when I was given the freedom and funding to pursue basic research interests and as well as commercialize the research in several biotech spinouts. It was also in that period that the CuAAC reaction was discovered as a result of a mixture of serendipity, detailed observations, and rigorous analysis of what happened when a reaction does not go as planned. You can learn more about the story of this discovery in my [Nobel Prize lecture](https://www.nobelprize.org/prizes/chemistry/2022/meldal/lecture/). When we announced the findings in 2001 at the American Peptide Symposium, I had no idea that this reaction would become so well-known and widely used in myriad applications, from drug discovery to materials science.  It is a universally acknowledged truth that no good thing lasts forever, and in 2005 the Carlsberg leadership decided to redirect the focus of the research center to the beer brewing processes. This change in strategic focus led to the complete closure of chemistry related research and disassembly of the associated facilities relatively quickly over a couple of years. During this period most of the professors and skilled researchers at Carlsberg Laboratory left the institute for employment in other organizations, while I tried to adapt my research to the new policies. For example, I worked on developing a new material that could be used for biodegradable beer bottles and packeting. It was challenging to secure funding for basic research in that period. Having lost many easily accessible in-house collaborators, I was somewhat despondent as I considered my next move. One highlight in that period from 2005 – 2011 was the honor of receiving the American Chemical Society’s Ralph F. Hirschmann Award in 2009 for my work in peptide chemistry and combinatorial science.  In 2011 I was contacted by the head of the Department of Chemistry at the University of Copenhagen (KU), Professor Mikael Bols. He invited me to apply for a position as a professor at University of Copenhagen and head of the associated Nano Science Center. I accepted his invitation, applied, and got the position. I started my research at KU with research grants from Novo Nordisk (2012) and the Lundbeck Foundation (2012). Shortly after in 2013, I was fortunate to be granted funding for a Center for Evolutionary Chemical Biology (CECB) for five years at the Department of Chemistry. We established a multidisciplinary center based on using click chemistries and combinatorial technologies in the studies of bio-macromolecules and cells. As a full professor at the university, one of my responsibilities was teaching. It has been some decades since I taught fundaments organic chemistry to students, and I spent a lot of time and effort creating new material and developing modern ways of teaching.  One of the problems were that chemistry majors were taught chemistry at the same level as all other students, and the students did not identify with their chemistry. I was allowed to separate out the chemists for their teaching in organic chemistry. To me it is important that students learn by curiosity and study in a positive spirit, while building their professional identity. Therefore, we as teachers need to meet the students where they are. Students need to be actively engaged during class. I produced advanced lecture material and teaching videos exclusively covering the first semester for chemists at University of Copenhagen. This was a great period and chemistry students thrived. Currently, I have successfully tried to implement some of the same principles for an advanced chemistry course at the master’s level.  In spite of fantastic evaluations, it was not possible to raise funding for the continuation of the CECB center. Starting in 2018, the center gradually lost its expertise in protein expression and cellular studies. In 2019, I and my friend and entrepreneur Dr Søren Mouritsen, with whom I had founded Combio 20 years earlier, established a company, Betamab, based on the betabody technology emerging from CECB. The company collaborated with the allergy drug company Alka Bello. With limited funds and resources, I worked day and night, weekdays, and weekends on complex synthesis of click-constrained betabodies and microproteins. Unfortunately, we were unable to produce results that could compete with monoclonal antibodies. In 2020, Betamab’s activities were discontinued. However, in CECB we continued the betabody and microprotein research with support from many master students who found the structure activity concepts of CECB fascinating. Since 2020, I have been focusing on teaching the upcoming generation of chemists. I have had many challenges securing new funding which would allow me to pay PhD and postdocs and have started wondering whether ageism could be at play. In September 2022 I received a grant from the Velux Foundation towards design and synthesis of functional microproteins.  Then on the 5th of October 2022, to my surprise and delight, I was awarded the Nobel Prize in Chemistry! This award has given me a new lease on life: new funding to pursue my research in chemistry and a platform from which I can advocate for combination of new chemistries, molecular design, combinatorial science, and new assays towards the discovery of new drugs and new materials to improve the sustainability and quality of life. I am also particularly excited to see what our improved understanding of quantum properties within chemistry will bring us in the coming years. I believe the Nobel Prize in Chemistry is instrumental as a tool to guide and direct future research on a global scale. It also inspires young curious students to venture into chemistry and other natural sciences. Now I am looking towards the next chapter in my research and my life. |
| **Autobiographical** |  |
| **Podcast** | [Meldal]  Morten Meldal: “Not all students come to school with equal ability to make abstractions or see images and so on, but if we are able to show this imaginary world — make cartoons of our chemistry world – I think we could really reach far with that.”  Adam Smith: Not everybody gets on with chemistry. But talking to the chemist Morten Meldal, you have to wonder why that is. The way he describes chemistry is as full of images, abstractions, possibilities. He connects the way he thinks about chemistry with the way he thinks about painting on canvas or playing music. And you can see that it’s all part of the same creative desire. He talks about the concept of pleasurable learning, a lovely phrase which I think for most people is a long way from what their experience of learning chemistry at school was. But he sees that it should be enjoyable and fun and enticing. And speaking to him, I can really see how that could be. With the hope that you’ll enjoy this conversation as much as I did, let’s listen to Morten Meldal.  Clare Brilliant: This is Nobel Prize Conversations. Our guest is Morten Meldal, the 2022 chemistry laureate. He was awarded the prize for his ground-breaking achievements in click chemistry – the art of snapping together chemical building blocks in quick and efficient ways. He shared the prize with Carolyn Bertozzi and Barry Sharpless.  Your host is Adam Smith, Chief Scientific Officer at Nobel Prize Outreach. This podcast was produced in cooperation with Fundación Ramón Areces.  Morten Meldal is professor of chemistry at University of Copenhagen. In this conversation you’ll hear him talk about the importance of honesty, going from painter to chemist – and the science of turning an oakwood plank into an electric guitar.  But first, he looks back on a memorable week in December.  Smith: How have these months been since the announcement?  Meldal: It’s been fantastic. The whole experience of Stockholm was amazing. It was like a mixture between the Wizard of Oz and Alice in Wonderland. The Swedish are very, very good at making those kind of statements as the Nobel Prize really is. I was very happy to go there with my family.  Smith: Let me take you back to one moment from Nobel Week in Stockholm.  *CLIP:* This is a truly great achievement for the benefit of humankind. On behalf of the Royal Swedish Academy of Sciences, I wish to convey to you our warmest congratulations. May I now ask you to step forward and receive your Nobel Prizes from the hands of His Majesty the King.  Meldal: That was truly a wonderful moment.  Smith: What was going through your head as you were there alone on this day?  Meldal: Several things that how big this really is. I remember thinking that and then my daughter was sitting on the second row or third row and I could see she was crying and tears actually are contagious. I was almost crying when I had to go up and receive the prize because of that.  Smith: It’s a strange moment in a way because you’re surrounded by people and everybody  else is talking, but you, the laureates, are silent on stage during all of that.  Meldal: Yes.  Smith: You have time to reflect and it may be in fact one of the few quiet moments for you during Nobel Week.  Meldal: Yes. I really like the fact that you can discuss and have a dialogue with people in  such situations. I truly enjoyed our meeting with the Royal Family of Sweden where we actually could talk like laymen with the Royals. That was really nice. I also really liked the Nobel Minds discussions. I think that was a unique moment.  Smith: Indeed, bringing all these disciplines together and seeing what bubbles up from the mix of ideas.  Brilliant: Before their discussion, Adam asked Morten Meldal to name a book that influenced him, both as a scientist and as a person. Morten selected two books. The first was the ´The limits to growth´, where a team of scientists used computer simulations to show how our over-consumption of natural resources would impact humanity and the planet. With translations in 30 languages and 30 million copies sold, many of the book’s predictions have turned out to be correct.  Meldal: It made a huge difference to me because it made it possible for me to distinguish between what the politicians are deciding in order to satisfy their next election and what they do to actually make a real difference in the progress of human beings in the society.  Smith: It was published in 1972 and was a simulation of what would happen if resource availability continued in linear –  Meldal: You read it?  Smith: Yes. You gave me my homework. I’m a good student sometimes. When the task is right and this was right. The simulation was of linearly increasing resource availability and exponentially increasing problems like population growth, pollution, industrialization, consumption. Some people ridiculed it at the time. When did you encounter it?  Meldal: It must have been in the late 70s or start of the 80s, something like that. I don’t remember exactly when it was, but I was very young at the time.  Smith: It was a forerunner, if you like, of the now very loudly spoken drive for sustainability.  Meldal: Exactly. It put everything in perspective already then. It was incomprehensible for me and many other young people at the time why the politicians didn’t take the simulation seriously because it actually would have the effects that we see today. I don’t think anybody can doubt that this is a really, really serious situation, which we just started on. We are not really seeing the actual consequences yet. That made a big difference to me.  Smith: How did it influence you?  Meldal: In my decisions to actually choose, including choosing to study chemistry, because I thought that chemistry would be a way to solve some of the challenges. I didn’t know what to do with the chemistry at the time, but since a lot of it had to do with the development of energy sectors and chemical productions and medicinal chemistry around the world, I thought that studying that would be the only way to be able to have an influence on that field.  Smith: It seems an enlightened view. Of course, you and all of the other people who are keen on chemistry know that chemistry can make a difference for good. There is, unfortunately, a general perception among the public that chemistry is a producer of bad things.  Meldal: There are two levels of chemistry. There is chemistry as an education. Chemistry as an education is often associated with the local production environment in the region and so on. Typically engineering and stuff like that within chemistry. Then there is chemistry as a fundamental science and as a way to actually see everything, the existence. Chemistry is involved in every single interaction between molecules that lead to organisms. It’s like the fundamental science underlying biology, underlying the whole nano sector where you have nanoscopic entities emerging like cell membranes and stuff like that. It underlies our food production, it underlies our consumer industry. Every single aspect of our life is sort of lined with chemistry. I think there is a lot of existential aspects to the study of chemistry. Understanding where we are from and what we are going to be if we don’t do this and that.  Smith: It’s a beautiful way to frame it. I suppose you already had the role of being a spokesperson for chemistry. But now with the Nobel Prize conferred, you’re very much in the limelight for speaking up for chemistry.  Meldal: That’s what I also used to say that the Nobel Prize makes a really big difference because it’s not only honouring what was in the past, it’s also setting all the directions for the future. If you take this opportunity, you get a really strong voice to talk about things. One of the things that I would really like if we could make chemistry part of the general education and have pleasure-driven teaching already from the first grades in chemistry, visualizations and so on.  Smith: Pleasure-driven teaching. It’s a lovely phrase. Tell me more about that.  Meldal: Pleasure-driven means that it should be very easy to consume for the students. Not all students come to school with equal ability to make abstractions or see images and so on. But if we make the images for them, if we are able to show this imaginary world as if it was something they could really see. To make cartoons of our chemistry world in order to make them understand this and not invoke any of all these calculations that you often have in chemistry at any early point but just let them be free and let them watch instead of let them use in the beginning. I think we could really reach far with that.  Smith: It’s a lovely point because chemists draw and children draw. There should be a lovely connection there.  Meldal: Yes, exactly. I think with today’s capacity of doing animations and doing chemical calculations and our fundamental understanding on how electrons are moving around and how they react with other molecules and so on. All of that can be boiled down in an animation studio to something that is really useful for the teaching.  Smith: When you think of chemistry in the way you framed it, of where we came from and what we will become, how could anybody not be interested in that?  Meldal: Exactly, that’s my point.  Smith: What have you learned about yourself during all of this then?  Meldal: What I’ve learned is that whatever honour you get, the most interesting thing is still what goes on in the fume hood. I’m really enjoying my time with the students, trying to solve some problems. You have to challenge the students and yourself and when you do that you often hit your head on a brick wall. Then you have to get together and solve that problem. I love that process where everybody is coming with input and we try to make a solution to those problems. That’s very important for me. That’s what I found about myself. I really like that. Teaching and the research environment is quite a unique thing. It’s the best working space you can have, in my opinion. So be careful with that. Of course, there’s a lot of travels now. There’s a lot of other things that are part of my agenda. But I will definitely be focused on trying to maintain that and also writing articles.  Smith: When I asked you about books, you offered two. You offered ´The Limits to Growth´. You also offered ´The Lord of the Rings´.  Meldal: Yes.  *CLIP reading an extract from the book ´The Lord of the Rings´:*  Three Rings for the Elven-kings under the sky,  Seven for the Dwarf-lords in their halls of stone,  Nine for Mortal Men doomed to die,  One for the Dark Lord on his dark throne  In the Land of Mordor where the shadows lie.  One Ring to rule them all, One Ring to find them,  One Ring to bring them all, and in the darkness bind them,  In the Land of Mordor where the shadows lie.  Smith: How has ´The Lord of the Rings´ influenced you?  Meldal: I read ´The Lord of the Rings´ in high school, long before any of the movies were ever made. I actually played sick during this period because it was so exciting to read this book. I love the level of the language, which is amazing. I read it in English, of course, and the original language of Tolkien is really nice. I think it’s very rich and you have this sensation that it’s almost like it was a Shakespeare novel. His world is so complete and it’s so good in distinguishing good from evil and all the aspects of turning evil from being good. I think that was really, at the time, something that resonated with my identity, the way that I was looking at the world and myself. That was a very, very important book for me. Before you had the movies, I built this world. When Peter Jackson recorded this movie, it was amazing to see how much his perception was exactly the same as I had had years before this, when I read it, because everything was just like I had imagined in the movie.  Smith: Did you visualize the characters when you read?  Meldal: Yes, yes. I’ve always been good at visualization. I think that’s my force, actually.  Smith: That’s very interesting that the personifications of these characters you’d read about were right. Aragorn was Aragorn and Legolas was Legolas. Amazing. Tolkien’s scholarship was I suppose essential to the creation of that world that was so well thought through, even differences in language between the different places and things. Marvelous. You read it in that single fat edition of all three books together.  Meldal: Exactly. Beautiful illustrations.  Smith: It’s a lovely thought of you skiving from school and reading that. It might be a difficult question, but how much does fictionalization, imagination come into the work you do?  Meldal: It’s a lot actually. I have a very good friend who is a painter. He was with us in Stockholm actually. We have always shared a lot of common ways of seeing things and experience the world in much the same way. We have been a mutual inspiration all of our lives.  Smith: You do many things. One of the things you do is combinatorial chemistry, where you create vast libraries of different compounds, things that have never been made before. You are just reaching out into the vast untapped regions of chemical space, all the different things that could potentially be made. When one talks about it, there seems a very strong visual image there. Is that how you think about it?  Meldal: I just have to see it a couple of times and then it becomes part of my inside world as an image of how electrons are and what residues are where and so on. Then I look at the library and I get the opposite component from the library and what that should look like and so on. Yes, I have a lot of ideas of how to actually structure the libraries towards a particular target because of this visualization.  Smith: Are these skills that can be taught to everybody or does it require some innate ability to visualise?  Meldal: I think you train this just as much as this part of your way of thinking. I think it actually starts very early on, this training. It’s not something that starts with chemistry in seventh grade, something that starts when you’re young. For some reason, you have an exciting experience where you need visualization and it just triggers something in your brain and you build it then from many years and become good at it. It’s very much an environmental thing. I think as our education system also shows you can be educated to do almost anything.  Smith: Indeed. How did your painting career go?  Meldal: When I was doing my engineering studies, I was painting at night and then I was very tired during the day. I had to stop that. I haven’t taken it up again since then. My most wonderful experience of that is I just went to the forest. I found a beautiful spot and I just draw, my eyes were looking at the scenery. The painting was following that without any sort of deeper thoughts, just following what you saw exactly. That was a really nice experience. In 20 minutes, painting wet and wet, I got the entire sensation of that beautiful place. That was good. That was very good.  Smith: You seem to have a very thoughtful approach to life, if I may say so. Where did that come from?  Meldal: I guess that my parents have had a great deal to do with that. First of all, when I was young, they always shipped me off to my grandparents’ farm in Bornholm. This is a beautiful place in the Baltic Sea. They had a big farm there with meadows and forests and beaches. You get a lot of thoughts when you are playing around like that, constructing your huts in the forest or how everything works together and so on. That, I think, made a big difference to me.  Smith: It speaks to the value of just allowing people to discover the world for themselves and live it free time.  Meldal: Yes.  Smith: Skipping school to read books, just –  Meldal: Pleasureful learning. I think that’s really important because I don’t think you can learn by force, external force. Of course, you can force yourself to learn and that’s because you want to learn and that’s still pleasurable. But if you are asked to learn against your will, that’s not going to happen. Nothing’s coming in.  Smith: I suppose where all this is going is that I’m trying to see if we can get some insights into how you became the sort of person who, when the CuAAC reaction popped up in your lab, the first click chemistry reaction, you were in the right frame of mind to discover it, if you see what I mean. You had the curiosity, you had the insight, you had the background that allowed you to say, well, there’s something that we need to pay attention to and to follow it through. Because that is, I suppose, one extraordinarily important art of discovery.  Meldal: I think that is probably one of the most important arts of discovery because if you look at it, many of the big disruptive discoveries that were made, were made in this way. I think that a lot of, if you go back, I wonder how many of the Nobel Prizes would actually, in chemistry, would actually be that kind of ”wow” experience for the researcher.  Smith: Can you spot in the young people that come through the lab, the sort of minds that are likely to be tuned to spotting new things?  Meldal: Yes, of course. I can see – it’s a sensation. You can sense that they have this kind of mixture of curiosity, ability to imagine some stuff, ability to think in abstract terms and so on. All of these things come together in a special way when you have this kind of person. It’s not always the ones that are best organised.  Smith: The reaction was, of course, discovered also and separately by Barry Sharpless.  Meldal: Yes.  Smith: Barry is a kind of maverick risk taker. Would you say that you and Barry are similar or do you have very different approaches to chemistry?  Meldal: I think we have the same kind of association disorder, you might say, which means that you make connections in your mind that are not coming naturally from your experience, but it just grows like that. You have new ideas. It’s a sort of a combination of previous things. But at the same time, at an abstract level, you make new bridges that were not there before. I think that’s what we are both doing.  Smith: That seems a perfect segway into another subject, which is music, which is also important to you.  Meldal: Yes.  Smith: You play in a band, right?  Meldal: Yes, I have my guitars.  Smith: These, which I have the privilege to be shown now, but our listeners will only have to imagine them. They’re very beautiful, rather different looking, rather futuristic looking guitars. How would you describe the guitars? These guitars that you yourself have built?  Meldal: If you look at them, they sort of have a design where most of the material was removed as much as you can, because this is made of quite heavy wood, it’s oak wood. I removed as much as I possibly can in order to make a good design.  Smith: They’re very beautiful. They’re very sculptural.  Meldal: Yes. So that’s a new kind of guitar design.  Smith: Now, okay, before we get into the design, let’s listen to your son-in-law, Kevin Shields, and your daughter, Anna, talking about these guitars.  Meldal: Okay.  *CLIP on Meldal’s guitars:*  Kevin Shields: We’ve had three or four, but they’re super high level, and they’re super interesting looking.  Jessica Gerdin (reporter): Yeah, have you played them?  Shields: Yes. And they’re kind of like, if you imagine a great scientist designing a guitar, how perfectly accurate it is, and it’s like super high level. You couldn’t buy something commercially that easily.  Gerdin: Have you given him any effect pedals? Because I know that’s an obsession.  Shields: Yeah, yeah, yeah. I mean, I’ve always given him guitars and effects. He loves my Jazzmaster. He plays a certain Jazzmaster he loves when he’s over, and he builds pedals as well. She builds pedals. He builds pedals.  Anna Davolio: Yeah, my dad and I build pedals together as well. We make from scratch. We make this, guitar pedals.  Gerdin: This is lovely.  Shields: I don’t even have to give him any. He’s building them.  Smith: So that excerpt from the hubbub during Nobel Week, Kevin Shields of My Bloody Valentine and your daughter, Anna Davolio, speaking about making pedals. What kind of guitar does a great scientist design?  Meldal: Yes, of course, you do a lot of calculations and exactly where you want your bands now, the distance between the bridge and the end of the guitar and so on. All of that is calculated using a scientific approach. Then you make it and you make sure that you have possibility for adjustment because as in everything else in nature, it doesn’t behave like the theory. There’s a lot of other factors like the thickness of the strings and the way they bend down towards the board and so on that plays a role. You make it as good as you can in calculation. You make sure you are accurate in your carvings and your carpentry. Then you make sure that you have adjustment possibilities that can accumulated whatever sort of little things that are not ideal.  Smith: Did you make them because you wanted a sound that you couldn’t get from something you bought or did you make them for fun?  Meldal: No, no, I made them for fun. I made them because when I was young, I helped a forester. Actually, he has a castle in Denmark. I helped him put his forest on to an Excel sheet so that he would be able to see where he needed to go and what he needed to do in his forest. As a thank you, an appreciation, he gave me an oak tree which was sliced in five, six centimeter planks that I could use for this.  Smith: That’s a lovely gift.  Meldal: I have had them in my shed and I just used them.  Smith: That’s what they told you they were. I remember the furniture maker James Krenov  used to stand by his wood for hours at a time waiting for the wood to tell him what it wanted to be. Was that your relationship with your oak boards?  Meldal: I make these drawings on computer, right? I have a technical drawing program and I put it in the computer so everything is accurate. I make the print out and then I glue it together from A4 paper and put it on the oak tree in different ways to see where it fits the best and so on. A similar process.  Smith: What sort of music do you play?  Meldal: I make my own, first of all. I make songs, I like to make songs, ballads kind of songs. I also play in a rock band where we play anything from back to old Elvis all the way up to Maroon 5 and stuff like that. All sorts of blues or reggae or whatever kind of music.  Smith: Is there one artist you particularly adore?  Meldal: I very much like Bob Marley. He was a very unique musician. I also like Weather Report. There’s a group called Entrance. I love African music like Salif Khaita or Barbara Kanaan. There are many musicians in the world that are essentially unknown in these countries up here but are very good.  Smith: Indeed. What is it about Bob Marley that you particularly like?  Meldal: His honesty with life. He was more or less seen as an outcast in the beginning, right? He built his life on trying to be honest with all the things that happened around him which was not always very nice from the people who have the money.  Smith: We began talking about music because of associations one makes between different spheres. Do you think that’s how you think about music? That it’s bringing things together from different places?  Meldal: Yes, of course. There’s a lot of atmosphere in music. The music is usually used to describe some sort of situation in, for example, in connection with a text or even without a text. I remember Pink Floyd has a piece of music where you start with seagulls making noise and drops of water and so on. That’s a whole piece of music that paints a painting with sound. I think that’s a very nice way to see music actually. That it is a picture with sound.  Smith: You’re still a painter. A painter in science, a painter with chemistry, a painter with music.  Meldal: Yes, you can say that.  Brilliant: Morten Meldal was awarded the Nobel Prize for developing the CuAAC click reaction. What is ‘click chemistry’, Adam?  Smith: Click chemistry is a really easy way of joining molecules together. Traditionally, it’s quite hard to get bonds to form between molecules in a selective way. Lots of groups on molecules want to react with each other and form bonds. But the problem is normally that you have all these different groups, all of which can do different things. Making them react in exactly the way you want is hard. In click chemistry, you have two groups, one on one molecule, one on another, which very selectively want to join together and make a bond, leaving everything else untouched.  Brilliant: That sounds really clever. How did Meldal and colleagues come up with the idea?  Smith: They found that these two groups, one is an azide, which is three nitrogens joined together, and one is an alkyne, which is two carbons joined by three bonds. These two groups would, under very, very mild conditions in water, together with a copper catalyst at room temperature, they would bond together and form a cyclic molecule, a thing that looks a bit like a ring, and that, as I say, almost magically, this happens without interfering with what else is going on around. This contrasts so starkly with what organic chemistry is often like. If you remember back to doing experiments at school, you tended to have to boil things up and you used all sorts of solvents that smelled terrible. Click chemistry dispenses with that. It just happens in nice, gentle conditions. It makes it much greener. I suppose it’s a more sustainable reaction, but it’s also a way of making things happen in a very predictable way. That means your yields can be higher. You can just spot opportunities to join things together.  Brilliant: What are the applications of click chemistry? You can build all sorts of molecules that formerly just seemed to be too complicated to make because you just couldn’t see how to selectively stick two things together. Given that, sort of the world’s your oyster, really, you can use it in the lab just to make more interesting chemicals. But you can also use it in biology to tag large molecules, see where they go in the body, or to create potentially therapeutics. You can target the active site of enzymes, for instance, inhibit them or turn them on more. That may be very important in treating disease in the future. There’s innumerable things you can do with it. Let’s listen to one of the ways that Morten Meldal himself is using the click chemistry he discovered.  Meldal: If we can make by this process an enzyme, in particular if we can make an enzyme with a target that is important, it could be anything from Alzheimer peptides to a pathogen protein that you don’t want. There are so many areas where you can think of using an enzyme instead of a drug in medicine. An enzyme has the advantage that the enzyme would be capable of neutralizing thousands of molecules where if you have the conventional drugs where you are generally using inhibition kind of processes or activation kind of processes, you need a molecule for the activation or the inhibition and that means that you need excess compared to the interactions you want to interrupt.  Smith: Do you see this coming to fruition in the foreseeable future?  Meldal: No. But I see it as being very exciting and something that could make a fundamental difference to what we do. That’s why we do it. I’ve never been thinking about having a tangible result immediately because that’s actually removing a lot of the challenge from what you’re doing because you have to do it in a very practically and applicable way. Where I think most of the bigger discoveries, they are actually where you don’t expect things to happen and are also in the challenging areas where it’s difficult to do what you’re doing at the moment. It might become easy later on like with click chemistry but it’s actually difficult to do what we tried to do before the click reaction was very difficult. With the click reaction it became easy, right?  Smith: Yes.  Meldal: I never had a program that was successful from the beginning. It’s always full of problems that have to be solved and it’s your persistence that really makes it come true.  Smith: Having a record of some of that thought process when you write is a very valuable thing to contribute as well.  Meldal: Yes, also you have to be honest when you talk about your work. You have to be very honest as a scientist and I think that’s maybe something that is forgotten once in a while, how honest you actually need to be. Particularly because a lot of other people’s destiny and what they invest their time in will be depending on what you have done and how you described it.  Smith: That’s a fascinating point. It must be true that it’s hard to tell things exactly as they are given as you say, your young people in the lab are clamoring for papers that will take them to the next stage of their career and your funders want to see success. A lot of conflicting demands on you.  Meldal: Yes, but the most important one is being honest about your results. Having a certain level of humility towards your own capacity and ability to do the right thing every time.  Smith: What I would like to know and what I suppose everybody needs to find out is how to combine these things we’ve been talking about. That everybody talks about how to hold on to your curiosity, but it’s how to have, it’s not just that. It’s about how to not get too set in your ways that you’re, you close your mind to different avenues, to new approaches. As you say, remain honest, because so often the story can take over and you become invested in selling yourself as the expert in this or that technology and stuff. Then that can let you down.  Meldal: I think a lot of it has to do with you being comfortable to not being in your comfortable zone, to be able to deal with a situation where you are not comfortable at all, including in research where you might have to enter into unknown space: electronics or physics or particular kind of inorganic chemistry you don’t know anything about. You can actually approach that because it’s part of the solution to your particular problem. It’s also stepping out of your comfort zone to actually admit that it didn’t work like you expected it to. It’s also out of your comfort zone to let other people actually take the honour for their work when they actually did it and so on. That’s very important issues, particularly for research.  Smith: How do you create the environment or do you actively curate the environment that allows people to be comfortable? Because it is competitive research.  Meldal: Research is competitive and I actually have four people that work in cohort on the same kind of project. They have different aspects of the same kind of project. Of course there’s a little bit of competition to that, but there’s much more collaboration actually. If you can create a collaborative atmosphere, you can relax that sensation of the egos from the very beginning, get them to understand each other as part of a greater process. It’s really important.  Smith: I suppose fundamentally it comes down to a deep and abiding interest in the problem, an interest which puts everything else aside. Is that learnt or does that have to come from within? Can you learn to be interested?  Meldal: I was always spurred by my parents to have interest in everything around. My mother actually used frogs and dried fish in her paintings and they were sort of smelly because she glued them on and they were swimming around in the ocean or whatever. She collected everything and I think you learn a lot about interest in everything from that. I’m very grateful to my parents for that.  Smith: Your mother was a painter?  Meldal: Yes, she was a painter. She spent the first half of her life as a teacher and then she started painting and became a painter.  Smith: What did your father do?  Meldal: He started out in the business of Kosan gas, these yellow gas cylinders that we have in Denmark. He soon became an employee in Philips and then he was director in Philips for many years.  Sith: You had arts and business mixed.  Meldal: Yes, my father was quite strict and my mother was quite emotional.  Smith: Which sort of parent are you? Strict or emotional?  Meldal: Probably a mix of both, but I allow a lot because as long as there’s no danger, I think that’s the best thing to do for my children.  Smith: Yes. It’s been a delight. Thank you very much.  Meldal: It’s been very good talking to you.  Brilliant: You just heard Nobel Prize Conversations. If you’d like to learn more about Morten Meldal, you can go to nobelprize.org, where you’ll find a wealth of information about the prizes and the people behind the discoveries.  Nobel Prize Conversations is a podcast series with Adam Smith, a co-production of Filt and Nobel Prize Outreach. The producer for this episode was Karin Svensson. The editorial team also includes Andrew Hart, Olivia Lundqvist, and me, Clare Brilliant. Kevin Shields and Anna Davolio Meldal were interviewed by Jessica Gerdin. Music by Epidemic Sound.  If you’re looking for more listening, check out our earlier conversation with David MacMillan, another Nobel Prize laureate with the ability to get practically anybody interested in chemistry. You can find previous seasons and conversations on Acast, or wherever you listen to podcasts.  Thanks for listening. |
| **Telephone**  **interview** | [MM]  Adam Smith: Hello. My name is Adam Smith, calling from Nobelprize.org. Well, many, many congratulations.  Morten Meldal: Thank you very much. Yes, I was not expecting it at all. It was really a surprise.  AS: So, of course, the first question is how did the news reach you?  MM: I was called this morning by committee, and they congratulated me. To win this prize together with Carolyn Bertozzi who I know from a very long time ago already, and also Barry Sharpless who I visited a couple of times, and I know both of those very well.  AS: Indeed, how nice. And your first action or reaction on hearing the news?  MM: Was just total surprise, and I … you know, I think that there’s a lot of research that goes by which are, is very exciting, and sometimes you just by serendipity have an orange falling into your turban and you have a very nice idea that can make a lot of people have an easier life in their research, or even in the, you know, in public. And that’s what happened. That’s what happened to me. So this was a very serendipitous discovery that we did. By analysing our results we found that there was something strange going on, and this was very useful.  AS: Indeed, yes, I mean click chemistry is transforming the ease of doing reactions.  MM: Yes. Once you have completely new organic reactions, that can completely change the field. And that’s what happened in this case.  AS: Isn’t it marvellous, the way that despite all the work that goes into organic chemistry new organic reactions keep appearing?  MM: Yes, because the reality is much more complex than we as chemists are able to imagine, and new things come up all the time, and will forever. And I think there is no way that we will ever know everything. And the complexity of organic chemistry, also reflected in complexity of life, is very, very high. And we are only scratching, you know, the beginning of our understanding of organic chemistry, I think.  AS: How marvellous to explore such an unknown universe. Is that what drives you when you go into the lab each morning?  MM: Yes, actually it is. I’m working on something that I find is very exciting at the moment. Also new stuff, and I think that everyone who’s interested in chemistry and works will be awarded because it is such an interesting field. It is actually describing our reality, and that is why it’s so important with chemistry as well.  AS: That’s a very nice point, because people in general tend to view chemistry – who are not involved in it – a little bit negatively sometimes. They worry about the effect of chemicals.  MM: Yep.  AS: But to describe it as exploring our reality is… puts an entirely different slant on it.  MM: Yes, and it is actually because … there are two really fundamental sciences, and that is chemistry and physics. Because chemistry and physics, those describe everything that happens everywhere, whereas the other science fields – like biology and so on – is very, very interesting, and essential to our understanding of life, and our own lives as well. But it’s not a fundamental understanding of reality as it is with chemistry.  AS: When you developed what the press release for this prize describes as ‘the jewel in the crown of click chemistry’, the copper catalysed azide-alkyne cycloaddition, and you co-discovered that with Barry Sharpless, but working independently, did you realise that this was an absolutely ground-breaking discovery?  MM: Yes, because we did some reactions which were not supposed to be able to happen, and so for example we took very reactive acid chlorides and reacted then those which had azides in them, reacted those with alkynes, without touching the acid chlorides which is a very reactive functionality. So we immediately saw that this was completely orthogonal to other chemistries and would have a huge potential.  AS: And one of the things that makes click chemistry so special is that it can happen while other reactive groups are around but they’re just unaffected by this.  MM: Yes, and I should in that regard also the PhD student Christian Tornøe who worked on this project and was very much involved in the discovery as well.  AS: Thank you. What would you say to young people contemplating chemistry as a career?  MM: I would say it’s a very interesting field because it has a lot of existentialism in it, so understanding how everything works is a very challenging but also a very rewarding experience.  AS: Very nice. Let’s hope this prize encourages yet more people to enter the field. It’s very encouraging for everybody that it’s a prize that unites male and female laureates.  MM: Yes, yes, that’s very nice. I know Carolyn for a very long time and she is a fantastic researcher.  AS: What would you say makes her special as a researcher?  MM: She has such a broad knowledge of both chemistry and biology, and knows how to utilise her chemical knowledge in a very exquisite way in understanding biology.  AS: That fundamental base of understanding is deeply important isn’t it.  MM: Yeah.  AS: It’s been a huge pleasure speaking to you, thank you very much, and congratulations.  MM: Thank you very much. Adam, I will talk with you later.  AS: Thank you, bye bye.  MM: Bye. |
| **Interview** |  |
| Q3 | What do you enjoy about science? |
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| Q3 | Where does your passion for science come from? |
|  |  |
| Q9 | How did it feel to get the Nobel Prize call? |
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| Q9 | What happened after the call? |
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| Q9 | In Denmark your prize has been very celebrated, some are comparing you to a rock star. How has that been? |
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| Q1 | What advice would you give to a student or young researcher? |
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| Q15 | How important is sustainability for you? |
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| Q15 | What are the key implications of your research? |
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| Q2 | How do you cope with failure? |
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| Q7 | What qualities do you need to be a successful scientist? |
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| Q11 | How important has collaboration been to your success? |
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| Q11 | How can we encourage more diversity in science? |
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| Q6 | How important is music in your life? |
|  |  |
| Q2 | Do you think music has been important to your scientific career as well? |
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| Q10 | What environments help with creativity? |
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| Q9 | Can you tell us about the object that you are donating to the Nobel Prize Museum? |
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| **Podcast** | [Sharpless]  Barry Sharpless: “I can’t resist taking a chance on something, in nature anyway, that looks like a place I haven’t been. I wonder what it’s like there.”  Adam Smith: I think everybody who talks to Barry Sharpless wants really to know the same thing, which is how can you be the sort of person who is so creative and brings so many new ideas into the world that you’re awarded not just one but two Nobel Prizes. If you could get the secret and bottle it, maybe even sell it, you’d be very happy. It’s a hugely pleasurable trip to talk to Barry. He himself would be the first to say that his conversation veers quite wildly around as new topics occur to him and that’s an absolute joy and quite a challenge to the listener to follow along with and concentrate hard to see where you’re going to go next. Do join me for this conversation with Barry Sharpless which I think does give at least me a greater insight into how he comes up with ideas and what an idea actually means to him and in particular how dangerous ideas can be.  Clare Brilliant: This is Nobel Prize Conversations. Our guest is two-time chemistry laureate Barry Sharpless. He shared the 2022 Nobel Prize in chemistry with Carolyn Bertozzi and Morten Meldal, for the discovery of click chemistry. Twenty-one years earlier, he was awarded for his work on chirally catalysed oxidation reactions.  Your host is Adam Smith, Chief Scientific Officer at Nobel Prize Outreach. This podcast was produced in cooperation with Fundación Ramón Areces.  Barry Sharpless is the W M Keck Professor of Chemistry at the department of Chemistry of Scripps Research in La Jolla, California.In this conversation he takes Adam on a journey into his fascinating mind. He explains how impatience has shaped his career, why he abhors writing research proposals and why he loves being terrified on a regular basis. But we start, with a frequently asked question.  Smith: I suppose what everybody wants to know from you is how it’s possible to generate so many good ideas. Let me start by just saying, have you got an answer to that question?  Sharpless: That’s probably the question that I’ve been asked to think about ever since it started happening. It’s a really good question. In fact, the most important question, if I could answer it, for advice for humanity and humans who want to have possibly more ideas that are really worthwhile. I guess I realised that it was happening to me – I was in Japan with a lot of experts on asymmetric synthesis, and Kagan and Noyori and Eric Jacobson and others at a meeting years ago. It was before the first Nobel Prize, I think, in asymmetric synthesis. Since I had done a number of different things that were asymmetric and also had other types of reactivity I’d found, I mean, Noyori’s a strong personality, but he’s very thoughtful because he said, well, Barry, we’ve all been talking, but one question I really think we need to ask you is how did you have so many ideas? That was a sort of kick-off for the thing when I realised Ryoji had this question. I didn’t have an answer at that time, and I just sort of shook my head. But the more I did think about it, Jan helped me with it, my wife. Basically it comes down to things like if you can’t plan ahead, you’re in a different boat than the rest of the team because you don’t know how you’re going to get through the day or what’s going to happen to you. You’ll tend to notice things in a different way, I think, in the events of the day, in the events of the chemistry you’re trying to do in front of you.  Smith: Let’s focus on that one first, because that in itself is an extraordinary statement that you can’t plan at all, that you’re living almost by the sort of seat of your pants. It’s not how most of us live. Is that really what it feels like, that you can’t plan ahead, that you’re just kind of living in the moment?  Sharpless: Jan knows the frustrations of it more than anything. She finally realised that that’s why I’m so difficult sometimes. I don’t know why I can’t do it. It’s like an aphasia in the mind. That’s why research proposals were painful as hell. I always just wanted to go down to the lab and try it, instead of more BS on the paper saying why it might work, why it might not work. I said, well, I’ll just try it. I took a week in the lab instead of writing. By the time it came time to get the thing across the transom to the government for the proposal, I was just desperate. I sent things and I started to have things to publish to talk about before I didn’t have support for them, but I’d done them. Then I could talk about the things that already work and just keep going. That seemed to patch along pretty well, at least with the study section I had in the National Science Foundation. Then came the asymmetric epoxidation. That got me in with the National Institutes of Health more firmly. They kept supporting asymmetric chemistry for me. Those are the only two grants I ever had continuity on. It wasn’t enough money to run my group on. I ended up going from dowry to dowry by having the success and moving and getting a dowry and then going through it. Finally, I ended up at Scripps with Richard Lerner, who’s really a visionary. He just said, Barry, I like what you’re doing. I’m going to support it and we’ll support it with the Skaggs Foundation and with the Annenberg Foundation. We’ve got money. We can support research, direct research here at Scripps. That’s what happened. I was able to keep this click chemistry going.  Brilliant: Let’s talk a little bit about the many discoveries of Barry Sharpless. What was he first awarded a prize for in 2001?  Smith: He was given that prize for a very brilliant piece of organic synthesis. At the time, many people said it was the most exciting development in organic synthesis for decades. It was a way of doing what chemists call asymmetric synthesis. In order to understand that, one has to understand the word asymmetric. Many molecules have the property of handedness, which chemists refer to as chirality. But if you look at your two hands, you’ll see that they’re mirror images of each other.  Brilliant: I’ve got them in front of me now.  Smith: Good. Now try superimposing them.  Brilliant: Okay.  Smith: You’ll see that somehow you can’t superimpose them despite the fact that they have the same things attached to them. Your fingers and thumb. They’re arranged in a different way in space, and you cannot superimpose one over the other.  Brilliant: I see that I can clap them together, but if I try and put them one on top of the other, they don’t overlap.  Smith: Exactly. Now, if your hands were organic molecules with this property of handedness, you’d find the same thing. Carbon atoms always have four bonds attached to them. If those four bonds lead to four different groups, so in other words that carbon atom has four different things arranged around it, then it will have this property of handedness or chirality. In that there are two ways of arranging those things that are non-superimposable, if you like, a left-handed form and a right-handed form. Those two molecules, despite behaving in the same way with respect to their physical properties, their boiling point or their melting point, have different chemical properties. That’s incredibly important because the different-handed forms of those molecules behave differently. When chemists are trying to make a molecule with a chiral carbon, they really probably want to make one form or the other, the left-handed form or the right-handed form. But most chemical reactions don’t give you one form or the other. They give you equal amounts of both forms. What you want to be able to do is to synthesise those things asymmetrically. In other words, make one form and not the other.  Brilliant: Oh, I see.  Smith: Barry Sharpless’ innovation for which he was awarded the 2001 Nobel Prize was a reaction called the Sharpless Epoxidation, which allows you to do that in a very selective way and produce just the form you want and then introduce all sorts of different functionality.  Brilliant: It’s pretty unusual to be awarded one Nobel Prize, let alone two. What was Barry’s second Nobel Prize awarded for?  Smith: Yes, it’s an incredibly rare thing. Interestingly, he was awarded the prize for click chemistry, and I remember when I spoke to him in 2001, 21 years before that prize, he wasn’t so interested in talking about what he was being awarded the prize for then, that epoxidation. He wanted to talk about what he was doing now, which was click chemistry. He was already very much focused on that when the first Nobel Prize came. Click chemistry describes a very small group of reactions, which are almost perfect. In most organic chemistry, the reactions that chemists use are far from perfect. They’re very difficult to make happen. You have to heat the system or put lots of energy into it to make molecules stick together. When they do, they don’t do so in very high yield. They also tend to produce lots of byproducts. They’re not the greatest thing for making exactly what you want. In click chemistry, you have reactions which happen under mild conditions with almost total efficiency, a hundred percent yield, and they produce no byproducts. They’re, if you like, the Holy Grail of chemical reactions. There aren’t very many of them, as I say, but those that there are incredibly valuable. It was for the development of those, and I suppose partly for dreaming of the possibility of making such reactions that Barry Sharpless was awarded his second Nobel Prize.  Brilliant: You mentioned when you spoke to Barry back in 2001, Adam, that he was already thinking ahead. What must it be like to always be sort of one step ahead of where everyone else is at.  Smith: I suppose broadly all scientists are trying to think of what’s to come. It’s just a bit extreme in Barry’s case that he’s just constantly focused on a new problem. I suppose sometimes that can be a bit of a disadvantage. In fact, it’s interesting to hear him speak about that.  Sharpless: Frankly, it wasn’t easy because the Germans who had come to me who were really marvelous chemists, they still are. They always will be. But they came and they want to do asymmetric things. I kept, oh, no, I can we try this new click chemistry thing? Basically it shut down the conduit that was bringing the Germans to La Hoya. They loved it here, of course, because all northern Western Europeans, especially those up north and probably in England and Scandinavia and Germany, they love Southern California for its contrast with their home. They wanted to come. I must say, I felt bad because I would just neglect them if they didn’t want to work on click chemistry.  Smith: I’m getting the view of you as an impatient person.  Sharpless: Yeah, you’re right.  Smith: It’s nice that that chimes with your own view of yourself. You just want to get things done.  Sharpless: The bad thing is that in everyday life, impatient leads usually to impulsive. The impulsive things really are – I don’t know. I did have an eye blown out when I was a young professor. Probably if I was less impulsive, that wouldn’t have happened. But basically, the impulsive part is what makes me want to get the reaction going in some way that we can get within a day’s work or overnight. At least we can get some answers about some crucial things that are hinging on this experiment. Yes or no things as far as being a go ahead for something more interesting than the average.  Smith: We’ll stick with impatience, but I just can’t let the comment about the eye go without just exploring that a bit more. That was an NMR tube exploding, wasn’t it?  Sharpless: Yes.  Smith: That’s a pretty enormous thing to happen to you to have an eye blown out. Or rather, you were blinded in one eye by the by the –  Smith: Yes, and that was for a while. But then I got an operation here in California years later that helped me get vision back in. You would have thought that having just one eye would have been really a huge disadvantage. But I couldn’t ride motorcycles anymore. Stuff like that. For a while, I had to learn to take the information in. Maybe there is something to the left/right brain, but it seemed to work fine.  Smith: OK, you mentioned motorcycles. Riding fast motorcycles, I suppose, goes along with an impetuous, impatient person.  Sharpless: I’m not too coordinated. That’s a problem. Skiing was a nightmare for me because I didn’t have that coordination. I wanted to go fast, but always got banged up because I couldn’t. On a motorcycle, a dirt bike especially, in the woods, in the logging trails of California, around San Francisco, you feel like you’re a wailing skier. Just amazing amount of things can be done, sliding and slipping. It was just so good. It was better than going out and drinking with the boys. It was so relaxing for me to get a little frightened. This has always been true for me. Getting frightened is really erasing somehow the nervous system, which is making me worry and stuff. It just sort of releases the tension. It’s addicting to get a little scared if you can. That’s sort of, I think, well-known human self-medication method.  Smith: I suppose so. But a lot of people try and get themselves out of situations of being scared. When did it start for you? What’s your earliest memory of wanting to be frightened?  Sharpless: It was out on the river, in the Manusquin River, which was really quiet in those days. It was almost like a private estuary of freshwater, saltwater and all these creatures. I could putter around. But I was told by my parents, I think I was nine or eight, and I was told not to go out in the ocean because the ocean was about two and a half miles away downriver. I ended up not being able to resist going out in the ocean because the fish were more reliable there. I felt that was something I was doing that was not allowed. I felt pretty excited and worried that I would get caught or something would go wrong. That’s sort of an example of it. I can’t resist taking a chance on something in nature anyway that looks like a place I haven’t been. I wonder what it’s like there.  Smith: Which I think also sums up your attitude to ideas. That’s the remarkable thing, because when you talk about having ideas in science, in chemistry, I get the impression that the excitement of it, the danger of those ideas, is one of the things that you find so appealing. That’s different from a lot of us. Most of us don’t have ideas that are that dangerous, but you do. Ideas for you are on the edge and thrilling. Is that right?  Sharpless: I think so. The ones that I’ve been able to stoke myself up to having since I was successful in my first go at research at MIT, I keep asking myself, well, what does this mean? The general phenomenon of seeing something about reactivity and realising why wasn’t it found before? What does it imply about what might be out there that hasn’t been seen? That’s the part that I do naturally now. People focus on things that are interesting in chemistry, and a lot of people are really good at that. But to focus on them from the standpoint of what they imply about things that haven’t been tried or haven’t been seen yet, I do it every time I hear something interesting, or at least a couple of days later, I sit down. I’m like, what does that mean, really? Then I try to say, well, maybe it means this. This means a set of conditions that might, if it worked, jump you a little, another little jump over a stream or a brook that might have held most people back. You just try it and it didn’t work and you come right back. Somebody tells you, oh, I’ve got this great new thing and it’s going to do this and that and the other thing. If you know a lot about your science and how you can do things in your field, then their idea is something you’re automatically going to analyse, because that’s what you’re about when you’re doing the chemistry the way I’m doing. You’re trying to find something that’s more useful in the long run. It’s not somebody’s idea of what they were told when they started writing their grant. This is important. People have these objectives for science. The country has needs for energy things and whatever. If people tell you that they’re doing something important in that regard, namely they’re aiming to solve the problem that has no linear solution – it’s a big problem – they’re not anchored to the foundation of what makes things possible on the larger scale where everything’s integrated. Even though I’m not a logical person when I’m speaking, I just go over and over like repetitively in my mind. I keep asking myself, wait a minute, why am I doing this? If something works really beyond your wildest imagination, then sometimes that thing that you’re seeking or hoping for may not amount to much from a certain point of view. It’s kind of bad to fool yourself when it comes to things like that, if you can avoid it. I’m afraid of being embarrassed by doing something not exciting.  Smith: Yes. Your threshold is very high indeed. I’ve heard you. I’ve heard you quote this beautiful thing from Einstein that if at first the idea doesn’t seem absurd, it’s not worth doing it.  Sharpless: He seemed like such a nice avuncular man. I guess he was a pretty difficult guy, too. Somebody told a story about him. It sounds like talking to me. Once I get started, you can’t stop me. This person had talked to [Einstein](https://www.nobelprize.org/prizes/physics/1921/einstein/facts/). He was, ”well, he can talk your head off”. I had never thought about that from Einstein. He seemed like a gentle old man when we knew him from the news anyway.  Smith: It’s a different view. It’s a nice view. How do your colleagues in chemistry take your approach? Because it must in a way be a bit challenging for them. They present you with their latest and greatest idea and you immediately take it apart and see what you can do with it and whether you can extend it or knock it down.  Sharpless: That’s true. I grew up in a continuum of rapid change, but it really was more or less trying to enrich the world that people believed in, making very complicated molecules and having more reactions almost endlessly because they might be useful, just somewhere. It kind of grew away from that naturally because I realised that man is really paying for its research. Most countries pay dearly and they have other things where people are suffering and they need money, but they give it to groups and scientific establishments for education and they don’t have the luxury of that money not being useful. Yet if you do useful research, academics scream about it. We want, what’s it called, curiosity driven research and not sort of, well, we’re supposed to make this compound or we’re supposed to solve that pollution problem. I guess really at the end of the day, the chemistry, if it can evolve, keep up with mankind’s ever-increasing needs. We really do need to keep up with the inventions that enable man to do what he continues to want to do. That’s something that people don’t want to hear. To me, practical is even part of the recipe. That’s part of the answer, that it’s practical, it’s conceivable at the beginning, not having to be reduced to practice at the end after you’ve got a very complicated scenario to solve a problem and you can’t afford it. I guess that’s where I get hard on myself. I’m trying to realise that you can’t do certain things. In this world, too much energy… like if I was to use osmium for a lot of reactions, it’s a wonderful metal and catalyst, but there’s just not enough osmium on the earth to deal with that many reactions.  Smith: The urgency comes both from your own impatience and also the urgency of doing something ”useful” for the planet.  Sharpless: That’s for sure. The urgency to do something important is just because it’s been done and it continues to be done by people. There’s no reason why you can’t think you’re going to do it.  Sharpless: What gets me is that in the history of human progress, literature and science and finding out a way to look at something for the first time, people ask you how the breakthrough occurred or how you were able to do something that looked hard. What happens is really weird. I can find over and over again examples where the person who made the discovery, who knows bloody well that it was a surprise the moment it happened, but they come up with ways to make it not a surprise. They start telling a story that slips into a just so-story. That is really something, our tribe can’t take this accidental thing. It wants to have the connection. I’m not a politician or anybody intelligent in that area, but I got to wonder here, the stories that people told around the campfires 200,000 years ago when man was struggling to really literally survive from animals attacking and getting food. The person that told the story that lets you lie down and sleep at night and somehow it didn’t have any more logical next day prediction than anybody could. Something terrible might happen. But no, the person who can make you feel like it’s OK to go to sleep and wake up again, that’s the leader. We see that in governments where they scare us a lot and they say they are the only ones who can keep us alive in a way. That gives them real power. I’m not saying it’s bad. Man really needs to be comforted. But they’re like our psychiatrists at large or something. I don’t know.  Smith: Such an interesting point that we do the same thing in science and that we make scientific stories more comforting by giving the rationale or inventing the rationale.  Sharpless: Yes, that’s right.  Smith: Again, it all fits in with your own uncomfortable view of chemistry. It shouldn’t be comfortable. If it’s comfortable, it’s wrong. Obviously, you also want to know a great deal. I was very struck by when you came to that water meeting we ran. You’re asking the simple question, why is water blue? Why does it look blue? It’s such a good question, which is the sort of question that most people never ask, even though they spend their life observing blue water and admiring it. There are so many questions. Life like that, which either don’t occur to us or if they do occur to us, we put them aside and don’t bother to think about it more.  Sharpless: Yes. Water is really the be all and end all of life.  Smith: It’s the fact that you ask the question. Is it just an insatiable appetite for knowing? Does everything make you question?  BS: No, I think it’s that I drove people crazy when I was younger asking questions. Why this? Why that? My wife points out that I sort of grew up specialising in throwing out answers right away when she asked questions and she before she knew I was not a genius that way. She was just taking it. But I can’t answer questions directly. I don’t usually do that. I just sort of get off into a zone of that question and start talking and then always thinking what really makes this work, in life systems everything is connected at some level. It’s so surprising how things are connected. We just won’t believe it if we last another 100 000 years and we have we keep some sort of system together where we have a history and we record what we’ve learned. It’s going to be amazing. Some of the things that we don’t even know are life and death right now that have to do with the way that our bodies work will no doubt surprise everybody, but they’ll be accepted and life will go on.  Sharpless: I never knew I had an idea that was worth much in anything until a college my senior year, I think I took a course in oceanography, which was, of course, a man in science and biology offered. It was fantastic. We got to do the fruit fly experiment, the cross of hybrids. I had the idea about how the eel, the American and European eel get back to the Sargasso Sea and how the come up every year and float in the North Atlantic Drift, one for one year and one for two years. I had this idea and I wrote this paper and I couldn’t find it since then. But I knew that was a new idea. That was the thing that started me thinking, well, gee, it’s really great fun having ideas. But I didn’t have an idea that I felt that way about until I was a senior in college. That’s probably good for people to know because if you’re interested in something, you’d be amazed what interest can do.  Smith: I better finish with a comparison to the only other person to have been awarded two chemistry prizes, [Fred Sanger](https://www.nobelprize.org/prizes/chemistry/1980/sanger/facts/). Now, Fred Sanger famously retired at the end of his research career. Two Nobel Prizes was enough, and he went off and spent his time gardening.  Sharpless: Good for him.  Smith: There doesn’t seem any danger of you doing that ever.  Sharpless: I get to the point where I feel pretty old and tired and dull. Then I think, God, I can’t do this. Because if you really know what it was like to have excitement and want to keep that up. But you’re right. I have friends like me. I just can’t imagine them retiring. But Sanger, I think, had a life. During his time as a scientist, he got the really great ways of analysing things for what? Both of them for genetic purposes, I think. That was so timely. My way of looking at it is that physics is the really underlying thing. Chemistry emerges from it. Then we got to do something to make that connection real more than we are. We have all this discipline. We’re doing amazing things. Science is dead, some people say, well, that’s the dumbest thing I ever heard, because we got a bunch of theories. It’s not about the theories. It’s about what happens because of the theories, right? What kind of things evolve and what you can make. I really feel that this idea that science can stop because we got the book written. I just don’t get it. I mean, it’s not possible. It’s too rich.  Smith: Barry, it’s really lovely speaking to you.  Sharpless: Really, you actually help support conversation between me and the world better than anybody. I’m glad to talk to you whenever I can.  Smith: Let’s continue another time. But for now, this has been just gorgeous. Thank you.  Sharpless: OK, thanks, Adam.  Brilliant: You just heard Nobel Prize Conversations. If you’d like to learn more about Barry Sharpless, you can go to nobelprize.org, where you’ll find a wealth of information about the prizes and the people behind the discoveries.  Nobel Prize Conversations is a podcast series with Adam Smith, a co-production of Filt and Nobel Prize Outreach. The producer for this episode was Karin Svensson. The editorial team also includes Andrew Hart, Olivia Lundqvist, and me, Clare Brilliant. Music by Epidemic Sound.  If you’d like to explore the mind of another brilliant thinker with irons in many fires, listen to our earlier episode with the 2020 physics laureate, Roger Penrose.  You can find previous seasons and conversations on Acast, or wherever you listen to podcasts.  Thanks for listening. |
| **Telephone**  **interview** | [BS]  Adam Smith: Barry, it’s Adam here.  Barry Sharpless: Hi Adam.  AS: Many congratulations.  BS: Oh, thank you, thank you very much.  AS: It’s… it’s just such a… such a joy to hear you. And here we are again – second time!  BS: That’s right, yeah, I can’t… Things are… I’m a little bit snow blind right now from no sleep, so…  AS: It’s just so nice to hear you, and to be part of this extraordinary day when you’re receiving your second Nobel Prize.  BS: Okay, because it’s really… it’s lucky, in some other ways you don’t know about, and that is, you know, I sort of changed fields. By the time I won the first I was doing… trying to do click chemistry. Now something’s happened again here… something changed me, got me, some accidental discoveries in materials that are… that looks pretty important for energy.  AS: It’s always the case that whenever one talks to you, we’re always talking about the last thing you did, and you’re always talking about the next thing you’re doing, because you’re just so chemically inventive. And I suppose that’s what people will want to know: what is it about you Barry that makes you so, so inventive?  BS: So that’s a good question, you know, because I remember a couple of times to my Japanese professor, very conservative, Ryoji Noyori, who was winning the prize… but once we were together, years before at a meeting he organised, and it was finally a quiet moment, a lot of famous chemists in the room, and he said ‘well Barry, tell us how you work, how you think, because you’re more successful than any of the rest of us.’ And that’s what you’re asking, and I kind of wonder about that because I’m very… in some ways very slow and, but, actually I think the easiest… I was just looking today, trying to describe for this thing I going to have to do at 1.30, say a few things about what do people want to know. They mostly want to know human things, like how amazing were you that this happened or that happened. One of my favourite quotes is by Einstein ‘If at first the idea is not absurd, then there’s no hope for it’. Now, that’s a weird one, right?  AS: It is, it is, but it’s very powerful. I get… I’m thinking that, I mean, the answer to this question of how you… really you fit in with this Einstein model of thinking the absurd, and somehow it comes into… it becomes reality and you make things happen. Is it to do with the fact you’re a thrill seeker? I mean you always were. When you were young…  BS: You know. Did you talk to me about that before? Because that is something which runs strong. In fact I was just reading that again, it’s the idea of uncertainty. You know it’s the guy who takes the fox to the machine gun nest, and why the hell does somebody do that when they’re going to get killed half the time? And some people just get… they get so excited. It’s like auto-medicating I think. You know, your brain loves that feeling, and it wants to be closer to the excitement. And almost by definition excitement can be equated with danger, so people who are close to making a big discovery just like back in the old days when they were looking for a dinosaur or a big mountain lion. Those who get worried and can’t make the next, can’t look over the next set of rocks or trees, feeling that they’re going to die, they don’t get the chance to get close enough often enough, and…  AS: But your description is very vivid, and it’s so nice that you find that excitement in ideas. Because you know for most people it means going out on a speedboat or a fast car or something.  BS: Yeah, right, right.  AS: But for you it’s an idea, which is very special.  BS: Oh, and it gets very exciting when you get… when you start… that’s where this absurd thing comes in, because some of the things I have had to work through and I realise they came very close to that. But now I’ve got really a main core absurd issue with bonding. You know, we’re at a very high level with computers and bonding but we’re still describing bonding in a way that works, and we don’t really know which is the best way to do it, but basically the bonding thing is like… and then it comes back to the guys who did chemistry in the beginning. I was just reading a… Oh, I’ve got a book you would love, it’s a… maybe you’ve read it already… it’s a… I think I… oh there it is. It’s my son, like, he’s into philosophy and keeps getting things, reading them and then giving them to me. It’s Philosophical Chemistry by Manuel DeLanda.  AS: I don’t know it, I don’t know it. No.  BS: Sounds strange, right? I mean he’s in Switzerland, but I’ve read it, and I don’t know if when you took chemistry you had this problem, but I felt really stupid at some point. They had all this combining ratios and then, you know, and then there was phlogiston … And one thing after another there were no atoms and no bonds, no wonder the poor bastards were lost! So this guy describes that very beautifully, and then he said the biggest thing that he’s interested in … he said there is no science or whatever. We’re trying to figure things out, and we work together or we don’t work together. He said the most incredible time was that bond… the evolution of Avogadro’s number and the bonding things that happened around 1800, 1900. I mean they… they really… they were seriously difficult. And so people that were in a different camp than you were, the camps listened to each other and they met together and they wrote things, and they didn’t get ostracised, so, you know, different groups said different things. They could contribute to the thing that was ephemeral and nobody know where the resolution was going to come. I mean doesn’t that sound really wonderful?  AS: It… Absolutely, that enlightenment approach of, yes, realising that you have different opinions, but coming together to try and work out what the truth is, which was so prevalent then, and really has, yeah… It’s… It’s not the way the world sort of works now. It’s a very, very important point Barry.  BS: So you… that’s one of your conclusions? Yeah, they were reaching… What enabled them to do that? Well they didn’t have much information to… and they had to go by feel, and I guess that’s where, I think instinct is important for me, I know that. And I told you that if I come back at an idea after whatever small timescale or large one, but if the damn thing comes back to me and says ‘you don’t know the answer to this,’ why is it coming back? And then I’d say, I’ve got to give that respect and try it again because it’s subconsciously alive, right? And, yeah.  AS: Lovely, lovely.  BS: Okay.  AS: Barry, Cathy tells me that I’m not allowed to use much of your time because other people want you, and I respect that, but it’s… I would keep you on the phone all day if I could. I think maybe we have to leave this conversation now and let it happen another time.  BS: I do too, I do too, yes. Because I’m really feeling nervous now. I’m getting excited because I have to say something, I don’t know what it’s going to be on this… I… you know… If I could plan what I was going to say. But once I get ideas from people like you and Jan, I can… I sort of get further along. I think the most important about, we came up with was, of course the unexpected phenomena, you’ve got to pay attention to those, but uncertainty, if you can’t… Uncertainty usually translates to danger, right, or trouble. And so if you can’t really, or aren’t… You should be drawn to uncertainty, that’s the point I guess. And as a discoverer, or adventurer, or somebody who wants to be a hero, basically we’re all trying to do something that most people aren’t. They’re just happy with their family and they’re not trying to, probably not trying to find out something amazing, but… But God, I mean, if you are, it’s not simple, it’s … curiosity is really dangerous, it’s hard to break curiosity, right? You can get out of… well boredom. You get curiosity, but you can’t get out of curiosity once you get it.  AS: I think it’s… that’s… it’s such an important point, and you know you might be attracting a whole different swath of people to science by telling them that there’s danger there. They might like that. That’s a good idea, bring in a whole new cohort of people who wouldn’t…  BS: So, you feel something there?  AS: I do indeed. I do indeed. It’s lovely.  BS: Listen, I got to go.  AS: Yeah, I know.  BS: Because you’re right, okay.  AS: Okay, congratulations again and…  BS: Yeah, thanks so much for getting in touch, and I realise now we, you’re just really a fantastic person to talk to. I talk too much, but I can start talking more if I talk to you again, I think.  AS: But there are really important things to talk about, Barry, and I very much look forward to exploring it all together.  BS: Okay, Adam, thank you so much, and take care man.  AS: You too, congratulations.  BS: Okay.  AS: And enjoy your day.  BS: Thank you so much.  AS: Thanks.  BS: Bye bye.  AS: Bye. |
| **Interview** |  |
| Q9 | How does it feel to be back in Stockholm to receive your second Nobel Prize? |
|  |  |
| Q3 | Do you think you were born with that curiosity? |
|  |  |
| Q9 | How did you celebrate the accomplishment of receiving two prizes? |
|  |  |
| Q7 | What do you think is the secret to success? |
|  |  |
| Q1 | What advice would you give to a student or young researcher? |
|  |  |
| Q5 | Your former professor Spencer taught you to “think like a molecule.” Can you explain what that means? |
|  |  |
| Q9 | Can you tell us about the object that you are donating to the Nobel Prize Museum? |
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| **Chemistry\_2024-2000** | |
| **ID** | 0309 |
| **Biographical** | I was born January 11th 1968 in Frankfurt am Main, Germany. I am a chemist and currently one of the directors at the Max Planck Institut für Kohlenforschung in Mülheim an der Ruhr. I also serve as professor of organic chemistry at the Universities of Cologne and Hokkaido. I wanted to become a chemist since I was eleven years old – and in 2021 I received the Nobel Prize in Chemistry together with David MacMillan for the development of asymmetric organocatalysis.  Born as a member of a family of scientists and artists, I spent my childhood in Frankfurt together with my mother and my brothers. The renowned cardiologist Franz Volhard and the chemist Jacob Volhard, student of Justus von Liebig, are among my ancestors. My aunt, [Christiane Nüsslein-Volhard](https://www.nobelprize.org/prizes/medicine/1995/nusslein-volhard/facts/), received the Nobel Prize in Physiology or Medicine in 1995.  In 1993 I obtained my diploma in chemistry at the Freie Universität Berlin, in 1997 I received my PhD degree at the Goethe University in Frankfurt. My dissertation was on the synthesis of a vitamin B12 semicorrin, and my supervisor was Johann Mulzer.  For my postdoc I moved to La Jolla, California. I had the opportunity to work at the Scripps Research Institute with Richard Lerner and Carlos F. Barbas from April 1997 to December 1998 with a scholarship from the Alexander von Humboldt Foundation, and I was an assistant professor at Scripps from 1999 to 2003. It was then that I discovered proline-catalyzed intermolecular aldol and Mannich reactions and published my paper “Proline-Catalyzed Direct Asymmetric Aldol Reactions” in the Journal of the American Chemical Society – the paper that was one of the first to open up the field of organocatalysis. It was also in 1999 that my wife, Dr. Sabine List, and I got married in La Jolla. We have two sons, Paul and Theo.  In 2003 I returned to Germany to become group leader at the Max Planck Institut für Kohlenforschung. Two years later I was promoted to a director at the institute. I have been head of the Department for Homogeneous Catalysis Department ever since. By now, we are a group of approximately 50 people from all over the world. I started working as honorary professor of organic chemistry at the University of Cologne in 2004. In 2018 I became a specially appointed professor at the Institute for Chemical Reaction Design and Discovery at Hokkaido University in Japan. I am also editor-in-chief of Synlett, a scientific journal of the Thieme Publishing Group.  When I found my fascination for chemistry at the age of eleven, I thought that chemists can explain everything, since they look into the smallest parts of matter. This vision of an eleven-year-old proved, of course, to be wrong. We cannot explain everything. Nevertheless, I am very grateful and happy that in my career I had the chance to contribute to understanding a little bit more of the world we live in. |
| **Autobiographical** |  |
| **Podcast** | No scripts |
| **Telephone**  **interview** | [BL]  Adam Smith: Hello, may I speak with Benjamin List please?  Benjamin List: Yes, he’s on the line.  AS: Thank you very much indeed. My name is Adam Smith, calling from Nobelprize.org, the website of the Nobel Prize.  BL: Yes.  AS: Many congratulations on the award.  BL: Thank you so much, I’m really happy and honoured. Wow.  AS: Tell me how you heard the news.  BL: I was sitting in the café with my wife. We were about to have breakfast. And then the phone came and on the display it said Sweden and we looked at each other in disbelief, like jokingly, ‘is this the call?’ you know. I went outside, and it was the call. So that was really … I don’t know, it was like a dream.  AS: Of course. Were you able to compose yourself for the call?  BL: I had to deeply breathe in and out, and then I felt like I had to feel composed enough at least.  AS: But how lovely to be with the family when you get the call. That’s special.  BL: Exactly. It was so beautiful, just my wife and I sitting in a café, and she’s been there all those years, from the end of my PhD until today. She was there when the discovery was made, and she supported me over all those years, and it’s great to actually get the call when she is around.  AS: How lovely that you can share it, and what a pity you can’t just sit there and savour the moment together quietly rather than be phoned by annoying people!  BL: Yes, that would be great! Yes. No, I’m happy to… I mean, I know that comes with this award, I’m happy to fulfil my duty. Because I consider it a duty also, right? I mean, this is kind of a …  AS: Thank you. Yes, I remember [Orhan Pamuk](https://www.nobelprize.org/prizes/literature/2006/pamuk/facts/) saying ‘Yes, I understand I have to do my homework now’.  BL: [Laughs] I am completely unprepared.  AS: There will be much focus on the myriad applications of the technique, but, I mean, you’re an organic chemist, and the joy is making molecules. Can you say something about that particular pleasure, in just building new things?  BL: Yes, I love … It’s difficult to explain to people who are not chemists, and specially not synthetic chemists, because we really think, and maybe it’s naive or weird, but we really think our molecules have a certain beauty to them. And then, making them is like creating something beautiful, especially if they’re natural products. Somehow natural products have a particular beauty often, but also like if you make a certain drug molecule that saves lives, I think it’s beautiful to do this. We as chemists, we’re often people who are responsible for plastic waste, or other, or glyphosate – I’ve nothing against glyphosate, just people don’t realise how much, how many great gifts this can provide to our lives, right? I guess. It’s making molecules, and making them … And then there’s another aspect. It’s not just the molecules that are beautiful but also the way to making them, how you make them, and there can be huge differences, like some processes require toxic reagents and produce waste and use a lot of energy. But if you do it elegantly and you don’t need … Like we have this great term that my colleague Barry Trost of Stanford University has coined, it’s called atom economy, when we make molecules from other molecules and all the atoms of these other molecules are still preserved in your product – that’s called atom economy. Like, perfect atom economy, and that’s for me a perfect and beautiful chemical reaction. Honestly it’s just a joy, and I would argue most chemists do this because they love it and enjoy it.  AS: Thank you so much for taking just a minute to talk about the beauty of the science. I think it’s special that people should understand that. That’s lovely.  BL: Yes.  AS: We don’t have long, but one last question. What is it that you think is special about your research environment, that you created, that allows you to be so creative, so innovative?  BL: Now is a good moment to thank my host institution, and that’s the Max Planck Society of course. Because, like the Max Planck Society, I also believe that what it takes to be creative is freedom. And sort of the trust by your funding agencies. They think, ‘this scientist has great ideas let’s give him the space and the resources to fulfil his dreams’. And this is totally also my philosophy, and that’s what I try to, in a small way in my department, try to recreate this freedom. I hope my graduate students will not be opposed to what I’m going to say, but I think I’m not a slave driver, and I’m not saying ‘work harder, work harder, work day and night’ – it’s not my philosophy. I also encourage them to think, and to enjoy life, and for example whenever we have something to celebrate, we celebrate it. Even if we, occasionally we may not have something to celebrate, we still do it. I would like to … When somebody has a nice little discovery, then we have a little party in our seminar room. And I think the people that have joined me over the years, they are in line with this spirit. Recently we had our international dinner last week, where my group of course is composed of many different nationalities, and each of them brought a special food from his or her own country, and there was this moment we tried all the food and everybody gave a little speech about the style of his country, and this internationalism and respect for each other, this diversity … and there was this moment, I was among my graduate students, I had goosebumps on my head because I was enjoying this so much, to work with these amazing, happy and creative people, it’s such a gift already, and that’s my sort of philosophy about freedom in science and how creativity is formed.  AS: Thank you so much. In this brief call we’ve talked about family, beauty, dreams, friendships, society, what an advertisement for science!  BL: [Laughs] That’s true. It may be a bit unexpected, but I come from a family of artists and scientists, and so we always have sort of both sides in my family.  AS: Lovely. I hope we’ll have the chance to talk more, but for now that’s fantastic, thank you very much indeed and congratulations.  BL: Wonderful, thank you very much, Adam. Pleasure to talk to you.  AS: Bye.  BL: Bye |
| **Interview** |  |
| Q3 | Where does your passion for chemistry come from? |
|  | Benjamin List: I think, in general, that I’m kind of the enthusiastic person when I’m into something I’m very passionate and enthusiastic about it, I think I’ve always been like this as a child already. This passion for chemistry came when I was really young, like 11 years old or so. I had this, I have to admit, wrong idea that chemists know everything, they’re like enlightened beings, they understand the universe, the world and everything. Of course, the physicists now in the society always make fun of me for that wrong understanding because they think it’s the physicists that understand the world. Which is also not true because neither chemists nor physicists really understand the world and the universe and have the answers to the big questions that I had at the time when I was 11 years old. So anyway, that’s how I stumbled into chemistry. When I realised I don’t receive the answers there, it was already too late and I was hooked and I loved it. I loved making gun powders and stuff like that. You know, the usual stories. |
| Q1 | What advice would you give to any young up-and-coming researchers? |
|  | My advice would be to follow your enthusiasm. That’s my number one advice. I always tell this to everybody. I was always hopeful that I can make a big discovery. Most of us in this world of science dream of that and maybe also secretly at the back of our minds we also dream of receiving a Nobel Prize at one point. When you are really interested in this and making really an impact, then you should be aware that the time when you have a revolutionary idea has to feel lonely, by definition almost. It cannot be the mainstream. If it’s going to be the next big revolution, it will certainly not be the mainstream. And yet there is this 10% when they have just finished their postdoc and then they start their independent research. There is this tendency. “I want to do something that everybody else wants to do. I want to be part of the community,” but that is detrimental. I would argue to do scientific revolutions, something you should keep in mind is this loneliness you have to be able to hold. |
| Q10 | What do you think has made it possible for you to cope with that loneliness? |
|  | I don’t know. I have to say I was really frightened at a certain point in the early days of my career. I was pretty nervous. I felt like I’m the only one in the world right now who’s doing this kind of research. And then of course the question is, “is it because everybody else is smarter and they already know this is kind of not a good idea or is it maybe a scientific, revolutionary concept that I’m following up upon?” So I mean, you have to also be aware that it’s a required condition if you have a revolutionary idea to feel lonely. I would really say that it is a sufficient condition. So many people feel lonely because they have silly ideas. In my case, I was really lucky that the success came so early. It was my very first independent scientific experiment. I wonder how long I would have survived in that risky environment if the first few months wouldn’t have given success. |
| Q7 | What qualities do you think successful scientists need? |
|  | Curiosity is important. We really have to burn for what we are doing. Enthusiasm, I have mentioned, it’s the most important driving force for all of us, not only scientists. And yeah, passion. I think also an openness. Because after all, it’s not us who shape or create the world and the universe, but we try to understand it. So we have to be a little bit open to surprises and don’t enforce new ideas onto the reality. It’s not going to work. |
| Q2 | You often also speak about your team and I know that after the award, you hugged every single person in your team. How important is collaboration and teamwork? |
|  | The team is of course extremely important. I love this interaction with my students. I try to have this hierarchy thing as low as possible. They should never hesitate to come and engage in a discussion with me. This is very important. I always say, and it’s literally what’s happening, my door is always open for them and I want them to challenge me. I wonder if this is even something that’s a little bit typical for Germans that your students, or let’s say your coworkers, criticise you as the boss. I think it’s part of our culture. It’s a little bit different from some Asian countries, for example, where you would never criticise a superior. But I think in the end, it’s a good thing. It makes science better. We always have to be critical with ourselves. That goes along with what I said before; you cannot enforce your ideas on the reality. Reality always tells you the truth. |
| Q11 | How do you think that we can encourage diversity in science? |
|  | I don’t know why, but in my lab right now, it feels like almost women are the majority. I think it encourages itself. Like once you have a critical group of female coworkers, then the other women dare to apply. I’ve been blessed throughout my career with awesome female students, graduate students and postdocs. In general terms, my view is that we should start as early as possible. First of all, even before we start, we should think about why do we want diversity? What is the reason we want diversity? Some people say because of justice, but I don’t agree with this argument. Our aim here in the Max Planck society, or in all top universities where we go for excellence, our aim of course is to foster top-level science. And how do we do this? By tapping into all brains on the planet, ideally, and not just into a small fraction. So that’s why naturally we need to be diverse. We need to represent the whole diversity of all humans in science, just because we want ideas. Not to be lost in talents that didn’t have an opportunity to get into science and then they became something else. So that’s why I’m totally in support of diversity in science. For example, when the kindergarten ask me, can you come and talk to our kids I go. I love to do lectures at schools. I went to a local gymnasium – that’s like a high school in Germany – and gave a talk in front of 300 ninth graders. And subsequently two of them joined us. They were kids, like 14, 15 or 16, really talented girls. I said, why don’t we do a little scientific project and you come here for weeks in the vacation or in the afternoon, or once a week to already sort of lighten the spark of science in them. And then they know, actually it seems like I can do this. That’s my approach to it. But I think we shouldn’t start at the end of the spectrum and just have a quota in hiring, for example, I’m not a great fan of that. |
| Q5 | You seem to really enjoy being a teacher. Can you tell me a bit about what is it that you like so much about teaching? |
|  | What I like most is really the shared enthusiasm for science. So I’m enthusiastic about what I do and then I speak about it. Then I see the light in their eyes and I see, wow, they get excited. And it’s the same as what I experienced with my teachers when I was an undergraduate student in Berlin. My professor, Johann Mulzer, who I also got my PhD with, always used to be very relaxed, but one had the sense, this is like the most exciting thing in the universe that you could be doing. I don’t know how he did it. We were all attached to every word he would say. Sometimes he would casually ask a question and then the smartest guys would give the answer. And that for me, I’m very sporty and competitive – I also wanted to give cool and smart answers. So that was what brought me into organic chemistry. So I know as a teacher, we can do a lot. We can really spark the interest in students. |
| Q8 | Speaking about being competitive, how do you like to spend your spare time? Do you do any sports nowadays? |
|  | We used to live just across a very old tennis club in Mülheim and my wife would play there and my two sons would play. After a while I felt like, “maybe I should also play a little bit,” and they were also encouraging me. So I started playing tennis, I think maybe 10 years ago or so. And now I enjoy it. I play once a week or so and it’s great fun. I also do lots of yoga in the morning, like body manoeuvres, and I enjoy this also quite a bit. It keeps you flexible, young, smart and open. So I’m open to fresh ideas every day. I think it comes from the yoga. |
| Q9 | You received the call about your Nobel Prize when you were in Amsterdam, weren’t you? Tell us about that, you and your family were at a café? |
|  | It was really a sweet event. I went with my wife to attend a great concert in the famous concert hall they have in Amsterdam, the concertgebouw. The famous conductor, Currentzis is his name, really a rising star and they played Mala. When I was a student in Berlin, I always went to the Berlin Philharmonics. I always loved classical music. At the time they had these cheap student tickets for five mark. I still enjoy this music. So we had this day trip to Amsterdam. We went to a fancy restaurant the night before and then we went to the concert and the next morning, my wife picked a fancy cafe, not a coffee shop. As I said before, it was just a regular cafe. And we were about to have great breakfast when the phone call came. |
| Q9 | After you heard about the Nobel Prize, you were in touch with your co-laureate [David MacMillan](https://www.nobelprize.org/prizes/chemistry/2021/macmillan/facts/). Can you tell me a bit about that? What happened there? |
|  | Well, you know the drill, right? They call you 45 minutes before the press conference and the 45 minutes is sort of the last 45 peaceful moments in your life. That’s I think the idea, right? That’s what they grant you. But in my case, it wasn’t like this because Göran Hansson called me again, like 10 minutes later and said, “Professor List, did you happen to have the phone number of Professor MacMillan? I cannot reach him.” So fortunately I have the number and I gave it to him, but then I also sent a text to Professor MacMillan literally saying “Dave, wake up.” Then a minute later he calls me and he’s a little bit tired because it’s in the middle of the night at the east coast of the United States.  I tell him, because Professor Hansson told me I should not tell anybody about the content of the phone call before the press conference, “Dave, I just received an important call from Stockholm. And they also tried to reach you. So you better pick up.” And then he goes, “Nope, I’m sorry, Ben. I don’t think that’s real. I think that’s a prank. I have students in my group. They always make these jokes with me. And I’m really sorry to let you down.” For a moment, I was a bit confused, maybe he’s right. But I told him, “Well, if it’s a prank, it’s a really good one. I mean, they have voice imitators and they really know what they’re doing.” So we hang up and he sends another text saying, “Ben, I’m really sorry, but this is a prank. I bet a thousand dollars against this is happening.” And I said, “Okay, I take it.” He still owes me the thousand dollars now. |
| Q9 | When you came back to your lab after receiving the news, you were greeted as a rock star. Can you tell us a bit about that feeling and that experience? |
|  | I get goosebumps when you mention it. It was really one of the most beautiful moments in my life. And it was so beautiful because of the fact that we were in Amsterdam, the people here had all the time in the world to prepare, right. And so my colleague Ferdi Schüth, our managing director right now, he was thinking, what can we do? First of all, they bought all the champagne they could get in the local areas and they bought 113 bottles. That was all that was there. We drank all of them, later of course! But he also had this idea that all the students put on their lab coats and go onto the balcony and that when I would arrive, they would all clap, and it really worked. It’s not the most beautiful place at our Institute. It’s lots of concrete and architecture from the city, but they brought so much joy and so much happiness and excitement there. That came back to me and then they saw how excited I was and that went back to them. What was so beautiful was that it was not just my group or just the scientists, but pretty much everybody from the Institute. And it gave a sense of satisfaction to the scientific support groups. The metal workers, the wood workers, the gardeners, the administrative people, they were all so excited. Finally, we see the fruit of all our work for all those years. It was really such an amazing day. I will never forget this, I’m endlessly grateful to the Nobel Foundation for that moment. |
| Q6 | In 2004 you and your family were in Thailand during the tsunami and you had an awful experience as your son went missing. Those experiences change one’s perspective on life. How has that experience affected you and how has your life perspective changed as a result of it? |
|  | It’s an interesting question. The thing is we all crave objects, I don’t know what else to call it. Like somebody may want a Ferrari or a Nobel Prize or a great job or the perfect partner. And we think that these, I call them objects, will make us happy. But when you are in a life-threatening situation, like I wonder, for example, sometimes how the patients right now in emergency units are feeling that don’t get enough air? You have a completely different perspective, all of a sudden, what will make you happy. And you realise just the ability to breathe is already such a beautiful blessing, right? And this almost dying in the ocean, and almost losing my family, that really for several months sort of fixed me in that I lost this desire for recognition that people cite me and that I get an award and that finally my great understanding is appreciated by the world. I completely lost it. This didn’t last forever. At some point I was again ambitious and I wanted to be cited by my colleagues and I was happy to get an award, but always this remained there in the back of my mind that I know the truth. I know what is important in life. And it’s definitely not the attainment of objects, even if it’s a Nobel Prize, I shouldn’t say this right. It gave me a lot of happiness and it gave a lot of happiness to so many other people so don’t get me wrong. I so appreciate it. But deep down, I know that this is not the thing that we all crave for. It’s being able to breathe, being able to enjoy life as it is, having a coffee in the morning as the sun is rising. These are the things that really matter and that make us happy. We should just open up to this. Now that’s my message. |

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| **Telephone**  **interview** | [DM]  Michael Hotchkiss: I have Professor MacMillan here if you’re ready to speak with him.  Adam Smith: Absolutely, very much so, thank you.  David MacMillan: Hello?  AS: Hello, this is Adam Smith, from Nobelprize.org, the website of the Nobel Prize.  DM: Hi Adam.  AS: Hi, many, many congratulations on the award.  DM: Thank you so much.  AS: Did you actually get the call from Stockholm?  DM: No, I didn’t. I got a text from someone in Stockholm, where my name was wrong, and I assumed it was a prank call. I’ve had a lot of mischievous ex-co-workers over the years, I just assumed it was one of them having a prank, so I actually just went back to sleep.  AS: When did the news actually reach you?  DM: Well, the news reached me because, after I’d … Actually the other winner, Ben List, also was trying to contact me. I contacted him. He told me what was happening and I said I actually didn’t believe him too. I thought maybe the same person was pranking him, so I basically bet him $1,000 dollars that this was not happening, went back to sleep, and then woke up with my phone going crazy, and I was $1,000 down but a very happy person.  AS: Yes, cheap at the price perhaps.  DM: Yes, I guess.  AS: When we spoke to Ben List, he was in a café with his wife, Sabina, on holiday, so it’s reached you in strange ways, this news.  DM: No, but you know it’s obviously for anyone it’s extraordinarily welcome news, and you know, and I’m incredibly … I’m still trying to handle it, and I’m sure you’ve talked to a lot of people in this position, and you get the same response. It’s hard to get your feet underneath you, to a certain extent, you’re just trying to take it all in.  AS: I guess the day carries you along a little bit. It must have been already quite a whirlwind.  DM: The very first moment I came out of my driveway and there was press at the bottom of the driveway, which doesn’t usually happen to me on a Wednesday morning, I would say. And then when I got to work there was press in the parking lot there too, so that was unique, and it’s just been a sort of whirlwind ever since. But what’s wonderful is these fantastic people sitting beside me, the communications folks at Princeton, who are just top, top range professionals at dealing with this kind of stuff, so they’re keeping me in check, which is good.  AS: Yes, they shepherd you about, and I guess you’re … I gather you’re within the kind of confines of your department now, so relatively safe. I spoke to your assistant earlier and she said you were doing an interview with your group.  DM: It wasn’t really an interview, it was a group meeting. We have group meeting every morning at 9 o’clock, and I thought, you know, for a little bit of sanity I would still have our group meeting, which was good, and so we just talked about science for an hour, which was kind of fun. And it was a very, as you can imagine, happy celebratory mood, and they’d sort of showed up with champagne and cakes. How they got champagne I don’t know, because you can’t buy alcohol in Princeton until 10 in the morning, but somehow they found champagne. So I’m not very sure how they did that, but it was … yes it was a very good meeting.  AS: Maybe they know more than you did, and knew that this was, or suspected this was on the way.  DM: Yes, I don’t know. It’s one of the things research groups are incredibly good at, solving problems at short notice, and once again they came through.  AS: I did want to ask you about that, because the inventiveness of all this is just extraordinary, and it’s, you know, what you’ve been awarded for, the asymmetric organocatalysis, and then adding onto that photoredox catalysis. Where do all these ideas come from?  DM: I don’t know. That’s a terrible answer I realise, and everyone wants a nice straight forward answer. I think everyone, all scientists, have these kind of wacky ideas along the way, and some of them work and some of them don’t work. And this was one that, you know, came and was successful and went forward, and again it sounds obvious to say we were lucky – but we were lucky, you know, there’s way more ideas fail than ever succeed, and this was one that, you know, we were very excited about at the beginning, we thought it had a very low probability of success, but it took off, and it took off like gangbusters. That was wonderful to see.  AS: Yes, I suppose it’s slightly a case of gambling on some risky ideas and seeing whether they come to fruition.  DM: I think that part is right, I think you have to gamble. You know, I think that’s why scientists in my opinion have the greatest job in the world, because we get to show up everyday, we get to take these sort of risks, and we get to work on things that should never work. And if you think about it, it’s the stuff that should never work which is where all the good stuff is, because there’s always … well, knowledge is incredibly important. There’s always parts of knowledge which are over-stated or are underappreciated too, and so there’s definitely things that people believe would never work that have a fantastic chance of getting there, and I think, honestly, I’m one of those people, there’s many like me, who think we’ve just scratched the surface on that kind of way of thinking.  AS: Certainly on the diversity of organic molecules to be built we’ve just scratched the surface – there’s a whole universe to explore.  DM: Oh that’s for sure. I mean that’s one of the things which is, you know, one of the most exciting parts I think, you know … in talking to incoming undergrads even, or a first year, the fact that the very first day they build a molecule, it’s never been made in the universe before, and you explain that to them and they get so excited about the fact they’ve just done that. You don’t sort of realise how open the whole field is and the whole science is towards doing new things, and I think that’s what keeps chemistry and science moving forward.  AS: Well, that’s nice to finish on a kind of recruitment drive for chemistry.  DM: [Laughs]  AS: I’m sure that people will be converted. I hope we’ll talk about all this more at greater length in the future, but I should let you get on with this day, and I guess people will be left wondering whether Ben List is going to collect on his $1,000.  DM: Oh, I would be the happiest person in the world to hand Ben the cheque for $1,000, and you know, I’m glad he won that bet.  AS: Excellent, lovely, thank you very much for speaking to us, and wishing you a fantastic day.  DM: Thanks a lot, thank you.  AS: Bye.  DM: Thanks Adam. |
| **Interview** |  |
| Q2 | Can you tell us a little bit about your childhood. Were you always interested in science? |
|  | David MacMillan: I was born in Bellshill and grew up in a small village called New Stevenston, which was located between two steel works and a coal mine. My grandfather was a miner. My father was a steelworker. I had a really fantastic childhood, I went to the local state school. It was an incredibly happy experience, it was just such a fun place to be. Great humour, fantastic teachers. We had great community – everyone would run in and out of each other’s houses all the time. My next door neighbours, I would never knock on the door, I would just always walk in. Similarly when I went to high school it was equally fun.  I wasn’t [always interested in science] to be honest, I always feel guilty answering that question. In fact I wanted a chemistry set when I was about eight or nine years old and I immediately destroyed it because I didn’t follow the instructions particularly well, whereas my older brother made all the soap and all the things you were supposed to do with it. So I would say I wasn’t exactly someone who was a classic phenotype who’s going to end up being a scientist. I was always a curious kid. I was always interested in new things. But I wouldn’t say I was someone who was obviously going to become a scientist. |
| Q6 | How did you end up going to university? |
|  | I’ve told this story a few times, but my brother was the first person I ever knew who went to uni and the only person anywhere in our community who went to uni and he got a bit of a hard time about it. People thought he was just being lazy – and that’s certainly what my mum and dad thought at the time! But he went off to uni, did physics and then at the end, came out and got a job. And the job actually had a salary that was higher than my father’s salary on day one. At that moment, my mum and dad, they decided that I had to go to uni too. But not only that, I had to be a physicist because that’s what my brother had done. So I think there was always encouragement to go off and do what you wanted to do. It was never that you had to go to uni per se. |
| Q3 | So you went to university to do physics, how did your passion for chemistry come about? |
|  | Basically I was this working class kid. I went off to uni and it was just really overwhelming for me. I remember getting there and the physics lecture was the first thing in the morning in this lecture theatre that was absolutely freezing and there was no heating. So in the dead of winter in Scotland you’d be in this freezing lecture theatre, and when it would rain – which in Scotland it rains – the roof would leak and you’d actually get water falling on you which, for me, was just a really tough time. I went to uni to emulate my brother and it was just clearly not working.  But what for me was kind of interesting, was an hour later you would cross the road and I was taking chemistry as my secondary subject. It was this beautiful, warm lecture theatre. It was this great place to be. And I started to realise I loved this thing called organic chemistry. And the more and more I read about it, the more and more I really enjoyed it and appreciated it. And I think for the first time in my life, I really began to understand what, when scientists fall in love with an area, that was what it was like for me. It was almost like second nature. I’ve told people it felt like breathing at times. It was really straightforward which sounds kind of braggy, but I don’t mean it that way. I mean, just that there was no resistance to learning it whatsoever. For me, almost immediately I knew that was where I was going to go. It was going to be in organic chemistry. It was a subject I’d not really thought about or spent time looking at before. But as soon as we started learning about it was pretty clear that this was where I was going to go. |
| Q12 | Your family sound very supportive – can you tell us a little more about your relationship with them? |
|  | I always tend to get a bit emotional when I get to these parts of these interviews. Starting off with my family in Scotland… I think I’ve said this before, we’re certainly working class, we didn’t grow up with really anything, but we had an incredible support system of parents and people around us who just thought you could do anything. So that was just remarkable in and of itself. My brother and sister, have always been exactly the same way, incredibly warm, incredibly generous, would do anything for you. And I think now in my family, we have exactly the same spirit.  We really care about each other. We know that family comes first. You’ve got to be able to enjoy yourself. You have to laugh. You have to have fun. If you don’t have that first, then you really don’t have anything. So I think one of the things which is maintained through all of my family is this closeness, generosity, but also support. But making sure you really have a good time together. I think that’s been pretty essential. |
| Q5 | Apart from your family was there anybody else that particularly influenced you when you were younger? |
|  | I had a teacher who was in primary school called Miss McKean. All my teachers in primary school were fantastic, but she was someone who just really worked hard, pushed hard. She would always go that extra mile to try and help you out. I always remember for example she knew I loved reading fiction and other books and she’d come in and give me books to read and say, “I know you like this book. Why don’t you read that book?”, and so on and so forth. She was a great example of someone who went the extra mile, but she would always push you as well: What do you know about this? What do you know about that?  I think as an individual who really helps spark your imagination, in thinking about different directions you can see the world, for a young kid in Scotland, she was helping open the world for you. And she was doing it through talking about the world, but also getting you to read about the world. To me, I think she was incredibly important, but also really inspirational in the way that she went about actually being a teacher. |
| Q5 | Do you enjoy teaching yourself? |
|  | I love to teach and I also love not to teach. I think, when I’m actually in the action of teaching and getting up front of people, I love to do that. It’s an incredibly fun thing. I think if you talk to almost any academic, they’ll tell you that the hard part is the preparation where you have to put in all the hours. That’s not my favourite part. I don’t think it’s anyone’s favourite part.  I think we all truly love getting up in front of a class. Just yesterday I was in the middle of teaching something and I could tell it wasn’t working. It wasn’t going anywhere. And I had to stop and go to the board, and start to try and engage them in a completely different way. All of a sudden you can see that they were getting it. It’s the best thing in world, you know, when you suddenly see that people get something for the first time and it suddenly clicks, I think for any teacher, that’s your favourite part. It gives you goosebumps a little bit. Whenever you can see people for the first time get that piece of knowledge that you know is going to be useful to them down the line. |
| Q3 | What’s the best thing about your work and being a scientist? |
|  | One of the greatest things about running a big research group is, for the last 20 years I’ve been interacting with people between the age of basically 19 and 27 and I’ve gotten older and they’ve stayed the same age. So they keep that sort of freshness and that enthusiasm that you get to work with every day. You feel incredibly privileged in that way.  In terms of the science, my absolute favourite thing in the world is whenever we discover or invent a new reaction. That happens a lot more than you would think. Still to this day it catches me unawares. Last week, actually we invented a new reaction and I was just sitting in this meeting with 35 people thinking, wow, we didn’t know that this existed yesterday and today this will exist forevermore. That’s a truly remarkable, wonderful feeling. Just to be part of it and see it in real time and know that other people are going use it really soon and use it for making medicines and maybe making materials. That’s a remarkably privileged situation to be in to be at that forefront of that scientific endeavour where you can see these innovations happen in real time. So without question, seeing new reactions being developed and seeing it in real time, that’s my favourite part of being a scientist. |
| Q1 | Do you have one piece of advice that you would give to a young scientist? |
|  | Am I allowed to give two pieces of advice? I’d say as a young scientist don’t hesitate to take chances, I mean in life, in general. When opportunities come along, one thing I’ve found is – it’s really difficult sometimes – but if you just decide that when an opportunity shows up just to go for it, even if you have incredible self-doubt just do it. In my experience, it always ends up being a hundred times easier than you think it’s going to be. I think we tend to hold ourselves back because we’re worried about what other people think, we worry if we’re good enough, imposter syndrome is just everywhere. I think the one thing that I’ve found has been really important in my life is to try and somehow put that on hold and go for things. For my life, it’s really been beneficial. Sometimes things don’t work out, but as a whole, it’s been great.  The second thing I’d say as a scientist, I would say that it’s never about the answers. It’s always about the questions. That’s sort of a bit vague. But what I mean by that is as a scientist, you can choose to work on thousands of different things. And from my mind, the most important thing you can do as a scientist is not to set off and work on something that at the end of the day, might be a curiosity to you, or might be somewhat interesting to other people. For me, it’s always better to think I’m going to spend my time and my energy working on things I believe are going to have an impact. You can do fundamental science and still have an impact on society. If you can merge those two ideas together that allows you to come up with questions of things that you could work on. A lot of times it’s not easy to have answers to those questions, but at least if you set out on trying to address the question at some point solutions will start to show up. You’ve got to have the questions and the good questions before you can ultimately get to those solutions. |
| Q10 | And what’s the best piece of advice you’ve ever been given? Was it the same? |
|  | That was probably one of them – make sure that you’re working on important problems. I think another piece of advice I got from a really great friend whose name is Dennis Dougherty – he’s a professor at Caltech. He said to me, there’s a hundred thousand ways to get tenure. And what he means by that is there’s no one size fits all formula to do it. You have to go your own way and invent your own path.  I know that sounds cliche, but if you try and do things the way that other people do it, you’ll just end up being a bad version of that person. What you should do is try and figure out what it is that gets you excited and don’t worry so much about how other people are doing things. Just go off and follow your own path and trust your own instincts. I think that piece of advice for me was just remarkable at the time, because it gives you some freedom, to not worry about watching all these geniuses around you do their thing because you can never do what they do. That’s who they are. You just have to do your thing. As long as you stick to that I think not only will it work you’ll have a great thing. It’s much more enjoyable to do it that way. |
| Q2 | One of the joys of your announcement was seeing you celebrate with your research team. How did it feel to be able to share it with them? |
|  | That was an amazing moment. It was one of the other parts where I felt like the whole world was going to go nuts that day for me. I could sense that. So I decided, wouldn’t it be great if we still had group meeting anyway, because we always have group meeting in the morning. So I wrote this email saying, despite recent events, I think we should still have group meeting this morning, which was I thought pretty funny. So when I came into work, my whole group was there. They actually applauded me, which is the first time in ever they’ve been nice to me! Again it was a whole new world, but then we went into the group meeting and the group meeting was fun. We were presenting the science, but what was really interesting was we had all these photographers and journalists there too who were rolling around group meeting taking pictures of people while we’re presenting the science. So my group were all having a blast with the whole thing. |
| Q9 | We understand that when you first found out about the prize you thought it was a prank. Can you tell us about that? |
|  | It’s a kind of sad story – a classic imposter syndrome story! I was lying in bed – I’m usually an early riser but this day, for some reason I slept in and my wife got up and she could hear my phone buzzing. It was about five thirty in the morning and she was kind of annoyed. It kept buzzing and she got up, and she goes, “It says here, Ben List is trying to contact you.” And then there’s a number that says someone who’s from Sweden.  So I get out of bed and I’m reading this and it says, “Dave”, and it’s from Ben and it says, “Call me.” So I call him and he didn’t say you’ve won it but he basically said, it’s happening Dave. And I was like, no, I really don’t believe this. I have some ex students who are in Sweden and my group are a very mischievous group. They’re the kind of group that would always be up for pranks. And they’ve either cajoled Ben List into doing this, or he’s part of the prank. He texted me afterwards. I said, “Look, it’s not, I bet you a thousand dollars it’s not.” And then I literally switched my phone off and went back to sleep.  Then after about maybe half an hour, I got up and went downstairs to see who had won the Nobel Prize. I looked on the New York Times to see if they had it and there was this artist rendition of Ben List, and someone who looked something like me and my name at the bottom. It was honestly the most surreal moment of my entire life. I almost honestly fell out the chair staring at this thing. |
| Q9 | So you bet Ben List a thousand dollars you hadn’t been awarded the prize! Have you paid him his money yet? |
|  | You know – I come across as being classically Scottish – I haven’t paid him yet. I need to pay him. I think we’re going to be together in San Diego in about a month and a half. I’m trying to figure out if I’m going to pay him in pennies or one of those big cheques. But I’m definitely going to pay him. It’ll be the happiest I’ve even been to pay someone a thousand dollars. But I’ll absolutely make sure to make Ben square on the whole bet – I think that’s the least I can do. |
| Q9 | What will you do with the rest of the money? |
|  | With my Nobel Prize money what we’re doing is we’re taking 100% of it and giving it to a new charitable trust I’ve started. It’s going to give money every year to underprivileged communities or classes for educational purposes, whether it’s for infrastructure, iPads, or to take trips to go to places they couldn’t go before. One of the great things is with all these invitations I’m getting, I’m taking all the honorariums from that as well and putting that all in the trust to build it up. So it has been a dream come true to pay it forward a little bit.  It’s one of those things where you realise that at some point there’s a little bit of your effort involved, but there is an incredible amount of fortune along the way. Once you know that, you realise there’s a lot of people who are not so fortunate, and you have to do things help everyone out. That is certainly the way I was brought up and certainly what I believe in going forward. |

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| **Chemistry\_2024-2000** | |
| **ID** | 0311 |
| **Biographical** |  |
| **Autobiographical** |  |
| **Podcast** | No scirpts |
| **Telephone**  **interview** | [EC]  Emmanuelle Charpentier: Hello?  Adam Smith: Oh hello, am I speaking to Emmanuelle Charpentier?  EC: Yes, speaking.  AS: Hello. So could you just tell us, how did you hear the news?  EC: The general secretary Göran Hansson called me, at 10:59.  AS: Very precise. And I mean there’s been so much speculation about the prize for so long, it must have been strange, because in some ways you must have been expecting a call.  EC: You know I have been reminded thousands of times that one day … I mean one day surely CRISPR would be awarded, and that in this regard most likely my name will be mentioned, but I have to say that when he called I was totally … I could not believe it, I mean I was really … I mean I’m still emotional, because you don’t … I mean, again … And I think it’s maybe, I have to say, the fact that you hear it and that, as I said, you connect to it, but you still believe it’s another person or it’s surreal, it’s not … and when it happens, now it’s real and now I have to deal with it. But I also have to say I think a lot of all my colleagues of the CRISPR field who have really supported the new field of research, relatively young, it’s only, let’s say, I don’t know, 12 years old, it’s very recent. And I also think of my colleagues for sure, of all my former members of my team, Elitza Deltcheva and Krzysztof Chylinski, who really also made this happen.  AS: It must be just extraordinary to see the explosion in the field, it’s having such an impact so fast.  EC: Yes, I think it’s very unique because when you see all the field of just CRISPR biology, understanding the CRISPR-Cas systems in bacteria and archaea at the physiological level and even more at the mechanistic level, I mean this has been, you know, an incredible, how do you say, explosion of knowledge and publications. And then, you know, following the publication of the Science paper of Jennifer and I, the … I mean it was clear the scientific community was waiting for, let’s say, a tool that will simplify the genetics of their organisms of choice, and that everyone jumps on it. The development is incredible, the spectrum of applications, is quite incredible. And it has created actually also a lot of interest and I have to say a lot of jobs in the biotechnology field, in the communications field, in the … there is even a new journal, the CRISPR Journal … it has developed in incredible way.  AS: Indeed, and it’s sort of humbling to reflect on the fact that this is derived from something that you learnt from looking at bacteria. It kind of changes your view of humanity, and what nature has to teach us perhaps.  EC: Yes, and I think in, you know, I’m a microbiologist and I have always been interested in infectious diseases and my field of research is not really well recognised at the fundamental level, and so it’s good to see that there is still a lot to be … to learn.  AS: So, another question, I mean you are, you and Jennifer are the sixth and seventh female laureates. That takes the total from a little under three to a little under four percent of the total number of chemistry laureates being female. Do you think there’s something particularly important about the fact that this is an all female prize?  EC: I mean, you know, first I’m a scientist, but no, I think it’s, I mean, I think it’s very important because, because we see even more, how do you say, girls and young women choosing science, at least for the field of biology, and it’s very important to provide a message that you know the ultimate recognitions are, you know, how do you say, independent of the gender, and that I think it’s most likely a very positive message for the girls and the young women who wish to start science, continue in science, and to really provide a clear message that it is possible to achieve ultimate recognition even if you are female. I think it’s … obviously this is the first time, as far as I heard today that the prize is awarded to only female scientists. No, I think it’s … you know it is a reflection of what is occurring nowadays. You don’t specifically look at the gender, and, you know, it’s a good example to show that nowadays it is what happens, you have a lot of collaborations happening among, let’s say, male leaders only or female leaders only, or a mix, and it’s fine, it’s the way it’s supposed to be, it should be a natural process.  AS: Indeed. Of course Dorothy Hodgkin was awarded the chemistry prize alone, but this is the first time for two women. And talk about your collaboration with Jennifer Doudna.  EC: The collaboration was short and intense! Because, yeah, because obviously this was clear that, again I would say this, it’s thanks to the natural mechanism of CRISPR-Cas9 in bacteria. Sometimes you work on systems and you know it takes a long time to see what you would like to see or the research is not you know black and white, it is light grey or dark grey. And here it was really white let’s say. And then you know for sure, a wish from both sides, and an understanding that we needed to go fast because, you know, the story was a great one, so that’s why it was intense – it was a common understanding that it was important to join forces, and you know, and be fast. And also I have to say this is also part of the reason why I approached Jennifer Doudna, also, you know, we were very much in line in the way to do very precise research. It was not … it was fast but precise, and deep. For this we recognised one another – we are the same type of scientist who, you know, want to see the details of the data, so this was … I mean it’s important because, I think, you know, it’s important because you … this is not about a paper published in Nature or published in Science, as a matter of fact, you know, these research papers published in the high impact-factor journals. It’s really about, you know, solid work. And I want to say this because nowadays where everyone is, you know, how do you say, evaluated through a potential number of publications and H-index factors, this does not … it’s nice, but sometimes you just need one story, one very good story. You need time to do the work in a proper way, in a deep way and … and I want to mention this because I would not like to see science having lost this sense.  AS: It’s so important – progress does not come through impact factors, it comes through solid work, yes. The potential, of course, of CRISPR-Cas9 is great and wonderful, but it also has a slightly dark side that it could be misused. How do you think that should be regulated, how can we make sure it’s used for good?  EC: First of all, CRISPR-Cas has facilitated a lot, and genetics in research and development. But as to have it as a technology that can be used safely for the editing of the human germline it’s something else, first of all. And second of all one should not underestimate that fact that CRISPR-Cas9, even though it is a wonderful tool, it would be extremely difficult to get the technology to modify more than one gene at a time. So I think, let’s say, indeed unfortunately we may see unfortunate and really unwanted experiments.  AS: It’s just … yes, sometimes the science moves faster than society’s ability to think about the science, and I suppose that’s the thing.  EC: That is I think the case indeed for a lot of technologies. Technologies go faster than …  AS: Yeah. It’s been a huge pleasure speaking to you, I hope we can speak at greater length about all these important things soon. In the meantime …  EC: Thank you very much.  AS: Thank you and congratulations again.  EC: Okay, thank you. Bye bye.  AS: Bye bye. |
| **Interview** |  |
| Q3 | Where does you passion for science come from ? |
|  |  |
| Q3 | Why were you drawn to biology? |
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| Q5 | Was there a particular person who influenced you? |
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| Q2 | How do you cope with failure? |
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| Q2 | Have you faced any barriers in your career as a scientist? |
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| Q1 | Do you have a message for young female researchers? |
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| Q1 | What advice would you give to a young researcher? |
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| Q7 | What qualities do you need to be a successful scientist? |
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| Q2 | How important is criticism in research? |
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| Q2 | Is it important to have hobbies outside your research? |
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| Q10 | Describe your relationship with your co-laureate Jennifer Doudna. |
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| Q15 | What is the “greatest benefit to humankind” of your research? |
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| Q15 | How would you describe the impact of CRISPR/Cas9? |
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| **Chemistry\_2024-2000** | |
| **ID** | 0312 |
| **Biographical** | I was born on February 19, 1964 in Washington, D.C., the oldest of three sisters. My father Martin K. Doudna was a speechwriter for the Department of Defense at the time and my mother Dorothy taught in community college. My family, including my siblings Ellen and Sarah, moved to Ann Arbor where my father pursued a Ph.D. in literature at the University of Michigan. After earning his degree, he received a job offer from the University of Hawaii in Hilo and moved our family there in August 1971 when I was seven.  Growing up as a “haole” (Hawaiian slang for a non-native), I felt really alone and isolated at school. This “outsider” feeling drove me to take risks and prove doubters wrong, and later influenced my choices as a scientist. In my isolation, I sought solace in books that spurred me to learn more about the world around me and how I fit in. As I made friends and expanded my social life, I fortified my reading with nature walks, hikes, bicycle riding, and explorations of lava-flow caves. With its mix of volcanoes, forests and beaches, the “Big Island” of Hawaii provided a rich palette of biological diversity that inspired my first questions as to how so much diversity came to be.  In the sixth grade, I came across a book called *The Double Helix* by [James Watson](https://www.nobelprize.org/prizes/medicine/1962/watson/facts/) that my father had laid on my bed. It told how Watson, an American biologist, and [Francis Crick](https://www.nobelprize.org/prizes/medicine/1962/crick/facts/), an English biochemist, led the discovery in 1953 of the “spiral staircase” structure of the DNA molecule, for which they received the 1962 Nobel Prize in Physiology or Medicine with [Maurice Wilkins](https://www.nobelprize.org/prizes/medicine/1962/wilkins/facts/).  DNA is formed from chains of nucleotides, each of which contains one of four nitrogen bases – adenine, thymine, guanine and cytosine. All of the information for carrying out the essential processes of life is encoded in the sequences of these AGCT base letters. A string of base letter sequences that contains instructions for making a specific protein is called a gene. *The Double Helix* explained how DNA’s double-stranded helical structure – commonly depicted as a twisted ladder that enables the molecule to unwind − exposes its sequences of AGTC letters so that the genetic instructions they carry can be copied onto messenger RNA (mRNA). In the cells of eukaryotic organisms such as humans, mRNA carries these instructions from the nucleus out into the cytoplasm where transfer RNA (tRNA) uses the information to assemble amino acids into proteins.  In reading *The Double Helix,* I was captivated by how scientists, working collaboratively, were able to meticulously piece together and solve what had been one of biology’s most elusive puzzles.  Learning about the role played by Rosalind Franklin, the so-called “Dark Lady of DNA,” whose X-ray crystallography images exposed DNA’s helical shape, it struck me then for the first time that a woman could be a great scientist.  Despite my outstanding academic record, especially in math and science, my high school guidance counselor strongly discouraged me from pursuing a college major in chemistry, or even aspiring to be a scientist. Undeterred, I applied to and was admitted into Pomona College in California and enrolled in the fall of 1981 at the age of 17. I studied chemistry, despite briefly considering switching my major to French.  That summer I returned to Hilo and worked in the laboratory of Don Hemmes, a biology professor and longtime family friend. I was assigned to a small team investigating how a fungus, *Phytophthora palmivora*, infected papayas, which was a big problem for Hawaiian fruit growers. I learned to prepare samples for analysis in an electron microscope and follow the chemical changes that take place as the fungus advances through different stages of germination. The research revealed that calcium ions play a crucial role in the development of the fungus by signaling fungal cells to grow in response to nutrients. It was my first taste of the thrill of scientific discovery, an experience that I had read so much about, and that left me hungering for more.  In the summer of 1984, following sophomore and junior years that solidified my commitment to science, I was invited to work in the lab of my advisor, biochemistry professor Sharon Panasenko. I was tasked with growing soil-based bacteria in such a way where we could study the chemical signaling that enables the bacteria to self-organize into colonies when starved for nutrients. My method of growing the bacteria in large baking pans instead of conventional Petri dishes was acknowledged in a paper published by Sharon in the *Journal of Bacteriology,* the first time my name appeared in a scientific journal.  I graduated from Pomona College in the spring of 1985 as the top student in chemistry. I remain grateful to Pomona for a liberal arts education that exposed me to so many ideas that I otherwise might have never had come into contact with and that were key to my later success.  Upon the urging of my father, I applied to graduate school at Harvard Medical School, where I enrolled in the fall of 1985. In 1986, I elected to do my dissertation work in the lab of [Jack Szostak](https://www.nobelprize.org/prizes/medicine/2009/szostak/facts/) (2009 Nobel Prize laureate in physiology or medicine with [Elizabeth Blackburn](https://www.nobelprize.org/prizes/medicine/2009/blackburn/facts/) and [Carol Greider](https://www.nobelprize.org/prizes/medicine/2009/greider/facts/)) who discovered how telomere caps prevent chromosomes from breaking down.  Jack was in the process of switching his research focus from DNA to RNA and the role it played in the origin of life on Earth. He suspected RNA preceded DNA and encouraged me to be his first graduate student to explore this idea.  In retrospect my decision to concentrate on RNA makes perfect sense, but at the time turning away from DNA was a bold and risky move. The public spotlight then was shining on the Human Genome Project, an international effort to map and sequence all the base letters in the human genome (an organism’s full complement of DNA).  Billed as “the Holy Grail of Biology,” the Human Genome Project promised to revolutionize medical diagnostics and treatments with the wealth of genetic information it would provide. Mapping and sequencing DNA garnered headlines and funding, but we saw the immense value to be gained from a better understanding of the multipurpose RNA molecule in all its many forms.  Jack and I agreed that the potential for RNA to have played a starring role in the origin of life hinged upon whether RNA molecules are able to replicate themselves. To answer this question, we reengineered a self-splicing RNA intron (a segment of a DNA or RNA molecule that does not code for proteins) into an RNA enzyme (a protein catalyst) that could splice together a copy of itself. This demonstrated that RNA could function as a polymerase, an enzyme that promotes the formation of molecules such as DNA or RNA. We published the results of the study in 1989 in the journal *Nature* in a paper titled “RNA-catalyzed synthesis of complementary-strand RNA,” marking the start of my journey in RNA research.  After receiving my Ph.D. in 1989, I continued my research on self-replicating RNA molecules in Jack’s laboratory as a postdoctoral fellow, but my curiosity grew around what sort of molecular structure would enable RNA to replicate itself. It was one of biology’s toughest challenges – determining the molecular structures of RNA enzymes and other functional RNA molecules.  In the summer of 1991, I relocated to the University of Colorado in Boulder to work in the laboratory of [Tom Cech](https://www.nobelprize.org/prizes/chemistry/1989/cech/facts/), who two years earlier had won the Nobel Prize in Chemistry with his collaborator [Sidney Altman](https://www.nobelprize.org/prizes/chemistry/1989/altman/facts/). In the 1980s they discovered that RNA not only serves as a genetic messenger but can also function like an enzyme. They dubbed these catalytic RNAs “ribozymes” by combining “ribonucleic acid” with “enzyme.” Their ribozyme was the same self-replicating RNA enzyme that Jack and I would later reengineer.  As a research fellow in Tom’s laboratory, I used X-ray crystallography to image the structure of RNA enzymes, similar in principle to how Rosalind Franklin imaged the structure of DNA. For this work, I teamed up with a graduate student named Jamie Cate who had been using X-ray crystallography to study protein structures. Although we were able to successfully crystalize RNA enzymes for imaging, exposure to X-rays quickly destroyed the crystalline structure.  It was a fortuitous meeting with Yale University biochemists [Thomas Steitz](https://www.nobelprize.org/prizes/chemistry/2009/steitz/facts/) (2009 Nobel Prize laureate in chemistry with [Venkatraman Ramakrishnan](https://www.nobelprize.org/prizes/chemistry/2009/ramakrishnan/facts/) and [Ada Yonath](https://www.nobelprize.org/prizes/chemistry/2009/yonath/facts/)) and Joan Steitz, a husband-and-wife team on sabbatical in Boulder for a year, where I learned of their technique for the cryogenic cooling of crystals prior to X-ray imaging. Flash-freezing crystals in liquid nitrogen preserved their crystalline integrity even when irradiated with X-rays. Steitz would share the 2009 Nobel Prize in Chemistry for his work in determining the structure of ribosomes, the macromolecules in a cell’s cytoplasm that use RNA’s genetic messages to synthesize proteins.  Eager to use cryo-cooling technology, I accepted an appointment at Yale in 1994 as an assistant professor of molecular biophysics and biochemistry, with Jamie Cate accompanying me as a graduate student in my new lab. With a technique devised by Jamie, we used X-ray crystallography to produce electron-density maps that enabled them to determine the location of every atom in a self-splicing RNA enzyme. With this information, we constructed structural models of the molecule, similar to what Watson and Crick did with DNA.  Just as the double-helix structure revealed how DNA is able to store and transmit the genetic code, the structural models that my team and I built showed how RNA is able to function as an enzyme capable of slicing, splicing and replicating itself, just as the double-helix structure revealed how DNA is able to store and transmit the genetic code. Tom and I were the principal investigators and Jamie Cate was the lead author on a 1996 paper published in *Science* titled “Crystal Structure of a Group I Ribozyme Domain: Principles of RNA Packing.” The paper is considered a scientific landmark for providing the first detailed look at a large-structured ribozyme. We hoped then that our discovery would provide clues as to how scientists might be able to modify the ribozyme to repair defective genes in the future.  In 1997 I accepted an appointment as a Howard Hughes Medical Institute (HHMI) investigator. In 2000 I was named the Henry Ford II Professor of Molecular Biophysics and Biochemistry and elected into the National Academy of Sciences. That summer I married my research partner Jamie Cate and we had a son whom we named Andrew two years later. It was also in 2002, after Andrew’s birth, that Jamie and I accepted appointments as professors in the College of Chemistry at the University of California, Berkeley (UC Berkeley). We also became faculty scientists at the Lawrence Berkeley National Laboratory (Berkeley Lab), which gave us access to the Advanced Light Source, one of the world’s premier sources of X-rays for crystallography research.  In the fall of 2002, soon after I started my work at UC Berkeley, there was a deadly outbreak in China of Severe Acute Respiratory Syndrome (SARS) caused by an RNA-based virus. The outbreak motivated me to pivot to RNA interference, a phenomenon that plays a fundamental role in a number of important functions, including how the human immune system fights off viral infections. RNA interference silences unwanted genetic messages, thereby blocking the production of the proteins they code for.  Using the powerful beams and sophisticated instrumentation at the Advanced Light Source, a synchrotron accelerator optimized for X-ray and ultraviolet light research, my lab and I produced crystallography images from which we determined that an enzyme known as Dicer functions as a molecular ruler to snip double-stranded RNA and initiate the process of RNA interference. We found that the molecular structure of Dicer features a “clamp” at one end to grab hold of a double-stranded RNA molecule, and a “cleaver” a set distance away at the other end to snip it.  Our findings set the stage for understanding how Dicer enzymes are involved in other phases of the RNA interference pathway serving as a guide to redesigning RNA molecules that direct specific gene-silencing pathways. Our work later led to a call from UC Berkeley microbiologist Jillian Banfield who first introduced me to the term “CRISPR.”  Jill was studying the genomics of microbes that live in extreme environments as a means of finding better ways to clean up polluted sites, and repeatedly encountered a unit or length of DNA base letter sequences known as CRISPR, or Clustered Regularly Interspaced Short Palindromic Repeats, which plays a role in the defense mechanisms employed by microbes such as bacteria and archaea for protection from viruses and invading strands of nucleic acid known as plasmids. Usually located on a microbe’s chromosome, a CRISPR unit is made up of base sequences called “repeats” and “spacers” that separate the repeated sequences. Interested in understanding how a combination of CRISPR and a complex of adjacent enzymes dubbed “Cas” for CRISPR-associated proteins allowed microbes to utilize small customized RNA molecules (crRNA) to protect themselves through a gene-silencing process, Jill found my lab’s website from a Google search and suggested a collaboration to learn how the CRISPR-Cas immune system might work through RNA interference.  A conversation over tea at a local Berkeley café followed, where we discussed this new, mysterious biological function of CRISPR and the possibility that it was the bacterial equivalent to RNA interference. While hypotheses about CRISPR had been floated, no one had yet conducted the experiments to prove or disprove those theories.  In 2008, Jill and I, along with Mark Young at Montana State University, organized the first international conference on CRISPR research, which was held in Berkeley. That same year, research out of Northwestern University had revealed that the CRISPR-Cas system did not work through RNA interference, but instead targeted the DNA of an invader. The implication of this discovery was highly significant. If CRISPR-Cas was identifying, targeting, and cutting invasive DNA, then it had potential as a DNA editing tool. However, crucial experimental information was missing, especially as to how the CRISPR-Cas system would be able to recognize and cut out unwanted DNA.  My Doudna Lab team began filling in this missing information by first developing a purification technique that provided them with highly concentrated samples of the Cas proteins they wanted to study. With this technique, we first studied Cas1, which we discovered is able to cut up DNA in a way that helps with the insertion of new snippets of foreign DNA into a CRISPR unit during the immune system’s memory-forming stage. It brought us a step closer to understanding how CRISPR steals bits of DNA from attacking phages and works that genetic information into its own, laying the groundwork for the targeting and destruction phases of the immune response.  In 2010 we used X-ray crystallography beamlines at the Advanced Light Source to produce the first atomic-scale crystal structure model of Cas6f, discovering that like Cas1, it functions as a chemical cleaver. However, we found that the job of Cas6f is to specifically and methodically slice long CRISPR RNA molecules into shorter chunks that can be used to target foreign DNA.  Our model showed that when a microbe recognizes it has been invaded by foreign DNA, it incorporates a small piece of that foreign DNA into one of its CRISPR units, which is then transcribed as a long RNA segment called the pre-crRNA. Cas6f cleaves this pre-crRNA within each repeat element to create short crRNAs containing sequences that match portions of the foreign DNA forCas proteins to use to bind the foreign DNA and silence it. These research results were reported in the journal Science in a paper titled “Sequence- and structure-specific RNA processing by a CRISPR endonuclease.”  In 2011 I met Emmanuelle Charpentier at the annual American Society for Microbiology meeting in Puerto Rico. A French biochemist, microbiologist, and geneticist, and one of the world’s top CRISPR-Cas researchers, Emmanuelle was at the time studying Cas9 in a CRISPR system known as type II at the Laboratory for Molecular Infection Medicine at Umeå University in Sweden. Her work had shown that in the human pathogen *Streptococcus pyogenes*, crRNAs could only be produced in the presence of a second CRISPR RNA molecule, or tracrRNA for trans-activating crRNA, and that CRISPR systems only need Cas9 to acquire immunity to viruses targeted by crRNAs.  Emmanuelle and I embarked on a collaboration to investigate how Cas9 and crRNAs function in the CRISPR microbial immune system and whether crRNA and tracrRNA could be linked into a single chimeric CRISPR RNA molecule to make the system easier to manipulate.  With Martin Jinek and Michael Hauer from my lab and Krzysztof Chylinski and Ines Fonfara from Emmanuelle’s, we unraveled the components of the CRISPR-Cas9 assembly. In our discovery that Cas9 requires binding to a molecular complex of tracrRNA and crRNA which then identifies and guides the Cas9 to the invasive DNA for cleaving, we realized that the tracrRNA and crRNA complex is programmable.  The next step was to engineer a single-guide RNA (sgRNA) molecule that would have the guide information on one end and the binding handle on the other. Such a system would provide a straightforward way to cleave any desired stretch of DNA sequences in a genome. New genetic information could then be introduced into the genome using well established cellular DNA recombination technology.  The results of this momentous study were published in *Science* on August 17, 2012 (it first appeared online June 28, 2012). The paper was titled “A Programmable Dual-RNA–Guided DNA Endonuclease in Adaptive Bacterial Immunity.” Emmanuelle and I were the principal investigators; the co-authors were Martin Jinek, Krzysztof Chylinski, Ines Fonfara, and Michael Hauer.  Our paper showed that an immune system evolved over eons by bacteria and other microorganisms to defend themselves against viral and other invasive DNA could be adapted into a relatively easy-to-use “CRISPR genome editing” technology for rewriting the genetic code within the cells of any organism, including humans, with unparalleled efficiency and precision.  It was an incredible, precious time of pure joy to discover that bacteria had found a way to program a warrior protein to seek and destroy viral DNA, and fortunate, even miraculous, that we could repurpose this fundamental property for an entirely different use. The joy of discovery was a feeling just like I’d felt in Don Hemmes’s lab all those years before in Hawaii.  In 2014, I founded the Innovative Genomics Institute (IGI) with Jonathan Weissman to realize the potential of CRISPR genome editing in human health, climate, and agriculture. The IGI, of which I am president, is made up of researchers at UC Berkeley and the University of California, San Francisco, who are developing foundational CRISPR technologies to advance genome engineering innovations for the benefit of humanity that are accessible and affordable to all. We continue to build upon what started as our curiosity-driven, fundamental discovery project into strategies to help improve the human condition.  One of the early initiatives of the IGI centered around expanding access to treatments for sickle cell disease. By this time, I had additionally launched my first company, Caribou Biosciences, and would come to co-found companies Editas Medicine, Intellia Therapeutics, Mammoth Biosciences, and Scribe Therapeutics to bring CRISPR from the lab into the clinic in the form of CRISPR-based therapeutics and diagnostics.  I accepted the positions of Li Ka Shing Chancellor’s Chair at UC Berkeley, senior investigator at the Gladstone Institutes, and adjunct professor of cellular and molecular pharmacology at UC San Francisco, persisting with my research on the exploration of delivery techniques for CRISPR-based therapies, the development of next-generation CRISPR diagnostics, and continued investigations into the structure and mechanism of CRISPR-Cas systems. Our ability to harness the immense “dual use” potential of CRISPR led to my decision to actively engage in and initiate the public discourse on the ethical use and responsible regulation of CRISPR, particularly in the case of human germline editing.  In 2015 I first called for a moratorium on the use of CRISPR in the human germline and arranged a meeting with 20 other researchers with the goal of discussing the ethics of germline gene editing. Modeled after the 1975 Asilomar conference that put forward guidelines for research on recombinant DNA and co-organized with two of its key organizers [Paul Berg](https://www.nobelprize.org/prizes/chemistry/1980/berg/facts/) and [David Baltimore](https://www.nobelprize.org/prizes/medicine/1975/baltimore/facts/), the discussions we conferred at the Napa Valley meeting were summarized in a report later published in *Science*. In it, we outlined the implications of human germline editing and ultimately called for a prudent path forward, including clear international guidelines, over instituting a moratorium.  I was also one of the organizers of the International Summit on Human Gene Editing in December 2015, the first international symposium at the National Academy of Sciences on the societal and ethical use of CRISPR technology. At the event, we further discussed the ethical considerations of safely applying CRISPR technology and came to a consensus similar to that which resulted from the Napa conference – that certain conditions should be met before human germline editing was permitted. As CRISPR began to enter the mainstream conversation, I detailed the ethical quandaries we faced and our rationale for calling on ongoing input from scientists and bioethicists as well as broader public discussion in my 2017 book *A Crack in Creation: Gene Editing and the Unthinkable Power to Control Evolution* co-authored with Samuel Sternberg. I had hoped that the steps Sam and I described would deter any premature attempts to perform inheritable gene editing but just one year later the type of reckless experiment that I had feared might happen did.  At the 2018 Second International Summit of Human Genome Editing in Hong Kong, news of the world’s first “CRISPR babies” born in China – a medically unnecessary, illegal human experimentation – propelled us into a new era. Along with my colleagues from the National Academies of Sciences and Medicine and the Royal Society, many of whom were participants at the 2015 Napa Valley conference, I maintained that the risks of germline editing remained too great to permit gene editing in embryos, egg cells, or sperm cells. Back in the U.S., I met with a number of senators to discuss the safest path forward for CRISPR technology – and its future impact on our health – and continued to guide conversations on the necessary regulations including the international commissions that have since been convened by the National Academies and by the World Health Organization.  In early 2020, I expanded my work with CRISPR as called for by the global COVID-19 pandemic. My colleagues at the IGI and I launched an automated coronavirus clinical testing laboratory in March 2020 built out of our research facilities over the course of just three weeks. Our group has since provided critical testing services to thousands across local and state communities. We also introduced a new initiative to develop a rapid CRISPR-based, point-of-need diagnostic test in addition to approximately two dozen additional research projects. We realized the need to further enable acts of scientific collaboration and innovation that would lead us out of the pandemic, releasing a roadmap detailing the transformation of our nonclinical labs into the testing facility and making all COVID-19 project-related intellectual property open source.  Our group continued to pursue genome engineering research that could elevate the standard of care for patients around the world and of the highest, currently unmet need. Our efforts to date, from Emmanuelle and my co-discovery of CRISPR to the genome editing revolution happening now, were chronicled by bestselling author and historian Walter Isaacson in his book *The Code Breaker: Jennifer Doudna, Gene Editing, and the Future of the Human Race* in March 2021. Shortly after, the IGI, leading a consortium of scientists and physicians across UC Berkeley, UCSF, and the University of California, Los Angeles, began the first FDA-approved clinical trial of a CRISPR-based therapy for directly correcting the genetic mutation that causes sickle cell disease. We are developing the sickle cell therapy, and future CRISPR gene therapies, to eventually treat disease from within the human body (in vivo) and extend to blood cancers, immunological conditions, and additional rare diseases that presently cannot be addressed. By improving our ability to rewrite the code of life and supporting the type of fundamental scientific research that made our discovery of CRISPR possible, I believe they soon can be. |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** | [JD]  Jennifer Doudna: Hello, this is Jennifer.  Adam Smith: Oh hello, this is Adam Smith calling from Nobelprize.org, the website of the Nobel Prize.  JD: Yes, hi Adam.  AS: How lovely to speak to you. Where are you at this moment?  JD: I am sitting on my patio outdoors in Berkeley at my house, and I’m with a few people from Berkeley, from my campus, and of course we’re outdoors doing our social distancing thing, but it’s kind of lovely out here. It’s a bit cool, we’re in the garden.  AS: Nice way to start the day.  JD: Indeed.  AS: I gather you were woken up by a call from a *Nature* journalist.  JD: Yes, isn’t that crazy. Heidi Ledford broke the news to me. And, Adam, I assumed she was calling me to ask me to comment on somebody else winning the Nobel Prize!  AS: The startling pace of CRISPR research and application must just amaze you. I mean you knew there was something there, but how does it feel to see what’s happened.  JD: It’s truly astounding. It’s extraordinary. Yeah, it’s just been amazing. I think we had a sense in those very early days, in my work with Emmanuelle, that you know we were onto something big, but I think we had no idea how big. And it still amazes me every day to see the extraordinary work that’s going on now globally with this technology, and yeah, thinking back about how it really started with just a curiosity driven project.  AS: That’s the lesson, what you can learn from bacteria.  JD: Exactly, and how much more they, I’m sure, still have to teach us.  AS: Yeah, precisely. In some ways it makes you look a little bit differently at nature to know that there are all these secrets hidden in what one would call ‘lesser’ species.  JD: You know, and I’ve heard many people say that to me, you know, when I would give talks about this work, many people have said almost exactly that, sort of surprised in a way, and saying ‘wow, bacteria are actually really cool!’.  AS: One thing people will focus in is the fact that it’s a prize to two female laureates, and what’s your … what do you have to say about that aspect of it?  JD: Well, I’m proud of my gender. I think, you know, and I’ve said this to my Berkeley colleagues this morning, but my feeling is that I think among women and girls that, you know, sometimes there’s a sense that no matter what they do that their work will not be recognised the way it would be if they were a man. And I just … I hope that this prize and this recognition changes that at least a little bit, and that it’s encouraging to other women who are in science, or even in other fields, to realise that, you know, their work can be honoured and that their work can have a real impact. And whether or not, you know, it’s a Nobel Prize or something else, that women have a really important role to play in the world, and that their contributions are, you know, can have real impact that is noticed.  AS: Have you had the chance to talk to Emmanuelle Charpentier yet?  JD: I’ve called her a few times, she’s called me a couple of times, we keep missing each other. I’m sure we’re both doing these sorts of things, and we’ve texted. I had the good fortune to have about an hour Zoom call with her a couple of weeks ago, which was great, and we had a chance to catch up on the Saturday morning, so I was … I’m glad for that, but of course I’m desperate to talk to her. I’m sure we’ll connect sometime today.  AS: I’m afraid it’s people like me phoning, and thousands of others phoning you all day long. It’s going to be quite a day you’ve got ahead of you.  JD: Yeah, I can see that.  AS: It’s been a huge pleasure speaking to you, thank you very much indeed, and congratulations.  JD: Thanks so much Adam, great to talk to you as well.  AS: Bye  JD: Bye bye. |
| **Interview** |  |
| Q3 | Why did you decide to pursue science? |
|  | Jennifer Doudna: I loved math when I was growing up. Nobody in my family was a scientist, but my father loved doing puzzles. So we did a lot of puzzles. I was growing up in a small town in Hawaii and I loved the natural environment there. I found myself fascinated by the evolution of plants and animals that survived in that native island environment. This was long before I knew anything about DNA, but I thought it was so interesting that I wondered about the chemistry of natural systems and natural organisms. I decided I wanted to be a chemist. Then when I learned about biochemistry, I thought that’s what I really want to do. I want to study the chemistry of living things. I set off on that journey in college and kind of never looked back. |
| Q5 | Did you have a particular person, a mentor or role model, who really influenced you? |
|  | I would say it’s probably first and foremost my father, because even though he was not a scientist, he was very interested in science and he read everything. He was an avid reader and a literature professor. He gave me lots of books. He gave me [Jim Watson](https://www.nobelprize.org/prizes/medicine/1962/watson/facts/)‘s book about the double helix as well as books by Harold Morowitz and a lot of classic writers who wrote about science for a non-scientific audience. He really encouraged me early on to pursue my interests. Later when I was in grad school, he was the one person in my family that when we got together, his first question would always be, ‘What are you working on in the lab?’ He would really want to know, like he didn’t just want a one sentence answer. He really wanted to get into it. ‘What are you doing and why are you doing it? Why is it interesting?’ So that was great.  Beyond that, I did have some wonderful teachers. My biology and chemistry teachers in high school were very encouraging. I had multiple great professors in college who also encouraged my interest. My biochemistry professor in college gave me a chance to work in her lab over the summer, which was critical, where I really figured out, ‘Wow! I love lab work. This is really great. This is exactly what I want to be doing.’ When I got to grad school, I really got lucky. I got into a lab of a wonderful person who now is a Nobel Laureate himself, [Jack Szostak](https://www.nobelprize.org/prizes/medicine/2009/szostak/facts/). He was an incredible mentor, very passionate about science and encouraging for all of us that were in the lab at the time. I feel like I really lucked out. |
| Q12 | Were you influenced by your father to be an avid reader too? |
|  | I have to say that in the roughly 10 years that I was pretty intensely working on CRISPR (like up until this year or 2020) I had to put a lot of things on hold. I’m an avid gardener and I gave up my garden. And I really stopped reading for pleasure. I had to mostly just read for work. Even trying to keep up with the scientific literature was very difficult. During that period of time, I had a young son, my mom was ill and then passed away. So we’re dealing with that. I was made division head in my department so I had a lot of administrative duties there. There’s this bunch of stuff. I really put all of that on hold.  What was really interesting for me was that last year in 2020, besides the year of this Nobel Prize, it was the year of the pandemic beginning. I think, like many people, I had to change many things about my lifestyle. I stopped travelling – I used to travel every week. Then I found that last spring, I just started slowly thinking, ‘Gee, I really ought to be composting.’ I started composting in my garden and that’s what took me up into my garden regularly. I started pulling a few weeds and pretty soon I had a very beautiful and active garden again. I loved it. I was in my garden every day and I had vegetables, flowers, fruit and lemons. It was really fun and I thought, ‘Oh my God, I don’t want to give that up again. You know, that’s too much.’ It was the same thing with reading.  There were a lot of very disturbing things going on in the US politically, so I had a number of sleepless nights. I found myself picking up books to help me kind of get through it. I love reading novels. I love reading science books. I love reading things that don’t have anything to do with work because I just I’m interested in them. Both the gardening and the reading are things that came back to me during the pandemic, and I’m going to fight to keep it in my life as we kind of slowly go back to “normal”. |
| Q2 | How do you cope with failure and with unexpected problems? |
|  | I sort of have three ways of coping. The first is that I always remind myself to take a long view of things; something that’s frustrating or disappointing in the moment, is it frustrating today or next week? I try to think about, ‘How am I going to feel about this in six months or a year from now, or 10 years from now?’ I also ask myself, in the scheme of problems in world, how big is this problem. Often it’s not very big. I try to remind myself of the context and I try to remember all the things I’m grateful for. I’m fortunate that I have a family, that I’ve had the successes and I’ve had my career.  That takes me to the second thing; I do really rely on friends, family and colleagues and I’ve been so fortunate to have a really great network of people who I rely on for support. I guess I actively now, even more than when I was younger, look for people that are going to be supportive and who I can in turn be supportive for as well. People that you can really build strong relationships with, I think is very valuable.  The third thing is because there was certainly some adversity when I was growing up in Hawaii, it sounds like a paradise, but it wasn’t. There were a number of issues when I was growing up. I had to learn to rely on myself. I had to kind of find an internal strength to deal with bullying, to deal with all kinds of name calling and resentment. I feel like I go back to that now, too. I kind of go to my inner core and I know that there’s a part of me that no one can touch and that no matter what happens, I know that I know who I am. I know what I value. If there’s adverse things going on there, there’s a part of me that no one can touch that way. That gives me some strength as well. |
| Q1 | Do you have any advice for young researchers or students? |
|  | I honestly think the most important advice is to go for it. That means to embrace your interests, your passions, and really give it your all. I think that is what I’ve seen both for myself and [other] people. People that I’ve had the pleasure to work with in my laboratory, the most successful of them are people who are able to deal with their fears. We all have fears but sometimes you try something and there is failure, right? You have to deal with that.  I think for me and for people that I’ve seen that are highly successful, they deal with that. Each of us has to find our own way to deal with that as we just discussed. But I just think you have to embrace your passions. You have to really go for it. People that have been less successful in my opinion, are those that dabble in something, but then don’t really give it their all. They almost never give themselves a chance to succeed, as they back off too soon. I think for young people, I tell them go for it, find supportive mentors who will help you through the tough times, and then just keep going. Because if you have a good idea, it’s probably going to work out in some way. You may not be able to predict how, but you should just keep pursuing it. |
| Q11 | Today it’s the International day for Women and Girls in Science. Do you think diversity is important in science? |
|  | Diversity is really important in science. First of all, I think that if you want to have the best scientific outcomes, you need a lot of different brains working on it. We all come to science (or anything really) with different perspectives, skill sets, interests, passions and ways of approaching a problem. The more of that we have, I think the more likely there is to be interesting science that gets done and frankly, interesting solutions to real problems. The pandemic is one very real example we’re dealing with right now where thank goodness there was creative work done years ago on using mRNA delivery. And now we have these wonderful vaccines, but it came together very quickly. |
| Q1 | Do you have any specific advice to young girls who want to go into science? |
|  | I would never want to stereotype, but I do think there’s more of a tendency by women and girls to underestimate themselves: ‘well, you know, I shouldn’t apply for that job or fellowship or graduate program because I’ll never get in.’ I feel like I hear it more frequently from my female trainees than from male. I don’t know all the cultural reasons for that, but I think it’s something that as women, we have to actively encourage both ourselves and other women and girls that might be following in our footsteps to actively put that little voice aside and trust that actually they’re probably better than they think they are. |
| Q10 | Tell us about the first time you met your co-laureate Emmanuelle Charpentier. |
|  | She and I were both invited to a meeting in Puerto Rico in the spring of 2011. This was a conference sponsored by the American society for microbiology meeting that she might very reasonably be invited to. But for me, not so much because I’m really not a microbiologist at all. It just so happened that they were having one session on CRISPR, which at the time was a fairly esoteric area of microbiology, but interesting.  A friend and colleague, John, was at this conference and he said to me, ‘Oh, Jennifer, I’d love to introduce you to Emmanuelle.’ I had read her paper in Nature and it was a really nice work. I thought it’d be really interesting to talk to her. When I got introduced to her, she was this very chic woman that is quite petite and very attractive. I was immediately impressed by her kind of stylish, very natural look and fashion sense, not fancy but just really nice.  She said that she really had been looking forward to talking to me and I thought, ‘Oh, that’s cool.’ We had our session and then we went for a meal. She said, ‘Hey, I’d love to talk to you about the possibility of doing some work together.’ We started walking around old San Juan. The atmosphere there feels almost a bit French or European. It has these cobblestone streets and is quite lovely. She and I were just walking around these streets and talking about this protein, which at the time was called Csn1 and later was renamed Cas9.  We were talking about the possibility of working together to figure out how it was able to work in bacteria, to defend against viruses. There was a hypothesis that it might be a DNA cutter, but nobody had demonstrated that. How it would recognise viral DNA was unclear. That was really the basis of our initial interactions. |
| Q10 | How was it to work with Emmanuelle Charpentier? |
|  | I loved working with Emmanuelle. She always had a great sense of humour, kind of a very dry sense of humour, even in email. She would say things like, ‘Oh, Jennifer, you have to excuse my Frenchy English.’ And I would say, ‘Oh my god, I’m so jealous of your Frenchy English. I wish I had Englishy French!’  She was in Sweden at the time. She was up at Umeå University so she was nine hours ahead of California time. When we were working really intensely on analysing data and writing a manuscript together, it was almost like working 24/7 because I would go to bed and she’d be getting up and she’d be working. By the time I got up, there would be a whole new set of things for me to work on and look at. It was just really intense and really fun. |
| Q8 | How did you hear about the Nobel Prize? What was your reaction? |
|  | I’m embarrassed to say, I’d had a very long day. This is the day before the surprise of when it was announced. I had been at an all-day meeting. I was very tired that night. Of course I was aware about the Nobel announcements being made, but I just didn’t really think too much about it. I turned the ringer off on my phone and I went to bed. I fell asleep and fell into it very deeply. I woke up at just before 3:00 am, California time. My phone was buzzing and I could see that somebody was calling and then there were some unanswered calls and messages. I picked it up and it was a reporter from Nature magazine who I know, Heidi Ledford.  She said, ‘Hi, Jennifer, sorry to bother you early. But I really wanted to be the first to ask you how you feel about the Nobel.’ I was literally coming out of a deep sleep and I said to Heidi, ‘Oh my god, I haven’t had time to look at the news. I don’t know who won it?’ And she said, ‘Oh my god, you haven’t heard!’  I honestly got very nervous. I started to think that I might be dreaming. I said, ‘I can’t talk to you right now. I feel like I need to hear this from somebody official.’ I hung up and another incoming call was coming in and it was Martin Jinek, who was the scientist who did the CRISPR/Cas9 research in my lab in collaboration with Emmanuel, calling me from Switzerland. I answered the call and he said ‘Jennifer, oh my god. It’s just so fantastic as this is so exciting.’ Honestly, I have to say at that moment I knew it was real. The reason is that Martin is the most down to earth and humble person on the planet, and for him to be calling me at three in the morning from Switzerland, with this news, I knew it had to be real. Then of course I got connected to the Nobel Foundation, but that was the first five minutes of my realisation. |

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| **Chemistry\_2024-2000** | |
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| **Biographical** | I was born in Jena, Germany, in July 1922, to American parents, Erwin Ramsdell Goodenough and Helen Miriam (Lewis) Goodenough. My father was working on his D. Phil. dissertation on the Church Fathers at Oxford University at the time of my birth. My parents lived in Oxford, England, for three years and my father enjoyed the culture of the Weimar Republic; he spent much of his long summer vacations in Germany as well as in Rome. My grandfather was able to support my father before the market crash of 1928. After my parents returned to the U.S. from Oxford, my father became a professor of the history of religion at Yale University. My grandfather Goodenough had bought for him with a large mortgage an old house on a five-acre lot complete with an adjoining woodshed, a large barn, an ice house, and a windmill for pumping our water from a spring in the back lot. A huge wisteria vine on which we could climb was supported on the south side of the house by a giant maple tree and on the east side by a trellis. On the north side, a U-shaped driveway leading past the house to a barn encircled apple trees. The windmill, which invited young boys to climb it, was then quickly replaced by an electric pump and the coal-fired furnace by an oil furnace. However, ice was still hauled to an icebox and kerosene for the stove was fetched from a little house on the north border of the property. A large veranda in the front of the house faced west overlooking a two-bar fence before a row of elm and maple trees bordering Amity Road, the main bus route between New Haven and Waterbury. We were located seven miles north of Yale University, which is in downtown New Haven.  My older brother, Ward, and I shared the north bedroom. Ward was the leader; I was the tag-along when he would tolerate me. My world was with my dog, Mack, in the nearby meadows and woodlands where there was so much life to discover and so much wonder to experience. I liked collecting trophies, whether it was butterflies, seashells, or animal skins. A special room halfway up to the hayloft in our large barn was where I housed my skin and hawk-wing collection. Despite many pleasures that I experienced throughout my childhood, my years through 7 were difficult for me. How I struggled to learn to read! I read mechanically without the ability to catch easily the meaning of a paragraph. I never was a good reader, and through my school years, I worked hard to cover my deficiency. I also had a deep sense of insecurity that only lifted slowly as I grew older. **Early education** I went to a private grammar school in downtown New Haven about a mile from my father’s office in Jonathan Edwards College at Yale University.  My father drove me to school on his way to work. I went with a lunch pail; the meal at school was too expensive. I didn’t mind eating separately. I made friends easily as I enjoyed sports on the playground and being mischievous with the other boys in the back row during French class.  I arrived with a full scholarship to Groton School on a warm September day in 1934. I was shown my cubicle in the Hundred House dormitory; each student had a bed, a dresser, and a place to hang his suits. Suits and neckties were worn at all times but on the athletic field; a stiff collar and patent-leather shoes were worn to dinner. On the first floor of the dorm, there were assigned desks in the study hall for First and Second Formers; Third Formers had a study hall in Brooks House at the other side of the chapel. Older boys had personal one- or two-boy studies.  The School day was regulated by bells. A School House bell rang out across the Circle at 7:00 a.m. After breakfast, the school day began with a 15-mintue chapel service at 8:15 before the trek to our homeroom desk. First Formers had their own homeroom; all others had desks in a large study hall where announcements were made after morning classes before being dismissed to Hundred House for lunch. Afternoons were for doing homework in a study hall for an hour followed by mandatory participation in sports until supper. The Rector kept boys occupied every hour of the day. The only exception was Sunday, a day for writing home, attending chapel morning and evening, and reading in the library.  Each class, with the exception of First Form and Sixth Form Sacred Studies, was assigned three sections: B, A, and upper A. I entered as a B student in all subjects. Even so, I was overwhelmed the first few weeks. The Rector taught First Form Sacred Studies. On our first class test, we were asked to name the 12 disciples of Jesus. As I was a poor reader with no religious training, I think I remembered no more than one. Latin class with the football coach went no better, but English grammar under Zahner turned out to be a memorable learning experience. In my Fifth Form year I had been advanced from the B through the A to the upper-A division in all my classes, and I managed to graduate magna cum laude at the head of my Form.  Little time was spent in New Haven after I left home for School. Invitations to spend days or weeks with classmates were common. One summer we were in Colorado and others were mostly relieved by working as camp counselor and lifeguard. I was 14 when I first became a counselor at a YMCA camp. The summer I turned 17, my father added $150 to my savings to allow me to go to Finland with a group from Putney School. **Undergraduate years** I entered Yale University as an undergraduate student in 1940. As I left home, I determined never again to take money from my parents; I had no idea how I would support myself at Yale, but my focus was to do well in my College Board Exams. Fortunately, I was given a summer job tutoring a grandson of the Rector; it would give me room and board for the summer and enough money to pay for a room in a dormitory at Yale the following year.  My freshman year at Yale I was permitted to take a junior course in Ethics and Aesthetics in lieu of English; a junior course translating the Greek plays, and a sophomore second-year calculus course also gave me a good start. My freshman chemistry, Qualitative Analysis, was to satisfy my science requirement and to give me the possibility of Medical School. Freshman Psychology proved to be an intellectual insult; I found Freud totally unconvincing in many of his assertions, and [Pavlov](https://www.nobelprize.org/prizes/medicine/1904/pavlov/facts/)’s dog seemed to be more trivial than made out. I was not drawn to the behavioral sciences even though Psychiatry was quite the in-subject at the time.  A common temptation of youth is the desire to be famous or glamorous or powerful. I realized that not everyone can be “king of the mountain” even for a short time. Can being king, therefore, be what gives meaning to life? I began to understand that any meaning to a life is not to be king of a castle, but the significance and permanence of what we serve. Is service to ourselves, our tribe (ethnic group or family), or to our country the highest service? In a time of war against evil, service to the cause of a more just world and therefore to our war effort was meaningful; but the destructive means of war is always an appalling waste on all sides. I struggled to find a meaningful calling beyond the war. Perhaps it would be in science; so, for my sophomore year, I decided to enroll in the philosophy of science and in physics.  In the summer of 1941, I tutored the son of a Chicago banker who lived in Wheaton, Illinois. Their home was a grand mansion built by the grandfather who had worked his way up to become Head of the First National Bank of Chicago. I slept on a porch with the two boys and three great Danes; I was treated as one of the family, and I earned enough money to pay for my room in Timothy Dwight College of Yale. During my latter years at Yale, a bursary job gave me 21 meal tickets during weeks when classes were in session; I was a grader of Freshman mathematics papers. But how was I to afford food during the vacations? Fortunately, the mother of my roommate, Stuart Little, would invite me to Hartford, Connecticut, to share part of my holiday there.  When I went to enlist in 1942, my mathematics professor, Egbert Miles, called me into his office and said, “John, don’t sign up for the marines like all your friends. The military needs boys with backgrounds like yours to sign up for meteorology in the U.S. Army Air Corps.” I had no stomach to play the hero in war, so I acted on this friendly advice. It gave me another year in college to finish my undergraduate degree, and I spent the summer of 1942 in New Haven. I was not called to active duty until February of 1943. At that time, I lacked one course for graduation, and Yale graciously gave me credit for my Army course in meteorology to grant me a summa cum laude Bachelor of Arts degree in mathematics in the spring of 1943. However, I was cognizant of the fact that, after completing successfully a second-year physics course, I had been saved from an embarrassing flunk of my first test in the Theoretical Physics course taught by Margenau by a telegram the night before calling me to active duty. I was pursuing physics after reading “Science and the Modern World” by Alfred North Whitehead. While reading that book one evening, it seemed to me that much of the intellectual ferment of my generation would be in science; and physics provides a fundamental foundation for science. If there was to be an opportunity to go to graduate school after the war, I felt that night that I should study physics. **World War II army meteorology** Entering the Army ended the pressures I had felt at Yale. The struggles to support myself, to find a calling and to finish my undergraduate requirements before being called into the Army all fell away. Most members of my Yale class were at different stages of entering the armed forces when I left, so I was not parting from a normal college experience. Adjustment to military life was not a problem for me. After a brief orientation in Boca Raton, Florida, I went by troop train to Grand Rapids, Michigan, for training to be a practicing meteorologist. The Army training, mostly by civilians, was efficient and quite professional.  Upon commission in the autumn of 1943, I was immediately posted at an air base in Houlton, Maine a few miles south of a more active air base in Presque Isle. Fighter planes were being dispatched from Presque Isle to England. After two weeks, I found myself in charge of the weather station in Houlton. In those days we drew our own maps and made our own forecasts; there was no satellite and no computer-aided forecast from Washington.  Maine proved to be a good training experience for my next posting the following summer in Stephenville on the west coast of Newfoundland. Stephenville was the jumping-off base for the cargo B54s flying to either the Azores, the base of the northern route, or directly to England. These planes also stopped in Stephenville on their way home to Washington, D.C. The B54s had a longer range than the fighter planes. The tactical bombers were dispatched from Gander on the east side of the island.  Although almost all my forecasts were reasonably accurate, including a clearing of Eisenhower from Stephenville that landed him safely in Paris within 6 minutes of his estimated time of arrival, a forecast could be dangerously wrong.  As D-day approached, we tried to predict from the weather when the allies would storm the beaches of France. Eisenhower and our forces had bad luck with the strength of the cold front behind which they attacked. We followed closely the battle of the hedge rows and the final breakout across France.  One December day, civilian pilots flying the B54s were congratulating themselves that they were going to make it home for Christmas. When I refused to clear them for the trip to Newfoundland because a strong headwind from there to the Azores would prevent them from reaching their destination, they set out anyway. Six hours later they were back on base; the headwinds were so strong they had barely cleared the islands.  At the end of the war in Europe in 1945, my thoughts began to return to my struggle with a Christian commitment. In Sta. Maria, a Lutheran Chaplain bowed his head to give thanks before eating, and that simple act in the Mess Hall stirred up into consciousness questions I had suppressed since leaving civilian life. I decided I should read the Bible to let it speak for itself; honest dialogue surely was where I ought to begin. However, life on the base was not conducive to this discipline; the fantasies of youth and the comraderies of my fellow soldiers usurped my leisure attention. With the surrender of Japan, our thoughts turned to the question of how to return to civilian life. A letter from headquarters invited me to stay in the Army as a meteorologist; I was then a Captain. However, I thought our responsibilities in peacetime would be less than those we had assumed in war, so the invitation was declined.  Although Law did not attract me as a profession, I entertained the possibility of studying to become an international lawyer. As this idea was developing in my mind, I received a TELEX in the spring of 1946 to return from the Azores to Washington, D.C., within 48 hours. I packed up my duffle bag with great excitement; my turn to go home had come, and I was to embark on a new adventure!  In Washington, I was told that I was one of 21 returning officers who had been chosen to do graduate study in either Physics or Mathematics at the University of Chicago or at Northwestern University; we would remain in-grade, but under the command of the Quartermaster Corps. My mathematics professor at Yale, Egbert Miles, had not forgotten me! His act was unusual; except for him, I was to return as an unknown to begin life all over again. My debt to Professor Miles is profound. He it was who put my name forward when some educators became aware that a sum of unspent money was available; Egbert Miles thought it would be best spent reintegrating a few promising scholars to civilian life by giving them an opportunity to go to graduate school. From Washington I was to go immediately to Chicago as I should have been there 24 hours earlier. That night, on my way to Chicago, a vivid memory returned; I saw myself reading “Science and the Modern World” by Alfred North Whitehead the day I decided I should study Physics if I ever had the opportunity on my return from the war. This opportunity was here! I felt called to sign up for Physics at the University of Chicago the next day even though I believed I would not qualify if they tested my aptitude for the subject. When I went to register, Professor Simpson said to me, “I don’t understand you veterans. Don’t you know that anyone who has ever done anything significant in physics had already done it by the time he was your age; and you want to begin?!” But my decision was made. I had decided to study physics at the University of Chicago. **Graduate years** After serving in the US Army as a meteorologist in World War II, I went to the University of Chicago to do graduate study in Physics from 1946 to 1951. The University of Chicago is located a few blocks from Lake Michigan on the south side of the city; it borders an open strip of grass, called The Midway, that separates 55th street, which runs west from the lake. On the north side of The Midway between the campus and the park was International House; it provided rooms and meals for graduate students and visiting scholars, men in one wing and women in the other with a common room and other facilities between and beneath the dormitories. I managed to secure a room there from the autumn of 1946 until I left Chicago in 1951.  Under president Hutchinson, the University of Chicago had a two-year undergraduate program followed by entrance into an Upper Division for graduate study. Unlike in England, where the Advanced (A) Levels before university provided the grounding for a university specialty, these first two years at Chicago were designed to provide a broad liberal education for intelligent citizenship. This arrangement was a perfect match for me. I had not majored in science at Yale but had entertained many subjects in search of a general training. However, students entering the physics program in 1946 were coming from very diverse backgrounds. Almost all had been physics majors, and many came with considerable experimental experience from service assignments at Los Alamos or the MIT Radiation Laboratory. Moreover, the Department was a bit overwhelmed by the number of students they had felt obliged to admit to the program.  My first textbook at Chicago was a tome on mechanics presumably designed some years before 1939 to help students in Cambridge, England, to pass the tripods with the help of a tutor. The first 10 pages so intimidated me that the book was quickly discarded! However, I had the good fortune that first semester to have professors who endeavored to communicate the fundamentals. In the spring of 1947, an examination covering the material of the first year was introduced for the purpose of reducing the class size by 50%. I had done well enough my first year to be exempted from this exam.  Later years proved more difficult. The Physics Department had decided to adopt the Oxford-Cambridge British system of self-study, but without tutors! Lectures covered aspects of a subject that interested the professor; the student was expected to develop on his own the context for the topics covered. Class tests were not necessarily on the lecture topics. Edward Teller, for example, only appeared for three lectures the entire semester I took his class. Moreover, texts on modern physics appropriate for students were scarce or not available. In my course on electromagnetic theory, the text used one set of units, the lecturer another, and the exams were in a third. Although Quantum Mechanics was being developed in the 1920s and 1930s, the war had prevented the appearance of a good text for beginning students. It was easy, therefore, for the student to become so absorbed with the mathematical derivations that the physics was lost. Fortunately, [Enrico Fermi](https://www.nobelprize.org/prizes/physics/1938/fermi/facts/) introduced us to quantum mechanics. His class on nuclear physics covered ideas developed during the war for which there was no text. His lectures seemed clear enough, but when I attempted to solve his assigned problem for the day, I often found that he assumed we already had the background needed to appreciate fully his expositions. Three of the veteran students developed his lectures into a text that was later used widely. There was no electrical engineering at Chicago. When I asked for a course that would teach me electronics, as I needed to build experimental equipment, I was told to go read the literature. Veterans who had been trained in electronics during the war had an advantage for developing into experimentalists.  At the end of four years, we took a 32-hour written examination on four successive days. Students were only told that the examination would cover all aspects of physics and pertinent topics in mathematics and chemistry. The first eight-hour day consisted of about 32 shorter questions; the second, eight more difficult questions. On the third day there were only four questions, two experimental and two theoretical; the student was to answer three of them. On the fourth and final day there was only one question. The student was allowed to use the library to answer this one. For example, one such final problem was to write a proposal for funding an experiment that required design of a bathysphere for a deepocean study, a defense of the scientific significance of the study, and a design of the instruments to be used to accomplish the desired measurements. The first time I took this examination, I did well enough to be granted an MS degree, but I would have to take it a second time to be allowed to go on for a Ph.D. On my second try six months later, I was so discouraged after the third day that I almost didn’t sit the fourth. I went out and played a game of softball that evening. More relaxed afterwards, I decided I had nothing to lose if I went for the fourth day. I have never really understood why they allowed me to go on for the Ph.D. degree. Only 10% of those with whom I entered the Department in 1946 had made it through this hurdle. In subsequent years, the Department changed this procedure; the veterans and foreign students that entered in 1946-1948 were more mature than those that followed. I knew that I had been exposed to the challenges and practice of the physics profession at its highest level; but for me it was a challenge indeed!  The Physics Department of the University of Chicago also had a policy that no professor was to attach his name to the publication of work reported in a Ph.D. dissertation. Work with the professor as a Research Assistant could not be part of a Ph.D. dissertation. The objective was to ensure that the Ph.D. dissertation represented original research developed and executed only by the student. I knew that I didn’t want to go into nuclear physics, so I opted to do my research in solid-state physics. Professor Clarence Zener was the obvious choice. Zener was involved in the physics of metals, so I asked him to take me on as a student in his group. I was to come back the following Thursday to learn of his decision. That Thursday I entered his office with some trepidation. To my relief, he said “Yes, you can be my student.” Then he added, “Now you have two things you must do. The first is to find your research problem and the second is to solve it. Good day!”  In fact, Zener proved to be helpful. First, he gave me a Research Assistant position measuring the internal friction of iron wires doped with carbon or nitrogen. Second, once a week he had a bag lunch with his students. One of them was to give a lecture on some topic that he assigned. After my first lecture, he called me to his office and asked whether I had found a research problem in the topic assigned. So, this was his game! In my next assignment I found a topic that proved too hard for me to solve. In my third round, the problem I found was too easy. Finally, in my fourth round I found one that would work for me. I would calculate how the interaction of the Fermi surface with the Brillouin-zone boundaries of non-cubic metal alloys would influence or change their structure. In momentum space, the position of the Fermi surface of a metal depends on the electron density in the conduction band, and the Brillouin zone is determined by the translational symmetry of the periodic potential in which the electrons move.  While I was engaged with this problem, Zener took a job as Director of the Westinghouse Research Laboratory in East Pittsburgh, PA. He invited his students to join him. My position there as a Research Engineer my final year enabled me to get married to Irene Wiseman Goodenough the Spring before we moved to Pittsburgh. When I was writing up my dissertation, Zener informed me that my employment at Westinghouse would be terminated; I was to start looking for another job.  The week before my final defense back in Chicago, I went to the American Physical Society meeting in Washington D.C. to present my work and to look for a job. After my 10-minute talk, an old man in the front row stood up and said, “That’s fine, young man, but you do not have the correct Brillouin zone for the hexagonal-close-packed structure!” The old man was Brillouin. The Head of the Chicago Physics Department was in the audience and witnessed the embarrassed silence after Brillouin had spoken. I went back to my hotel room demolished! Any Ph.D. defense the following week would be lost, I thought. However, that weekend I was able to show that although Brillouin was mathematically correct, he was physically wrong. There is no energy discontinuity across the zone face that I had omitted. The zone that I had used was the one that was physically meaningful. When I defended my thesis in Chicago the next week, another professor challenged me. He had a student working on the same problem from a different point of view. This time I was able to better the challenge, and the confrontation had pleased the examiners. I was finally awarded the Ph.D. degree! **Lincoln Laboratory years** When I received my Ph.D., three options were offered to me: (1) to be an Assistant Professor in the Physics Department of the University of Pennsylvania, (2) to be a Research Engineer at the MIT Lincoln Laboratory, and (3) to be a Research Fellow at Harvard University. The position at the Massachusetts Institute of Technology seemed to be the best match for me, and I went to Boston with an inner assurance.  The MIT Lincoln Laboratory was supported by the Air Force to create a defense against aircraft; the ballistic missile was not yet a threat. The defense system brought together the radar installations developed at MIT during World War II, communications, and the digital computer. In 1952, the digital computer ran on vacuum tubes and filled the space of a large dance hall; but it had no memory. Jay Forrester of the Electrical Engineering Department of MIT had invented the concept of a random-access memory (RAM) storing binary numbers, 0 and 1. His memory used as the memory element a ferromagnetic transition-metal alloy with a square B-H hysteresis loop formed by rolling alloy tapes into thin sheets. Frustrated by the inability to switch the magnetization direction fast enough, Forrester had concluded that his problem was due to eddy currents in the metallic alloys. Since the entire project depended on a faster RAM memory of the digital computer, he decided to investigate the possibility of developing a square hysteresis loop in a ferrimagnetic oxide that was an insulator. Ferrimagnetic oxides had been developed secretly in France and Holland during World War II. I was assigned to a small group to develop the square hysteresis loop in a ceramic that cannot be rolled. The magneticians of the day assumed it would not be possible, but the group of ceramists and electrical engineers that I joined were empirically synthesizing and testing ferrimagnetic spinels that showed some promise; the oxospinels contained Mg, Mn, and Fe and were supplied by a small ceramics company.  Within three years, systematic empiricism and quality control enabled the experimentalists of our group to develop a recipe for reproducible fabrication of polycrystalline ceramic cores with the needed squareness of their M-H loop. This success involved optimizing the composition and specifying accurately the firing time at specified temperatures as well as the cooling rate for some unknown atomic-ordering process during synthesis. My contribution was, first, to identify the factors that controlled the shape of the M-H hysteresis loop and to show that the lower value of M in the ferrimagnetic oxides compared to the ferromagnetic alloys alleviated the requirement of aligned crystallographic axes between grains. Next, I showed that the switching speed was controlled by an intrinsic damping factor, not eddy currents, and by the magnitude of the driving field H, which was limited by the application to less than twice the critical field Hc at which the magnetization is reversed. We were fortunate to have a larger Hc in the oxides than in the rolled alloys. Although I had not yet identified the defect that triggered nucleation at Hc of a domain of reverse magnetization that would also grow at Hc to switch the total direction of M, I had shown that the atomic-ordering process occurring at the annealing temperature was associated with a critical concentration of manganese in the oxide. I had also recognized that a distortion from cubic to tetragonal symmetry occurring above this critical concentration of manganese was due to a cooperative orbital ordering at the manganese. This recognition introduced a fundamental new insight into a factor that determines crystal structure. It is now referred to as a cooperative Jahn-Teller effect since Jahn, as a student of Teller, had years before shown that where an isolated molecule has an orbital degeneracy in a state of high symmetry, the molecule is made more stable by a deformation to lower symmetry that removes the degeneracy. It was only some years later that I was able to show that the critical atomic order that we were controlling was a chemical inhomogeneity induced by a dynamic site distortion that cost less elastic energy in the crystal if it occurred cooperatively within manganese-rich regions. Nevertheless, I was able to predict that ferrospinels containing a critical concentration of Cu2+ ions would also yield the desired square M-H loop. I had also been able to apply the insight of a cooperative orbital ordering to articulate chemical rules for the sign, parallel or antiparallel, of the interactions between atomic magnetic moments. These rules are now known as the Goodenough-Kanamori rules; Kanamori subsequently provided a mathematical formalism justifying these rules.  One Friday afternoon after we had delivered the fast RAM with a ferromagnetic spinel memory element, Jay Forrester summoned the group to his office. I thought he might give us a raise. Instead, he thanked us for solving his problem and asked, “Now that you have worked yourselves out of a job, what are you planning to do?” The response of half of the group was to take their know-how to industry. My response was to spend the weekend thinking what we should do next. I came up with the idea of a magnetic-film memory in which all the individual atomic moments would switch simultaneously rather than sequentially. On paper it promised to increase the switching speed one-thousand-fold. However, magnetic cores could be made smaller and realization of reliable switching of films meant slowing of their switching time. Since the film technology was more demanding, the eventual difference in switching speeds was not great enough for a move to magnetic films except for a few niche operations. With the advent of fast transistors that could be miniaturized, the Whirlwind Digital Computer and its magnetic memory became obsolete, but this technology was a critical step in the evolution to today’s supercomputers and laptops.  With the exodus of half of the group and its leader, I was put in charge of the remnant and charged with realizing the magnetic-film memory and rebuilding the ceramic facility. After two years, I gave the magnetic-film project to Donald Smith who asked for it and devoted my time to devising experiments with transition-metal compounds, mostly oxides, that would reveal how competing interactions between atomic moments would give unexpected and/or complex magnetic order; I also investigated the role of cooperative orbital ordering in determining not only magnetic order, but also magnetostrictive phenomena that could be used in devices. This work resulted in my first book, published in 1961, “Magnetism and the Chemical Bond”. At the same time, I realized that the transition-metal oxides and sulfides also permitted a systematic study of the transition from the localized-electron behavior responsible for atomic magnetic moments to itinerant-electron behavior as the strength of the interatomic interactions between atomic magnetic moments increases beyond a critical strength. Intraatomic interactions localize the electrons to an atomic site; interatomic interactions delocalize them. Itinerant electrons belong equally to all the like atoms of a periodic array, which allows metallic conductivity and suppression of any spontaneous magnetism. Studies of phenomena at this cross-over led to a long review, “Metallic Oxides”, published in 1971; it was translated in French into a book, “Les oxydes des métaux de transition” published in 1973. Clearly, the move to Lincoln Laboratory had been a good match; it had allowed me to find my own scientific voice and to contribute at a critical point to the development of the digital computer, a revolutionizing technology for a growing, diverse global population.  In the mid-1960s, I was moved with the ceramics and magnetic measurement part of my group to the Solid State Division where I was also to have charge of the chemists investigating the growth of single crystals and the semiconductive materials finding application in the blossoming fields of microelectronics, photovoltaics, lasers, and solid-state lighting. A high-pressure facility was also available in that group; it was a tool wellsuited for my studies of the transition-metal oxides. I transferred to my new group a vibrating-coil magnetometer we had built for the purpose of making magnetic measurements under pressure. Working with John Longo and James Kafalas was very productive. High-pressure synthesis and the ability to make magnetic measurements under pressure proved fruitful, but I was forced to suspend these studies in 1970 until I moved to Texas in 1986.  An amendment to a bill of Congress in about 1970 forbade research in a government Laboratory that was not targeted towards a specific application, and I was ordered to terminate my fundamental studies. At the time, I had just started a study of the copper-oxide system in which [Bednorz](https://www.nobelprize.org/prizes/physics/1987/bednorz/facts/) and [Müller](https://www.nobelprize.org/prizes/physics/1987/muller/facts/) made the discovery in 1986 of high-temperature superconductivity that won them the Nobel Prize in Physics; but I was not looking for superconductivity in 1970. However, I had done enough work on the transition from localized to itinerant electronic behavior to know that lattice instabilities are found at this crossover. This knowledge enabled me to identify the critical role of these instabilities not only in the surprising phenomenon of high-temperature superconductivity, but also in that of the colossal magnetoresistance discovered later in the manganese oxides. However, this insight was resisted by the orthodox theoretical physics community for nearly 20 years.  At Lincoln Laboratory in 1970, I turned my attention to the problem of renewable energy and energy conservation. It was obvious already in 1970 that our dependence on foreign oil was making the country as vulnerable as the threat of ballistic missiles from Russia. Solar energy was an obvious renewable source to be harnessed; our profligate use of energy made conservation an obvious target also. Since solar energy is variable in time and location, it was also obvious that we needed to find a way to store the solar energy that is converted into electricity. The best place to store electrical energy is to convert it to transportable chemical energy. Two clean routes to storing electrical energy in chemicals are electrolysis, as in the electrolysis of water to produce hydrogen, and in the anode of a rechargeable battery. Both options interested me. For improved efficiency of a power plant, I proposed use of the exhaust heat in a solid oxide fuel cell. Although we had, at Lincoln Laboratory, the facilities and interested scientists and engineers to tackle research and development targeting these applications, we were told that we were an Air Force laboratory, and that energy was to be the domain of the National Energy Laboratories and of Industry. Politics, not potential productivity, is the bull in the china shop of science administration. It was a discouraging moment, and I realized it was time for me to leave Lincoln Laboratory. **Tenured years: Oxford** During the late 1970s and early 1980s, I continued my career as head of the Inorganic Chemistry Laboratory at the University of Oxford. In 1976, Oxford had four chemistry laboratories, each headed by a Class A Professor: Organic, Physical, Theoretical, and Inorganic.  The Oxford educational system provided me a relatively smooth transition from a research laboratory to an academic post. Most of the teaching is done by the Dons in the Colleges; lectures are a supplement. The Dons act as coaches to self-teaching in preparation for the big final examination at the end of the third year. They also act as admissions officers to their college and compete with the other colleges for best scores in the finals. Laboratory instruction, lectures, and research are carried out in the Chemistry Laboratory. Competition for scholarships for D. Phil students between the three large Chemistry Laboratories − Organic, Physical, and Inorganic − sometimes required diplomacy between the professors. Fortunately, good applicants to Inorganic Chemistry always put me in a favorable position.  For my research program, I initially selected two primary targets; the direct methanol-air fuel cell and the photoelectrolysis of water. The former requires for its electrolyte a solid proton (H+-ion) conductor that is an electronic insulator and can operate near 300°C or an anode that is catalytically active for the oxidation of methanol (CH3OH) below 80° C and chemically stable in an acidic solution. I soon found that good proton conductivity in a solid electrolyte only occurs where the solid is wet, which means operating below 80°C. Our unsuccessful search for a sufficiently active and chemically stable anode for a direct methanol-air fuel cell introduced me to the field of electrochemistry. Our attempt to realize a practical electrode for photoelectrolysis also involved electrochemistry. I had hoped to be able to use most of the spectrum of visible light by using a filled as well as a nearly empty d-electron band of a transition-metal oxide. However, the filled d-electron band proved to be too narrow for this strategy to be practical. The alternative was to attach a dye to the surface of the oxide. This exercise provided a good D. Phil. thesis, but it did not give a practical solution. I realized it would probably be better to separate the steps in the process by coupling a photovoltaic cell to an electrolysis cell in order to store solar energy as chemical energy in hydrogen gas, a portable fuel. More successful was my effort to identify a suitable cathode material for a lithium battery, an effort that has done much to bring together the solid-state chemist and the electrochemist.  The most mobile working ion in a rechargeable battery is the H+ ion. But these protons are only mobile in an aqueous acidic or alkaline electrolyte. To avoid electrolysis of the water, the single cell of an aqueous-electrolyte rechargeable battery is restricted to a voltage less than 1.5 V if the battery is to have a long shelf life. This restriction limits the energy density of a rechargeable battery, which is why the advent of the cellphone and the laptop computer had to await the arrival of the lithium rechargeable battery. The working Li+ ion of a lithium battery is mobile in a nonaqueous electrolyte, which permits single-cell voltages over 4 V. However, realization of a competitive rechargeable lithium battery requires identification of electrode materials into/from which Lithium can be inserted/extracted reversibly over a large solid-solution range. Moreover, the active redox couples of the insertion-compound electrodes must have energies matched to the allowable energy of the electrolyte if larger voltages are to be achieved.  Before I left Lincoln Laboratory, I had been asked to monitor the Na-S battery project at the Ford Motor Co. This assignment introduced me to electrochemistry and the problem of designing fast cation conduction in a solid electrolyte. With Henry Hong, a crystallographer and chemist, I explored framework structures for a 3D Na+ conductor as against the 2D Na+ conduction in β-alumina. We came up with the Na1+3xZr2(SixP2-xO4)3 framework structure that was called NASICON (NA SuperIonic CONductor) by colleagues after I had left for Oxford. This structure is now being explored further for cathodes and solid electrolytes of sodium rechargeable batteries.  In about 1974, Brian Steele of Imperial College, London, was aware of the Rouxel and Schöllhorn work on the chemistry of reversible Li+ insertion into layered MS2 sulfides and suggested at a conference the use of TiS2 as the cathode of a Lithium rechargeable battery. Primary Lithium batteries using a flammable organic liquid carbonate electrolyte with an ethylene-carbonate additive to passivate the Lithium anode from reducing the electrolyte had been marketed. M. Stanley Whittingham was a postdoc at Stanford with Bob Huggins and Fred Gamble was a physics student there with Ted Geballe studying intercalated TiS2 as a 2D superconductor. They were hired by the Exxon Mobil Corporation to develop a commercial Li/TiS2 rechargeable battery, and in 1976, Whittingham reported fast, reversible Li+ into TiS2 in a rechargeable Li/TiS2 cell. However, on charge, the lithium anode formed whiskers (dendrites) that grew across the electrolyte on repeated charges to cause an internal short-circuit that ignited the flammable organic-liquid electrolyte. This effort was, therefore, terminated in the U.S. However, the concept of a reversible intercalation of Li+ into layered compounds was established, and several laboratories were exploring Li+ insertion between the layers of graphitic carbon. At the SONY Corp. of Japan, they were planning to use lithiated graphite as the anode with a TiS2 cathode.  In 1978, an undergraduate thesis at Oxford on the structure of the LiMO2 oxides reminded me of work I had done with Donald Wickham in the 1950s on LixNi2-xO2. The MO2 oxides are not layered as is TiS2; the electrostatic repulsive energy between the O2- ions of MO2 sheets is larger than the dipole-dipole [Van der Waals](https://www.nobelprize.org/prizes/physics/1910/waals/facts/) binding energy. However, layered LiMO2 is stabilized by the Li+ ions between the MO2, sheets, and the ions are well-ordered provided the sizes of the Li+ and M3+ ions are sufficiently different from one another. I decided to investigate how much lithium can be extracted reversibly from a well-ordered LiMO2 layered oxide. Since I wanted an M4+/M3+ redox couple that had an energy well below the Li+/Li0 couple of a metallic Lithium anode, I chose to study chromium, cobalt, and nickel for the M atom. An experimental physicist, Koichi Mizushima, had just come from the University of Tokyo to work with me at Oxford. I teamed him with my chemist post-doctoral assistant, Phillip Wiseman, to work on this investigation. We found that over half of the lithium could be removed reversibly with cobalt or nickel as the M atom; each of these Li1- xMO2/Li half-cells gave an output voltage near 4V.  No battery company in England, Europe, or the U.S. was interested in licensing a patent for these cathode materials; they could not imagine starting with a discharged cathode. The University of Oxford was not interested at that time in the intellectual property of its academics. As I was working with scientists of the AERE Laboratory in Harwell, a town near Oxford, to obtain joint funding for battery research from the European Economic Community (EEC), I arranged for them to apply for a patent on the understanding that, once they had retrieved their filing expenses, my two colleagues and I would share any revenue. On the day of signing, I was told that the AERE Harwell lawyers would not proceed unless we signed all our rights away. Not knowing either the full potential of our invention or any other option, we signed our rights away. Meanwhile, others were exploring the chemistry of Li insertion into layered compounds. In Switzerland, Rachid Yazami showed that reversible Li insertion/extraction into graphite occurs at only 0.2 eV below the electrochemical potential of metallic lithium without dendrite formation. In Japan, Akiro Yoshino of the Asahi Kasei Corp. then realized that he could assemble a discharged rechargeable battery using graphite as the anode and my LiCoO2 as the cathode. Scientists at the SONY Corporation commercialized this Li-ion battery to market the first cell telephone that launched the wireless revolution. AERE Harwell received many millions of pounds; we received nothing. I was disappointed that not even a contribution to St. Catherine’s College was forthcoming. However, the joy of having helped to enable a technology that has transformed for the better so many lives is reward enough.  Cobalt is expensive and toxic. In 1981, Michael Thackeray came from South Africa to work with me. He had been inserting lithium into magnetite, Fe3O4, the original ferrospinel used by the Greeks for navigation. He wanted to develop a less expensive cathode than Li1-xCoO2. Bruno Scrosati of Rome had reported a similar experiment in a seminar I had attended two weeks before Thackeray’s arrival. I was skeptical of this report as I knew that the spinel structure cannot tolerate excess cations. Therefore, I asked Thackeray, when he arrived, to repeat his experiment in my laboratory. When he confirmed the insertion of lithium into magnetite, I realized that the insertion of lithium must be displacing the tetrahedral-site iron to the empty octahedral sites of the structure to form an ordered rock-salt phase. This insight made me realize that the spinel octahedral-site [M2]O4 array represented a three-dimensional framework into/from which lithium could be inserted/extracted reversibly. Therefore, I told Thackeray to insert lithium into the manganese spinel Li[Mn2]O4.  The Li1+x[Mn2]O4/Li half-cell gave a flat 3 V open-circuit voltage. Thackeray would later extract lithium from the tetrahedral sites; the Li1+x[Mn2]O4/Li half-cell gave a 4 V open-circuit voltage. A sharp shift of 1eV in the energy of the Mn4+/Mn3+ couple occurs where the Li+ ions change their occupancy cooperatively from all-tetrahedral to all-octahedral sites. I gave Thackeray the patent rights to the spinel framework, but that patent was changed in South Africa to cover only the 4-V range of Lix[Mn2]O4 (0<x <1). Donald Murphy of the Bell Telephone Laboratory had independently prepared the spinel framework [Ti2]S4 by extracting copper chemically from Cu[Ti2]S4. In the sulfospinel framework, lithium enters only octahedral sites and the [Ti2]S4/Li half-cell gives a voltage identical to that of the original TiS2/Li half-cell. In LixTiS2, lithium also occupies only octahedral sites. Chemical instability on cycling Lix[Mn2]O4 over the 4-V solid-solution range 0< x <1 prevented its commercialization as the cathode of a lithium battery. However, addition of some nickel and lithium to the [Mn2]O4 framework has provided chemical stability at the expense of discharge capacity. NISSAN has used this stabilized cathode material in their initial hybrid car.  At Oxford, in addition to the cathode materials for a Li-ion battery, I learned about oxide surface reactions with the medium in which they existed, including the zeta potential in aqueous solutions and Li+ attraction to an oxide surface in a non-oxide solid to create Li+ vacancies for Li+ conduction in the non-oxide solid medium. With the realization of structural reconstructions at an oxide surface, I understood how it frustrated study of heterogeneous catalysis by oxides. Therefore, I investigated the partial oxidation of acrolein to methacrolein on a Keggin 12-molybdophosphate of known surface structure to determine the role of a stable reduced molybdenum Mov displaced from an oxygen vacancy in the catalytic process, a possibility occurring to me from my earlier studies of solid molybdenum-oxide chemistries.  At Lincoln Laboratory I had initiated work to strengthen interactions between the solid-state chemist and solid-state physicist; at Oxford, I brought together chemistry and electrochemistry to stimulate both communities. It was for work fostering these interactions that I was to be awarded the Japan Prize in 2002 and given the highest awards of the Material Research Society, the Electrochemical Society, and the 3M Society. **Austin years** In 1986, the politics in the laboratory at Oxford anticipating my retirement had begun, so I accepted a call to take the Virginia H. Cockrell Centennial Chair of Engineering at the University of Texas at Austin. Retirement before age 67, was no longer required in the U.S. which has enabled me to keep working for another 32 years in Texas as a Professor of Materials Science and Engineering.  In 1986, Bednorz and Mueller of IBM Zurich reported their discovery of high-temperature superconductivity below 40 K in a copper oxide while exploring whether a dynamic Jahn-Teller electron-lattice interaction at octahedral Cu ions might provide a needed electron-lattice interaction for superconductivity. Their superconductive compound was shown in Japan to be La2-xSrxCuO4. While I was setting up a chemistry laboratory in Texas with the aid of a postdoc, Arumugam Manthiram whom I brought with me from Oxford, a superconductive transition at 90 K in YBa2Cu3O7-δ was announced. Hugo Steinfink, a crystallographer in our ME Department who had supervised Henry Hong and had brought me to Texas, determined the structure of the 90 K superconductor the day before the structure was also announced at the ”Woodstock of Physics” in New York. Subsequently, Arumugam Manthiram and I explored extensively the chemistry of the copper-oxide superconductors.  In 1987, a letter from the University of Jilin in China asked if I would take a physics student to do his Ph.D. thesis with me for graduation from the University of Jilin. The physics student is now Research Professor Jian-Shi Zhou in my group; interested in high-pressure studies of solids; he had followed the high-pressure work we did at the MIT Lincoln Laboratory. Since a discarded and broken copy of the Kafalas high-pressure cell resided in the laboratory of Hugo Steinfink, I accepted Jian-Shi Zhou, who was able to refurbish the Kefalas cell; and he has remained with me ever since. Over the last 30 years, Jian-Shi Zhou has built up a competitive high-pressure facility, a single-crystal furnace, the ability to synthesize under pressure to 26 GPa, and to measure structures as well as magnetic and transport properties under pressure and the thermal properties of his materials at ambient pressures.  At MIT, we had shown that SrRuO3 is a ferromagnetic metal and that the paramagnetic susceptibility of the Sr1-xCaxRuO3 system exhibits a change to a negative Weiss constant, but with no long-range magnetic order in CaRuO3. Much later, Rob Cava of Princeton University showed a peculiar transition in the paramagnetic susceptibility of Sr1-xCaxRuO3 near the [Curie](https://www.nobelprize.org/prizes/physics/1903/pierre-curie/facts/) temperature of SrRuO3, and Jian-Shi Zhou pointed out that the Cava data represented formation of a Griffiths phase in which the magnetic ions are diluted by nonmagnetic ions, which means there is a segregation into RuIV with magnetic 4d electrons and RuIV with nonmagnetic 4d electrons localized by spin-orbit coupling. He further found itinerant-electron ferromagnetism in the high-pressure Sr1-xBaxRuO3 perovskites with an abrupt transition under pressure from ferromagnetism to Pauli paramagnetism in cubic BaRuO3. The structure-composition property relationships in the single-valent oxoperovskites have been shown to be rich as also have the mixed-valent manganese perovskites.  On arriving in Austin, I set up my chemistry laboratory for work on electrochemistry and ionic transport in solids with a view to continue work on energy-related materials. We finally had a chemical hood installed by Christmas! By that time, not only had the structure and composition of the original copper-oxide superconductor been identified; doping of the phase had led to the discovery of another copper-oxide phase that becomes superconductive at 90 K, well above the boiling point of liquid nitrogen! Announcement of this discovery in the New York Times created a stampede of crystallographers in Japan and the U.S. to be the first to determine the structure of this new phase. Hugo Steinfink solved the structure and was the first to announce it at a crystallographic meeting in Austin the day before the “Woodstock” of the American Physical Society Meeting in New York City where other groups also announced the solution. Steinfink’s contribution was overshadowed by the trumpets of the larger laboratories that had solved the structure independently.  Although I had not previously been interested in working on the superconductive phenomenon, this development in a transition-metal oxide captured my attention; Manthiram and I began to study the chemistry of these copper oxides. It became immediately evident to me that the extraordinary superconductivity in the copper oxides was occurring in a phase intermediate between an antiferromagnetic parent compound that was an insulator and a non-superconductive metallic phase. Superconductivity was appearing at a much higher temperature than predicted by the existing [Bardeen-Cooper-Schrieffer](https://www.nobelprize.org/prizes/physics/1972/summary/) theory and at a transition from localized to itinerant electronic behavior in a transition-metal ceramic, a transition that I had explored in these perovskite-related oxides in the 1960s. However, in this case the crossover was occurring in a mixed-valent system whereas I had been studying it in single-valent systems. I knew that lattice instabilities were always encountered at this crossover in single-valent systems, so I suspected that a dynamic segregation of localized and itinerant electrons was occurring in the mixed-valent copper oxides. This idea was aggressively dismissed by the leading solid-state theorists who were the opinion leaders for the majority of physicists; but when Zhou arrived, I persisted to explore this possibility with him. Manthiram became a professor in his own right and returned to the development of energy materials independently of me.  We had a first-rate high-pressure facility in Austin. Together, Zhou and I have explored the transition from localized to itinerant electronic behavior in other mixed-valent and single-valent transition-metal oxides with perovskite-related structures. We have clearly demonstrated a dynamic segregation into localized-electron and itinerant-electron domains in other mixed-valent systems as well as in the copper oxides.  The copper-oxide problem is complicated by the existence of two types of phase segregation, one a dynamic segregation into localized-electron and itinerant-electron domains and the other a static phase segregation of the superconductive phase from the antiferromagnetic parent phase on the one side and the metallic over doped phase on the other side. As the oxidation state of the superconductive CuO2 sheets of the copper oxides increases, the charge carriers introduced by the oxidation change their character. In the antiferromagnetic phase, isolated carriers occupy a volume of about 6 copper centers. Where the oxidation is too great for the charge carriers to remain isolated from one another by electrostatic coulomb forces, they condense below room temperature into spin-paired carriers in a volume of four copper centers or into multiple spin-paired carriers in itinerant-electron chains along the Cu-O-Cu bond axes. This phenomenon represents a dynamic phase segregation in which the charge carriers are mobile. A structural distortion may trap the carriers in static itinerant-electron stripes separated by ribbons of localized electrons. These static stripes have been observed by conventional neutron-diffraction experiments, but a dynamic phase segregation requires a faster experimental probe. A pulsed neutron-diffraction experiment coupled with a pair-distribution-function analysis of the data is such a probe. This technique was developed by Takeshi Egami while he was at the University of Pennsylvania. His preliminary data show evidence of the predicted phase separation, but the complexity associated with isolated charge-carrier pairs coexisting with chain segments has made difficult a definite statement about the nature of the dynamic normal state in the superconductive phase. We have established the existence at room temperature of isolated charge carriers with a volume of 5 to 6 copper centers in the underdoped phase; in the metallic overdoped phase the localized electrons appear only as fluctuations. How the paired charge carriers become long-range ordered to give superconductivity is still to be resolved. I have pointed out that this can be done by coupling the domains of paired electrons to cooperative lattice vibrations (phonons) to give vibronic charge carriers.  In my chemistry laboratory, we also continued to develop materials for the lithium rechargeable battery and the solid oxide fuel cell. I assigned to my engineering student, Akshaya Padhi, and my post-doctoral fellow, Nanjunda Swami, the task to explore the relative energies of transition-metal redox couples in the NASICON framework M2(XO4)3 that we had shown in Lincoln Laboratory supports fast transport of the Na+-ion guest species. Different transition-metal atoms M and polyanions (XO4) can be accommodated in the framework, with the charge of the framework being balanced by Li+-ion guests over the range 0< x <5 in LixM2(XO4)3. In this framework, the energy of the redox couples appear to be essentially insensitive to the location and number of Li+ ions in the interstitial space. I was also interested in knowing how those redox energies shifted on changing from (SO4)2- to (PO4)3- or (AsO4)3- polyanions.  During the course of this work, Padhi found that Lithium can be extracted reversibly from LiFePO4, which has the olivine structure. The LixFePO4/Li cell gives a constant 3.45 V open-circuit voltage over the range 0< x <1. Made as small particles, this cathode is capable of extremely fast rates of charge and discharge. The Hydro Quebec Corporation licensed the patent granted to the University of Texas; but the A123 company in Cambridge, Massachusetts, was the first to market the LiFePO4/C battery and to demonstrate its use in medium-power applications such as electric power tools and small electric vehicles.  Our work on the solid oxide fuel cell has involved the development of new oxide-ion electrolytes as well as new electrodes. Dr. Kevin Huang worked with me as a post-doctoral fellow on these problems before going to become a key player in the Siemens-Westinghouse development of a commercial hydrogen-fueled solid oxide fuel cell. After his departure, I investigated a novel class of anode materials that can operate on natural gas without becoming poisoned by sulfur impurities in the gas. The move from the internal combustion engine to batteries to power our automobiles would reduce distributed CO2 emissions responsible for global warming; the development of electrical energy storage is needed to make viable the substitution of solar, wind, and nuclear energy sources for the fossil fuels that emit CO2 on burning; the sequestering of CO2 and other pollutants emitted from coal-fired power can reduce CO2 emissions; and the introduction of more efficient energy distribution and use can reduce energy consumption. All represent urgent challenges confronting the scientific-engineering community today. The implementation of a serious national effort to meet these challenges, an effort initiated in the early 1970s, was stalled by special interests more concerned with profits than with our national vulnerability and the global environment.  In the end, I have had an extraordinary journey, but it is the many colleagues who have worked with me over the years that I wish to thank for making it extraordinary. They are the ones who have performed the experiments and each of them kept an open dialogue with the aim to teach me as much as I tried to teach them. |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** | [JG]  John Goodenough: Hello?  Adam Smith: Hello, this is Adam Smith calling from the website of the Nobel Prize in Stockholm. Many congratulations.  JG: Yes, well thank you very much, indeed, it’s been a wonderful surprise.  AS: It’s quite a day, receiving the world’s oldest scientific prize in London and then hearing about the Nobel Prize on the same day.  JG: Yes, it’s quite a day. Yes, it is!  AS: This puts you in the company of everybody, of Darwin, of [Einstein](https://www.nobelprize.org/prizes/physics/1921/einstein/facts/), you name it.  JG: Yeah, well. You know, you live long enough, you never know how it’s going to come out.  AS: Well, since you mention it, I guess people will be asking you a lot about the fact that you are the oldest ever person to be awarded the Nobel Prize. How do you feel about that?  JG: Well I’m very happy to be able to live this long! That’s right. [Laughs]  AS: Have you any secret to impart for a long life in research?  JG: No, I just say don’t retire too early. [Laughs]  AS: Good advice. Now the committee have cited your work in Oxford in the early ‘80s when you developed lithium-ion batteries, but the work continues, doesn’t it?  JG: Well, we’re working on how to develop a polymer which has an immobilised liquid in it, so that it conducts lithium or sodium as fast as in the liquid. That’s what we’re working on and the liquid is immobilised so it’s like a solid-state material.  AS: I wanted to mention to you, Professor Goodenough, I was an Oxford chemistry undergraduate when you were head of the department of inorganic chemistry.  JG: I see, and so you’re glad you didn’t have to listen to my lectures! [Laughs] You know Clare Grey put a bunch of teddy bears in the front seat to make sure that I had a bigger audience! [Laughs]  AS: [Laughs] At least they didn’t fall asleep right?  JG: No, the teddy bears managed to stay awake.  AS: Can you describe how you feel when you see everybody using the batteries that you helped develop?  JG: Well, let me say again, it’s how people use the technology that’s the important thing. You put the technology out there and it can be used for ill or for good. And if they use it for good, I’m very happy. And if they use it for bad, well I feel badly about it. But that’s the way life works. Technology is morally neutral; it’s how we use technology that determines everything.  AS: So, yes, the onus is very much on us to make the right choices. It’s a huge pleasure to speak to you. I very much look forward to speaking more when you come to Stockholm in December. For now I should let you get on and receive your Copley Medal at the Royal Society today.  JG: Yes, thank you very much.  AS: Thank you very much indeed.  JG: Bye bye.  AS: Bye bye. |
| **Interview** |  |
| Q1 | What advice would you give to a younger version of yourself? |
|  | John B. Goodenough: Oh, that’s a difficult question! Cause I hope the younger version of myself that you are talking about would be a little bit brighter than I was (laughing) as a younger person. But dialogue, dialogue, dialogue is always very important. We both learn that way. |
| Q5 | How do you recognise a good teacher? |
|  | John B. Goodenough: First, if they are clear and understand what they are talking about but they also have to know how to challenge you. Not in a way that turns you off, but in a way that challenges you to turn on. So a good teacher always makes you do something a little bit more than you thought that you could do. |
| Q5 | Do you see yourself as a mentor now? |
|  | John B. Goodenough: I go to the lab and in order to interact with my postdoctoral students and try to see if I can shape them to not copy but to ask questions and to think. We have to have a little dialogue because you don’t pretend to be the fountain of all wisdom. Wisdom comes out of dialogue so you have to develop the capacity to expose your own ignorance in order that they may discover their own wisdom. |
| Q7 | What qualities do you think you need to be a successful scientist? |
|  | John B. Goodenough: First, don’t copy. Think about the problem and to remember that we compete against problems, not against people. Well as I say, don’t believe everything that you read and don’t be afraid to think and it is alright to understand what has gone before but don’t just rely on copying but develop your internal voice and your own internal means of interpreting. That is a very individual thing and there are many different ways to be successful. Some people are very good at building equipment, you got to be able to measure and you got to be able to know what you are measuring and to interpret and so on. There are other people who do theory and develop theoretical understanding. And then there are people who develop intuition. You have to have some scientific intuition as well. And every scientist is an individual and brings a different talent to the problem. But you have to be willing to dialogue so that we can all benefit from one another’s intuition. |
| Q2 | How do you cope with failure? |
|  | John B. Goodenough: We all have to recognise that we are going to fail sometimes alright, but some failures are more traumatic than others. (laughing) |
| Q17 | How has your dyslexia shaped you? |
|  | John B. Goodenough: It meant that I learnt to love nature. It meant also that I would never have been a very good reader. You have to struggle to read as best you can. But you have to not worry, you have to just get out and enjoy life and enjoy what you can do well and do it as well as you can. |
| Q6 | How important has nature been for you? |
|  | John B. Goodenough: Well, we are supposed to love the Lord our God with all our heart with all our mind and with all our strength. But that is separate from loving our neighbor as ourselves. It means that nature is God’s creation. So we should love nature and understand nature the best we can in order to show our love for the creator. It is a wonderful thing, this nature, this Earth and its abundance and its surprises and its resources and its change. So for me, it’s just I am grateful to be a part of nature. |
| Q2 | Has music played an important role in your life? |
|  | John B. Goodenough: I can’t say that I am a good musician. I am not particularly musical. But I got rhythm! (laughing) I prefer… you know… I like Bach. |
| Q6 | How did your interest in poetry start? |
|  | John B. Goodenough: I was to take a course in poetry but of course if you don’t read very well poetry is more difficult thing to really understand, metaphors and so on. That remark is the best way to teach somebody. You say ‘Well, alright, get going boy! Maybe you can do a little better!’ (laughing) So I had to try to see how will I learn to read poetry and I thought the only way to do that is to write poetry. And if you start to write poetry then you realise the problems you have to make the metaphors and so on. That’s how I started to write poetry. I tried to write a poem for my wife every birthday and every Christmas. My wife and I shared very much a vision of Christianity. So I would always write something that was relating to a character or to something rather of that nature. It always had a religious bend to it. |
| Q6 | How did you meet your wife? |
|  | John B. Goodenough: I was in graduate school and she came a little later on than my graduate school time. I was living in the international house and she was living in the international house. Girls lived in one side and boys in another. We met at the dining room table in between. She didn’t blow me over because she was glamourous. She wasn’t glamourous, she was just herself. She was very comfortable with herself so it was very easy for me to make a friend. You see, love has to do with friendship. Friendship. |
| Q11 | What life advice can you share? |
|  | John B. Goodenough: The most important thing is that you have a companion that you share the deep things of life. But it is always difficult for a man to understand the secrets to a woman’s heart. Well I think you should be enthusiastic about life. You should enjoy what you do and I say to myself each day: “Help us oh lord, so long as we live to live nobly and to the good cheer of our fellow man.” I think to live life to the fullest you have to be able to have dialogue with people who want to dialogue with you. I think you have to just be thankful for life and be thankful for people who like to engage in meaningful dialogue with you. Yes, I don’t think pessimism gets us anywhere. (laughing) Even though we main live in illusions we have to work very hard to fulfill our illusions as best we can. |
| Q6 | How do you remember so much of your life? |
|  | John B. Goodenough: One of the great mysteries of life is memory. I helped somebody who was trying to understand memory and the sources of memory and so on. But I learnt that it was a rather complex problem. |
| Q6 | How does it feel to be back in Stockholm after 80 years? |
|  | John B. Goodenough: My first visit here, that summer or that autumn was the autumn that Hitler moved into Poland. I am very grateful to the city of Stockholm and to all the people who are here and not only to this city but to what this city represents. Thank you all for your hospitality and for even embarrassing me by asking me so many questions I don’t answer very well. |
| Q6 | How has living through World War II influenced you? |
|  | John B. Goodenough: I realised the stupidity of war, the waste of war, the bravery of some. I believe not in walls but in building relationships, alright. If we can build relationships, we minimize the attempts to go to war. I think that science is an international language and helps to build the relationships that are necessary to suppress the greed and stupidities that lead to war. |
| Q2 | What is your relationship with your lab colleagues? |
|  | John B. Goodenough: My lab colleagues are very good to me. We enjoy working together in the laboratory but I don’t necessarily hobnob with all of them at recreation times. We do it in the laboratory and so on but that doesn’t mean that I don’t like other friends and that I have other friends too. I dialogue with them about other things than just their work. So if they bring me some lunch, we are having some lunch together we talk about other things. When my wife was living, she was a gracious hostess and a good cook so then we would invite students who couldn’t go home for their holidays always to come and enjoy their holidays. She would cook very well. I am afraid I miss my wife quiet a bit. She was very special. |
| Q2 | What are the characteristics of a very good team? |
|  | John B. Goodenough: A good team is never selfish, it shares. Recognising that they do things together. I shouldn’t steal the intellectual property of my students and they shouldn’t steal the intellectual property of one another. You know, science is an international language. And I have enjoyed travelling all over the world and sharing scientific discussions with people from almost every country in the world. |
| Q2 | What is your relationship with Akira Yoshino? |
|  | John B. Goodenough: Well, we are not good friends in the normal sense of friendship but he has always been a person who has listened to what I am doing and reacted to it. We have had dialogue in the science together. In that sense we are good friends. For example, when I say well LiCoO2 is going to be a very good cathode he immediately comes up ‘yeah, but you got to join it with carbon!’ (laughing) |
| Q4 | How has the scientific landscape has changed over the years? |
|  | John B. Goodenough: Science is an international language, that is one of the beauties of science. As so, there is always international interaction in all aspects on science. That’s why people publish papers and read papers in order to be able to interact and dialogue as best you can with everybody who is interested in the same kind of problems as you are. I am not an astrophysicist to continue with our exploration or a particle physicist who keep looking at what are the building blocks of nature and so on. But people do learn some things and even I learn some things (laughing). So my scientific landscape changes according to how much I have learnt in the last year. The science hasn’t changed it is just my understanding of the science has changed to come along. |
| Q10 | What environment encourages creative thinking? |
|  | John B. Goodenough: Quietness. (laughing) I mean you have to think, that’s hard work. You know some people can listen to music and think at the same time but if you are a musician they never want background music, right? You either listen to the music or you turn it off. (laughing) I suppose I do my best thinking when I am in dialogue with somebody about a problem. I think dialogue is very important for thinking. And sometimes when you have to write something up, you are dialoguing with yourself as you are writing something up and you think about things. You have to try to be clear when you write. And you have to try to be brief. Get away with the clutter and just get to the point. |
| Q4 | What research are you working on now? |
|  | John B. Goodenough: We are still trying to get better batteries, of course, and I have some people who have come and are here with me at the moment. They are two people from Iran, Hadi and his wife Isl. They are polymer people and they are trying to teach me a lot about polymers. So you see, through dialogue with every people you have then you keep learning. They keep teaching me something all the time. I think I have some contribution to make, they seem to be happy to talk to me anyway and I am very happy to talk with them. |
| Q15 | What are your thoughts on sustainability? |
|  | John B. Goodenough: The dependence in modern society and the energy stored in fossil fuel is not sustainable. We have to learn to harness the energy that comes to us from the sun either in the form of wind or in the form of radiant energy. And we have to be able to convert it into electric power which we know how to do. But as diverse… you can transport electric power over wires over some distances but you have to have a collection site. But you have to be able to store that energy because it comes in at time scales that are very different from the time scales of demand. So that is one of the reason you work on batteries because they store electric power. |
| Q14 | What future do you see for sustainable batteries? |
|  | John B. Goodenough: Well they have to come! But we have to keep working hard on it to improve it, okay? We haven’t solved all the problems yet but rechargeable batteries exist. Rechargeable batteries do a fairly good job but they don’t do as good job as they need to do so we keep working to see if we can improve them. |

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| **Chemistry\_2024-2000** | |
| **ID** | 0314 |
| **Biographical** | I was born on December 22, 1941 in the Carlton suburb of Nottingham in England in the middle of the Second World War. My father, William Stanley Whittingham, was a civil engineer and the first in the family to go to college, and my mother Dorothy Mary (née Findley) was a chemist before marriage. My father was responsible for repairing the runways in East Anglia, so we were constantly on the move. I spent my childhood in Lincolnshire county attending primary school in Grimsby and travelled each day by train and bus from home to school. When I was around age 10, the family moved to Swallow Hill House in Thurlby, near Bourne.  Looking east from our house the next higher hill was in Germany, as we were on the edge of the fens. I attended Stamford School in Stamford, about 8 miles away. Stamford is a medieval town then on the main A1 road from London to Edinburgh; it was my father who was in charge of building the by-pass around the town, that eliminated the need to go through the alternating one-way street in the center of town. It was there that I got attracted to science through the inspired teaching of Major Lamb and Squibs Bowman in chemistry and physics respectively. The school had a well-equipped new science building. The school and my teachers in 1960 are shown in Figure 1. The school dates from 1532, and its chapel (formerly known as St Paul’s church and shown in Figure 1) originated in 1152. The St. Paul’s Street in front of the school is named after the church. School days started with chapel at 8:45 am, and finished at 3:45 pm six days a week, with Wednesday and Saturday afternoon reserved for sports. I remember Squibs Bowman started a sailing club at a local gravel pit, and I got deeply involved in that. But my parents got totally hooked, so they took up sailing in the English Channel when they retired to Flushing in Cornwall. It was at this time that I got very interested in growing cacti, and my family built a greenhouse at our house so I could grow my hundreds of them, together with more useful tomato plants which I sold to neighbors. I still grow cacti and am an active member of the Desert Botanical Garden in Phoenix, Arizona where my daughter and her family live.  In the autumn of 1959, I went for several days to Oxford to take the entrance examination, which included several languages as well as chemistry, physics and mathematics. After I was offered admission to New College in Oxford University to study chemistry, Headmaster Basil Deed tutored me in Latin to pass the then required classics examination before I could go to Oxford in October 1960. **College** Arriving in Oxford, I took the 1st Public Examination. This was followed by the Final week-long examinations after three years of study. A fourth year was spent doing full-time research. The college rooms were somewhat rudimentary then, with no running water. A “scout” brought a bowl of hot water each morning to my room to wash and shave with. Breakfast was served in the hall until 9 am, and the lectures that also started at 9 am were in the University chemistry buildings a good 10–15 minutes’ walk away. These were not mandatory but were very helpful for the weekly tutorials. Each week I prepared a lengthy paper on the weekly topic and then presented and discussed it with my tutor for an hour. I still remember going to Peter Dickens’ lodgings in the College each Sunday morning for this, and his wife Mary would prepare biscuits and tea. Although life at Oxford afforded much time to watch 1st class cricket in the Parks behind the Science buildings, much time was spent in doing required laboratory experiments.  At New College, my key tutor was Peter Dickens, under whom I would do my Part II undergraduate research and my D. Phil. Peter attracted me to Solid State Chemistry. Also, at that time metallurgy was part of the Inorganic Chemistry Department, so I took metallurgy classes from William Hume-Rothery, who was deaf at that time but whose lectures were intriguing. Those were exciting times, with the US Air Force Office of Scientific Research in London supporting my undergraduate research on the recombination kinetics of oxygen atoms on the tungsten oxide bronzes. This was the sputnik era, and there was interest in possible atomic reactions on the nose cones of satellites. This work resulted in my first publication in the *Transactions of the Faraday Society*.  For my D. Phil. studies I won a Gas Council scholarship to study catalysts to convert coal gas to natural gas. However, just before starting this research the UK struck natural gas in the North Sea and the Gas Council gave me the freedom to do whatever research I liked. I studied the reduction by hydrogen of the same tungsten bronzes and a range of tungsten oxides and discovered how the fast ionic mobility of the alkali ions dictated the reduction reaction pathway. **Postdoctoral studies** In 1968, I moved to the materials center at Stanford University in California to work with Robert Huggins on advanced materials. After about three months there, Bob moved to Washington, DC for a two-year stint as Program Officer for the Materials Research Centers. I became the de-facto leader of his group for those two years, a great learning experience. There I studied the fast ion transport of alkali ions in the recently discovered beta-alumina materials, amongst other compounds, using the mixed conducting tungsten bronzes as electrodes. For this beta alumina work, I received the young author award of the Electrochemical Society. I still remember going to the Shamrock Hotel in Houston to pick up the award at a black-tie dinner. Norman Hackerman was President of the Electrochemical Society, and he brought in the Texas Rangers on their horses to the reception around the hotel pool.  At Stanford I met Georgina Andai on a trip to the San Francisco Opera in August 1968 organized by the Bechtel International Center. Georgina had just arrived from Queens College in New York to study for her graduate degree in Latin American Literature. Georgina was an immigrant from Budapest, Hungary by way of South and Central America. We were married in the Stanford Chapel on March 23rd, 1969, and spent our honeymoon travelling around four of the Hawaiian Islands. About a month later, we spent a week at a solid-state chemistry meeting in Scottsdale, Arizona at a Moorish looking hotel, organized by Leroy Eyring and Mike O’Keefe. The field was just taking-off in the USA, unlike Europe where it was strong. We had two children whilst at Stanford, Jenniffer and Michael. We were the first family living in Stanford married student housing, where the wife was the student. I still remember the looks when I went to a spouses meeting – what are you doing here? When our second child was born, we rented a home on Maureen Avenue in Palo Alto, a nice two-bedroom house with a garden where the children could play winter or summer. Just before we left California, our landlady offered to sell us the home for $30,000! Last year, we celebrated our 50th Anniversary in Bermuda, and rented one of the first electric vehicles on the island and learnt all about range anxiety (Figure 3). **Exxon Corporate Research Laboratory** In 1972, I moved to the newly formed Corporate Research Laboratories of Esso (now ExxonMobil), who were initiating research efforts in energy beyond petroleum and chemicals. It was there, whilst working with such key scientists as Fred Gamble and Arthur Thompson in a very vibrant and intellectually stimulating interdisciplinary group, that I discovered the key role that intercalation played in the reversibility of chemical reactions. I was asked to describe this finding to a committee of the Exxon Board of Directors in New York; this would be described today as an elevator pitch. Within a week, Corporate Research was given the go-ahead to build a team to develop this invention. Exxon treated research like drilling an oilwell; not all will work, but some will but for success serious investment was needed. They did this and established a large lithium battery engineering, development and manufacturing effort. That effort resulted in the first rechargeable lithium-ion batteries, which was published in *Science* in 1976, some three years after the patents were filed.  The field of solid-state electrochemistry was just getting started due to materials scientists getting involved in energy research. One of the earliest international meetings in the area was a two-week NATO conference in Belgirate, Italy in 1972 which had many junior scientists present but also senior legends like Carl Wagner, the father of defects in solids. I was sitting next to him in the conference photo. Some 20 years later, when this meeting was repeated the field had dramatically changed – the lithium battery had arrived. I still remember arriving at the hotel in Belgirate and commenting to the owner that we had been there 20 years earlier and he said let me check. He went to his file cabinet, and pulled out a photograph of the earlier meeting, and saying there you are.  At that time, the journals available for publishing our work were limited. *Materials Research Bulletin* tended to be a favorite for both myself and John Goodenough. So North-Holland in the late 1970s proposed that I and Hans Rickert from Germany start a new journal for the field of ion transport in solids. I said there was no need. They responded by saying let’s do a survey of the field. Well, the field voted over 90% in favor of a journal, and the first issue of *Solid State Ionics* was published in 1980. I remained Principal Editor for 20 years. At that time the journal published in English, French and German.  At Exxon, I moved from a bench scientist to group head to Director of the Solid State and Catalytic Sciences Laboratory in Corporate Research. Then in the early 1980s I became Manager of the Chemical Engineering Technology Division of Exxon Engineering, which at that time was expanding fast in order to explore synthetic fuels, such as shale oil and coal liquefaction/gasification. An interesting assignment that certainly was a broadening experience, but not really aligned with my interest in research. After a brief period in research at Schlumberger leading a high-powered group of scientists understanding rock science (most of whom are now in academia), I returned to academia in 1988. **Binghamton University** In the fall of 1988, I joined the Chemistry department of Binghamton University (State University of New York) with the goal of introducing materials across the curriculum, and to emphasize to students that science is interdisciplinary. I was the founding Director of the Institute for Materials Research and led it until 2018 and was the driving force behind building the graduate program in Materials Science and Engineering, which I also led for more than a decade. The move to Binghamton was great for me. I enjoyed teaching young excited students.  In 1993 I spent two months as a JSPS Fellow at the University of Tokyo in the physics department with Professor Suematsu. I arrived on April 1st in Tokyo just at the beginning of the cherry blossom season, and the students there took me to the tradition of drinking sake under the cherry trees. I managed to get back to my lodging at the Tokyo Institute of Technology, where I spent my first week until space was available at the International House of the U. Tokyo in Roppongi. I got much fitter there with the healthy food and the commute to the University each day, more than half a mile walk to the subway and another half a mile from the subway to the University. I still remember the lines of university faculty at the McDonalds at the subway exit picking up their coffee each morning. Each week I would leave Tokyo to give lectures at other universities and labs throughout Japan. Whilst there, my secretary reminded me by fax that there was a proposal call from the U.S. Department of Energy due in a few days, and was I going to apply. The next day I sent a handwritten proposal by fax to her; she typed it up and submitted it. That was the start of my DOE funding which continues to this day. Elaine still works with me and came to Stockholm for the Nobel celebrations. Half-way through my stay in Tokyo, my father passed away, and I flew back to England. At that time cash was dominant in Japan, so I had to go to the bank to get the cash for the ticket; even that was an experience as all transactions were performed by hand in a large ledger. For the last week of my stay in Tokyo, my family joined me, and we managed to squeeze into the apartment, which was little larger than our present living room.  On returning from Japan to Binghamton, based perhaps on my prior management experience at Exxon, I was invited to become the Vice-Provost for Research at Binghamton (the chief research officer on campus). I did this for five years part-time, whilst still carrying out my own research. I also took on the responsibility as Vice-Chair of the Board of Directors of the Research Foundation of SUNY; the senior faculty member on the Board. In 2007, I took a lead role in a DOE workshop on the research needs for energy storage. A series of these workshops led to the formation of the Energy Frontier Research Centers in 2009, and I was a member of one led by Clare Grey at Stony Brook (SUNY). When Clare moved to Cambridge University in 2011, I took over as Director with an associated position at Stony Brook. On renewal in 2014, the Center moved to Binghamton. This Center has been an exciting and invigorating experience comprising some of the leading scientists around the country and enabled a fundamental understanding of the reactions occurring in lithium battery electrodes. I am also a member of a more applied battery consortium, the Battery 500 group, whose goal is to enable batteries with an energy density of 500 Wh/kg. This has allowed John Goodenough and me to work together again (Figure 4). **My family and final notes** I have been very fortunate in my life by having a very supportive family, starting with my late parents who supported my goals of being a scientist, of being a cactus fanatic and of my two-year move to California, which they told me later they knew would be permanent. My wife, Georgina, has been especially supportive over the last 50+ years putting up with the long hours and all the travel. She now has her own career as a Professor of Spanish and Latin-American literature at the Oswego campus of SUNY, and is also thoroughly enjoying interacting and teaching the younger generations. Our children now have children of their own, the oldest of whom are now in college. Both of them vowed when they were old enough, they would move back to California, which they did and all four of our grandchildren were born in the San Francisco Bay area. Besides our immediate family, I was joined in Stockholm by my brother William, a PhD chemist from Cambridge and my niece Helen, a PhD Materials Scientist also from Cambridge. Both live in Britain, as do my two sisters, Anne and Susan. The family is shown at the Nobel Ceremony in Figure 5.  My life and that of my family has changed dramatically since the Nobel’s recognition of our team’s work on lithium batteries, that was announced whilst I was at a battery meeting in Ulm, Germany. My wife was the last of the family to hear the news as her phone was off due to the Yom Kippur holiday on October 9th. That of my University has also changed; the excitement was palpable from the virtual press conference from my room in Ulm to the reception when I returned to Binghamton (Figure 6). It is indeed humbling to join all those famous previous Nobel Laureates. I was also very pleased to join my colleagues John Goodenough and Akira Yoshino in this recognition.  Finally, I must thank all my past and present friends and collaborators at Oxford, Stanford, Exxon, Schlumberger, Binghamton and the chemistry, materials and battery communities without whom my work and this recognition would not have been possible. It is my hope that this recognition will allow all of us to achieve a cleaner and more sustainable world for our children and grandchildren. |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** | [MSW]  Stanley Whittingham: Hello?  Adam Smith: Oh hello.  MSW: Just one minute please, I’m just stepping out of the meeting room.  AS: Sure.  MSW: OK.  Adam Smith: My name is Adam Smith. I’m calling from Nobelprize.org, the website of the Nobel Prize in Stockholm. I gather I’m talking to you in France, is that right?  MSW: No, I’m in Ulm, Germany at the moment.  AS: Oh right, okay. So how did you hear the news of the Prize then?  MSW: I think the committee called me up about 11.15 this morning.  AS: And you’re at a scientific meeting, or …?  MSW: Yes, I’m at a, very appropriately, a battery meeting in Ulm.  AS: You were the first to develop lithium-ion batteries when you were at Exxon in the early ‘70s. How does it make you feel to see their ubiquitous presence now?  MSW: Oh, it’s great. The field started off small and it has just mushroomed since then. It’s great to see all the changes, how it’s impacting everybody’s lives.  AS: They’ve truly changed the world.  MSW: Yes.  AS: It was a very special research environment at Exxon in those days, wasn’t it?  MSW: Yes, it was very special. Exxon wanted to be the world’s top energy company, and they essentially said to the whole group of us “Do great research, get it published, don’t work on chemicals that are [inaudible]” and we started working on batteries and many other things at that time. They treated researchers like drilling an oil well. Only 10% work out, but if it’s looking promising they’ll put a lot of money into it, and they did.  AS: That’s lovely. That sounds like the much talked-about environment they used to have at Bell Labs, letting people get on with it.  MSW: Yes, and you’ve got to realise that Exxon’s labs were 20 miles from Bell Labs’ labs.  AS: So it was a culture of the time in a way.  MSW: Yes. There was a lot of competition between the two labs.  AS: Given the grand challenges we face now, I suppose people might say we need that environment again.  MSW: Yes, I think so, but it’s going to be very difficult to recreate that environment. Most companies are beholden to the stock market.  AS: So what was the secret of Exxon being able to do that at the time?  MSW: It’s just a different attitude at that time, I think. And you can look at a whole range of American companies, you know General Electric, DuPont, IBM: all had fundamental research labs, which looked out ten years or more.  AS: Now, with so much focus on becoming a fossil (fuel) free world, there’s really no way of doing it unless we make the necessary improvements in battery technology. Are you hopeful that things are going very much in the right direction at the moment?  MSW: I’m very hopeful. I think it’s happening faster than anybody expected.  AS: Well, I must say you sound very calm.  MSW: Well, I don’t think it’s got home yet.  AS: Have you managed to at least tell your family the news?  MSW: Some of my family I’ve got hold of; others are still sleeping.  AS: Well, it’s been a huge pleasure to speak to you, thank you very much indeed. And see you in December.  MSW: Thank you very much.  AS: Thank you.  MSW: Okay, see you, bye. |
| **Interview** |  |
| Q5 | Do you remember a teacher that inspired you? |
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| Q5 | What kind of teacher do you aspire to be? |
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| Q1 | What advice would you give a young researcher? |
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| Q1 | What advice would you give a younger version of yourself? |
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| Q2 | How do you cope with failure? |
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| Q10 | What type of university environment stimulates creativity? |
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| Q2 | How important is collaboration in science? |
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| Q9 | How has your life changed since the Nobel Prize? |
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| Q10 | How well do you know your co-laureates? |
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| Q4 | How was the battery produced from the beginning? |
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| Q15 | What are your thoughts on sustainability? |
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| Q2 | What have you learnt from doing sports? |
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| Q8 | What hobbies do you have besides sports? |
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| Q6 | Are you an enthusiastic traveller? |
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| Q9 | How will it feel to talk to astronauts in space? |
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| Q4 | What research are you working on right now? |
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| Q2 | What discovery do you wish that you had done? |
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| Q14 | What discovery do you hope will happen in the battery industry? |
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| **Chemistry\_2024-2000** | |
| **ID** | 0315 |
| **Biographical** | I was born in Suita City, Osaka Prefecture, in 1948. My father, Sojiro, was an electrical engineer who worked at a power company. My mother worked at a bank until she married, after which she became a housewife. Suita is located about 10 km north of the center of Osaka City. My home was surrounded by bamboo groves. As a child, I enjoyed playing in this nature-filled environment.  My path to chemistry began in the fourth grade of elementary school, when my teacher recommended that I read *The Chemical History of a Candle* by Michael Faraday. The book made it easy to understand why a candle burns, what happens when it burns, and why it has a wick. This stimulated my curiosity, and I became fascinated with chemistry. In 1966, I entered Kyoto University as a student of the Department of Petrochemistry, Faculty of Engineering. My major was quantum organic chemistry. At the time, the Department of Petrochemistry was a very prestigious one at Kyoto University. The faculty included Professor [Kenichi Fukui](https://www.nobelprize.org/prizes/chemistry/1981/fukui/facts/), who would go on to receive the 1981 Nobel Prize in Chemistry. My university research involved quantum chemistry theory and observation of experimental results. I focused on organic photochemistry in particular. Professor Fukui was the mentor of my mentor at the university. I entered graduate school at the same university and studied photochemistry of charge transfer complexes. By irradiating ultraviolet to charge transfer complexes of 1,2,4,5-tetracyanobenzene as electron acceptor with electron donors such as toluene, I discovered that a previously unknown reaction occurred.  After receiving a master’s degree from Kyoto University, I joined Asahi Kasei Corp. in 1972. I was assigned to a laboratory in Kawasaki City, Kanagawa Prefecture, and began my career as a corporate researcher. My work was basic exploratory research, which meant I was expected to find the seeds of new technology. I had to decide what subjects to research, and I performed experiments myself. My first idea was to develop a new interlayer film for the laminated safety glass of automobiles. At the time, polyvinyl butyral film was used. I worked eagerly find a new material to replace it, but without success. The performance requirements for safety glass are extremely demanding, and I was unable to obtain suitable characteristics. Polyvinyl butyral is still used as interlayer film in laminated safety glass today. I was up against a formidable opponent.  In 1974, I married my wife Kumiko. We have been blessed with two daughters, Miho and Yuko, and a son, Satoshi. My next project at work was to develop nonflammable thermal insulation material. Saving energy was a hot topic at the time, and high-performance insulation was considered important. Polyurethane foam and polystyrene foam were available, but they are both flammable. I tried to develop inorganic polymer of phosphate as a nonflammable alternative, but this too was unsuccessful. Although I was able to reach fairly high insulation performance, the material had insufficient mechanical strength. My third project was for something like what we now call photocatalysts. I wanted to develop a product with a sterilizing and deodorizing effect by activating the oxygen in the air using sunlight. The foundation of this research was the photochemistry I had studied in college, specifically photosensitized oxidation. I kept at it for four years and achieved reasonably good results, but once again I could not succeed. The market was too immature. Photocatalyst technology would not be commercialized until thirty years later.  In 1981 I began looking for my next line of research, and this would turn out to be a fateful year for me. There was a new material that everyone was excited about: electroconductive polyacetylene. Although it was a plastic, surprisingly it could conduct electricity. It was discovered by Professor [Hideki Shirakawa](https://www.nobelprize.org/prizes/chemistry/2000/shirakawa/facts/), who would go on to receive the 2000 Nobel Prize in Chemistry along with Professor [Alan Heeger](https://www.nobelprize.org/prizes/chemistry/2000/heeger/facts/) and Professor [Alan MacDiarmid](https://www.nobelprize.org/prizes/chemistry/2000/macdiarmid/facts/). At the time, Professor Shirakawa was doing joint research with Kyoto University. I visited Kyoto University, the first time for me to return to my alma mater in a long time. I was amazed when he showed me a sample of polyacetylene in a test tube. It had such a metallic luster that I could scarcely believe it was plastic. I decided that this amazing material would be my next subject of research. I visited Kyoto University many times after that, and he taught me all about it, including how to polymerize it. The year 1981 turned out to have another surprise in store as well: Professor Fukui’s Nobel Prize in Chemistry. The frontier molecular orbital theory for which Professor Fukui received the Nobel Prize was the very theory that explained why polyacetylene was electroconductive.  I synthesized polyacetylene at the Asahi Kasei laboratory in Kawasaki. Next, I began thinking about what kind of product to use it for. Among polyacetylene’s many unique properties, I was most interested in its electrochemical properties. This meant that polyacetylene could be used as a battery material. What’s more, since its electrochemical reactions were reversible, it could be used as a rechargeable battery material. I surveyed the battery research being done at the time and learned of Professor Stanley Whittingham’s then novel concept of intercalation. He first applied this concept to battery cathode material in 1976, and after that there was a groundswell of work to develop a small and lightweight rechargeable battery utilizing the concept of intercalation. Successful commercialization, however, proved extremely difficult due to issues with the anode material. I was thrilled to find that polyacetylene would work as an anode material which could be doped with cations such as Li ions. I confirmed this idea and concluded that the ideal use for polyacetylene was as anode material for a rechargeable battery.  I was not an expert on battery technology, but from that point forward I became deeply involved in battery technology. I began tests to evaluate the polyacetylene I synthesized as rechargeable battery anode material. The results were encouraging. The material had large charge and discharge capacity, and it didn’t deteriorate even after repeated charge/discharge cycles. The next step was to decide what cathode material to pair with it. But this turned out to be a bigger problem than I had anticipated. There weren’t any cathode materials that were suitable. Since polyacetylene doesn’t contain Li ions, I needed a cathode material that contained Li ions. I struggled in vain to find one until I at last encountered Professor John Goodenough’s 1980 paper on lithium cobalt oxide (LiCoO2) as a new cathode material. Without hesitation, I assembled a test cell using LiCoO2 cathode and polyacetylene anode. This was the first instance of the new rechargeable battery system that would later become known as the lithium-ion battery. It was 1983. While the weight of the new rechargeable battery was reduced to about one-third that of a nickel-cadmium battery, the volume was unfortunately unchanged. This was a disappointment because the objective was to achieve both lighter weight and smaller size. Nevertheless, I began to show my new battery system to potential customers. I didn’t know whether they considered smaller size to be more important than lighter weight or not. Unfortunately, I was told that smaller size was indeed more important.  Once again, I found myself at a crossroads. The reason I couldn’t reduce the size of my new battery system was that the specific gravity of polyacetylene is 1.2, relatively low. While the low specific gravity was advantageous for achieving lighter weight, it turned out to be disadvantageous for achieving smaller size. My calculations indicated that I needed a material with a specific gravity of at least 2 in order to reach the desired size. It immediately occurred to me that carbonaceous material would have a specific gravity of 2 or more while having conjugated double bonds similarly to polyacetylene. I evaluated the many carbonaceous materials then available but could find none that would function as anode material. When I was beginning to lose hope, I learned of a new kind of carbon fiber called VGCF that was being developed at another laboratory of Asahi Kasei. I obtained a sample and found that it performed very well as an anode material. VGCF is made using a very special process that gives it a very special crystalline structure. This special crystalline structure is what makes it work well as an anode material. By replacing polyacetylene with carbonaceous material, I thus completed the basic configuration of a practical new rechargeable battery. After further development of technology required for commercialization, the first lithium-ion batteries made their debut in the world in the early 1990s.  On October 9, 2019, I received a surprising notification from Stockholm. I had been chosen for the Nobel Prize in Chemistry along with Professor Goodenough and Professor Whittingham for the development of lithium-ion batteries. Two reasons were given for the award. The first reason was the huge impact that lithium-ion batteries had for the achievement of today’s mobile IT society. The second reason was the vital contribution that lithium-ion batteries are expected to make for the achievement of a sustainable society moving forward. While the latter of the two is still a work in progress, emboldened by my receipt of the Nobel Prize I am determined to do my part to make it happen. |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** | [AY]  Akira Yoshino: Moshi moshi.  Adam Smith: Hello. Am I speaking to Professor Yoshino?  Akira Yoshino: Yes, this is Yoshino speaking.  AS: Congratulations on the award of the Nobel Prize.  AY: Thank you very much, thank you very much. Amazing! Very, very, very happy!  AS: Thank you. You developed the lithium ion battery that first went on sale in 1991 and now powers our world. Why did you decide to work on batteries?  AY: The initial stage of my research is not for secondary batteries. The first step is new materials, electroconductive polymers.  AS: What are the great challenges ahead for battery production?  AY: Increasing of energy density. Yes, it is a very important technical issue. And also the durability is very important to improve.  AS: What is the secret of your creativity?  AY: It’s a very, very difficult question to answer. I think it is important to thinking every day.  AS: To keep thinking every day – never take a holiday from thinking.  AY: Yes, yes. That’s right, that’s right.  AS: Professor Yoshino, we very much look forward to welcoming you to Stockholm in December.  AY: On the … yes, December, December, yes. Thank you very much.  AS: Thank you. Bye bye.  AY: Bye bye, thank you. |
| **Interview** |  |
| Q5 | Do you remember a specific teacher? |
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| Q5 | What is the most important characteristic of a good teacher? |
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| Q5 | Who was your role model? |
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| Q3 | How can we inspire children to pursue a career in science? |
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| Q1 | What advice do you have for young scientists? |
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| Q7 | What qualities do you need to become a successful scientist? |
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| Q2 | How do you cope with failure? |
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| Q6 | How did archeology become one of your biggest interests? |
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| Q2 | Do you see any similarities between archeology and science? |
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| Q2 | Has doing sports been important for you? |
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| Q9 | How did you react to the news of your Nobel Prize? |
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| Q10 | How well do you know John Goodenough? |
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| Q2 | Has collaboration been important to you? |
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| Q4 | What research are you doing now? |
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| Q15 | What does sustainability mean to you? |
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| Q15 | What are your thoughts about electric cars? |
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| Q14 | What future do you see in the battery industry? |
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| **Chemistry\_2024-2000** | |
| **ID** | 0316 |
| **Biographical** | I was born in East Pittsburgh, Pennsylvania, on July 25, 1956, misshapen after my mother’s twenty-four-hour labor and with no hair. My father called me his ‘Swan’ (until that nickname was swapped for ‘Vampira’ when I was a teenager). William Howard Arnold and Josephine Inman Routheau, both twenty-five, already had two-and-a-half-year old Bill when I came along. I was followed thirteen months later by Edward (a sweet ‘surprise’), then by David, and finally by Thomas when I was twelve and old enough to take care of a baby by myself.  This crowd of boys, which I learned to navigate, was usually organized by Bill, named after my father and after my grandfather, General William Howard Arnold, who had served in the U.S. Army in the Pacific theater during WWII, commanded the U.S. forces in Austria after the war, and retired as commander of the 5th U.S. Army. We were part of an extended Catholic family, many of whom to this day gather at summer cottages in Macatawa, on the east shore of Lake Michigan. The women in the family ran the show, ably filling in to organize the troops at home. For years we shared my grandparents’ turn-of-the-century cottage “Stack Arms” with various cousins, until my father built his own place in 1965. My grandfather, the powerful general, died of a broken heart only weeks after his beloved and even more commanding wife, Elizabeth Welsh Mullen, succumbed to breast cancer in 1976.  Macatawa, Michigan was paradise because we could run around freely, sometimes in packs, and sometimes alone. My mother nearly had a heart attack one day upon seeing my tricycle abandoned at the end of the dock. I was found underneath the dock, digging up crayfish. A couple of summers later, I had to be persuaded not to launch the raft I built to take me to Chicago, ninety miles across the lake. I learned to sail, and to respect and use the forces of nature, on Lake Michigan. Without television or internet, we enjoyed books, bicycles, and friends. I read every single issue of the 1950s *Readers’ Digest* from the stack next to the *Analog Science Fiction and Fact* magazines my father adored. I was especially entranced by the reports of severed limbs being reattached in miraculous surgeries. I envisaged myself following an early idol, Dr. Christiaan Barnard, who performed the first human heart transplant in 1967. In a single summer I tore through every medical book available in the local Holland Public Library. But I abandoned the idea of being a transplant surgeon when I found out that the mere sight of blood made me nauseous.  Summers were heaven, but the school years in Pittsburgh were another story. No one knew what to do with a smart little girl in the 1960s. Attempts to keep me busy included music lessons (piano and violin), any number of sewing and art projects, ice skating – which involved walking more than a mile in freezing weather to the rink – and Saturday catechism classes in Wilkinsburg, again on foot, snow, rain, or shine. I spent as much time as I could outdoors, digging under stones for salamanders, and also finding and collecting used soda bottles which I could turn into the local drug store for two cents. Three bottles = one fudgesicle. I led my younger brother on adventures that involved exploring large drainpipes; and when that was not possible – it seemed like we were in an ice age then, with regular school closures for four feet of snow – we watched *I Love Lucy* re-runs on the round TV set and played infinite variations of war games.  My father, an experimental physicist who received his PhD from Princeton in 1955 at the age of 24, spent 1954 doing experiments on top of Mt. Evans in Colorado. My mother was not thrilled to be in such a remote site (elevation 10,700 ft), and they moved down-mountain to Idaho Springs (7,500 ft) shortly before my brother Bill was due. Both my parents contracted polio there and spent time in iron lungs, cared for by my fearless maternal grandmother, Josephine Routheau. Upon graduation, my father set aside academics to work in the nascent nuclear industry. The Westinghouse Electric Corporation in Pittsburgh was going to provide “electricity too cheap to meter,” and my father helped design the pressurized water reactor technology needed to make that dream come true.  In the 1960s, my father was away from home much of the time. He seemed to be in Nevada a lot; later I learned it was for nuclear testing. He would bring us silver dollars from the casinos to which he had to accompany the big bosses on their gambling sprees. When at home, he loved to build houses or model airplanes, listen to classical music, read, and work on his coin and stamp collections. I thought he was the smartest person in the world because he knew all the answers, could explain how everything worked, and could fix nearly anything. To spend time with him, Eddy and I vied for the duplicates of the stamp collections. We divided up the world: I got the British colonies; Eddy took the rest of the world. From stamp collecting I learned geography, and learned that geographical boundaries, governments, and even languages, changed over time. I learned that empires crumbled, and former colonies gained independence.  My brilliant success in elementary school got me into typing class. At the age of ten, far ahead of my classmates, I spent most of my time drawing pictures, making little paper people for my friends, and perfecting my mirror writing (being left-handed made it easy for me to write backwards and impress my friends when they held my coded messages up to the bathroom mirror). My parents somehow convinced Edgewood Elementary School to allow me to take some classes at the high school next door. One of my favorite extra classes was typing, although I was not very good at it. I would perch on two telephone books in order to reach the typewriter while the high school students laughed at the tiny 5th grader with legs dangling from the elevated seat. I still have letters I typed to my father during class. I also took mechanical drawing, which was also challenging, but taught me the important skill of looking at and describing objects from different perspectives.  By age 13 I was pretty much fed up with classroom learning. It was 1969, and Baltimore, the city we lived in at that time, was burning. I was not invited back for 9th grade to the private girls’ school that my mother had worked very hard to get me admitted to, and which I hated anyway. Instead of attending school, I began hitchhiking to anti-war protests in Washington D.C. I spent only half of 9th grade at the large public, inner city high school before my father’s job took us back to Pittsburgh. The move back North just made my trips to the protests longer.  At Allderdice, an excellent public school in the Squirrel Hill neighborhood of Pittsburgh, I picked up a few words of Yiddish as my second foreign language (after French) and delighted in a whole new set of descriptions far more colorful than the morose ones of Catholic culture. As a teenager who needed to understand the world, but who lacked the power to navigate it, I distanced myself from my classmates and parents. I lived on my own in a terrible, run-down, and bug-infested third-floor apartment in a gritty neighborhood, working at various jobs to pay my rent and bills while dreaming of a future that would free me from the limitations of being young and female in the 1960s and early 1970s. My jobs included selling seeds (yes, I earned the bicycle at age 10), lunch counter waitress (age 14), pizza parlor helper (15), department store clerk (16), receptionist (16), cocktail waitress (17, I told them I was 22 and no one ever checked, as fewer young people had driver’s licenses then), waitress in Pittsburgh’s famous jazz club Walt Harper’s Attic, and finally taxi driver (age 18). By the time I left for college, I had become adept at maneuvering a massive 1960s Yellow Cab up and down the terrifyingly steep hills and pot-holed streets of Pittsburgh. Those streets were narrower than my cab, but my customers would insist I could get through, and they were (usually) right. Without GPS, I constructed maps in my head and still benefit from the good sense of direction that I developed. Driving a taxi was hard work.  Long days (sometimes more than 10 hours) netted 20 or 25 dollars, but in just a few weeks I worked my way up from the filthy, banged up cabs the old dispatchers gave to new drivers, to clean, newer (but still just as wide) cabs that elicited better tips. The fun had to end, however, because I was on my way to college.  In 1974 I somehow managed to convince the admissions officers at Princeton University to admit me. I thought it was my convincing essay, or perhaps the fact that I was a very rare female candidate applying in engineering, but it probably also did not hurt that my father had received his PhD in physics there and knew the Dean of Engineering well. I started in 1974, when the first women were graduating, since Princeton only began accepting them in 1969. There were probably about 15% women in my class, and far fewer in Mechanical and Aerospace Engineering. But being the only female was nothing new to me, and I stayed in MAE because there was no good reason to switch to something else. I was busy absorbing as much knowledge and as many new ideas as I could: Italian language, economics, socialist theory, Russian language and literature, art history, and plenty of math and physics. My lack of interest in chemistry was reflected in my freshman grade, and I did not progress in that field at that time.  At Princeton, I continued driving taxis, worked at the library, assembled electronic equipment, and cleaned the house of philosopher Thomas S. Kuhn. I needed the money to support my addiction to Laker Airways, which made it possible to fly to London for $99 if you were willing to line up at the ticket office in Manhattan at 4 am and fly out around midnight the same day. During my last two years at Princeton, I spent every break in London or Italy or Paris.  Travel opened a fascinating world of different cultures and especially cuisines (I love people’s creativity with food and was delighted to learn that daily food could be completely delicious). After my junior year in high school (1973), my maternal grandparents took my brother Bill and me to Europe for The Grand Tour. They had been visiting Europe for many years, traveling to their favorite little towns in Austria, Germany, France, and Italy. We spent two full months on the road, never staying more than two nights in any one place. Everyone seemed to know and love my grandparents, Col. Edward and Josephine Routheau. “Mama” and “Baba” taught me everything I needed to know to enjoy life with little money. Their secret: a bottle of wine, a fresh baguette, and a bit of pâté on a sunny, grassy knoll by the side of a country road in southern France.  Eager to return to Europe and experience it on my own, I took time off after my sophomore year at Princeton to work in Madrid and Milan in 1976–1977. During this time, I never spoke English, and discovered whole new cultures and friends. My Italian boyfriend and I motorcycled all over northern Italy, and in the summer, we went all the way to Istanbul and back on his 1956 Moto Guzzi 500, the classic bike of the Italian carabinieri. We traveled to the Cinque Terre, before there was a paved road, and camped or slept wherever a farmer would have us. With my guitar I shared the songs of Bob Dylan and Italy’s equivalent, Francesco Guccini, with anyone who would listen.  During my last two years at Princeton, with renewed interest in completing my degree and finding something meaningful to do, my former lackadaisical attitude to coursework changed. I loved the upper level classes and found that, with a little bit of effort, I had genuine talent for math and engineering; in 1979 I earned my degree magna cum laude in Mechanical and Aerospace Engineering. The energy crisis of the 1970s and mentors at Princeton whose passion for connecting science and benefits to society sparked what became a lifelong interest in alternative energy.  After graduating, I donned my backpack once again and, with about $2/day saved for expenses, traveled from Ecuador to São Paulo, Brazil, for an internship on solar energy projects with Professor José Goldemberg, who later became Brazil’s Minister for the Environment and the ‘father’ of its ethanol fuels program. It took six weeks over the Inca trail by bus to make my way from Guayaquil, Ecuador, to Santa Cruz, Bolivia. The trip from Lima to Ayacucho took more than 36 hours on a slow, steep climb up a rocky path, shared with a goat covered with fleas. We stopped every hour, it seemed, so the federal police, looking for Shining Path members, could empty the bus, puzzle over my passport, and hours later send us on our way. I loved Peru, but not the regular bouts of food poisoning. That summer I perfected an ability to sleep anywhere and bolstered my immune system. During my time in Brazil, I picked up a bit of Portuguese and a taste for beans and rice, served for lunch every single day in the cafeteria, and especially for the traditional feijoada, a fantastic, rich stew of black beans and every part of the pig, served on Sundays at noon because it required the rest of the day to digest.  With a degree in mechanical engineering and the Carter administration’s emphasis on clean, renewable energy sources, I took my first ‘real’ job (1979–1980) at a new national laboratory, the Solar Energy Research Institute (now NREL) in Golden, Colorado. My duties in Frank Kreith’s Heat Transfer Group were primarily to develop new passive solar heating and cooling technologies; I also helped write position papers for the United Nations on solar energy in the developing world. Outside the office, I was learning how to ride an off-road motorcycle and improve my skiing, which I had tried for the first time while living in Italy. In exchange for free rent, I lived on a horse property and cared for the animals when the owner was away. I took up classical guitar to combat the onslaught of country western music blaring from every radio station. **1981–1985, University of California, Berkeley** With the election of Ronald Reagan as President of the United States, the future for passive solar heating and cooling seemed somewhat limited. I’d never been to California, but at the end of 1980 I packed my few belongings into my 1971 red Volkswagen Super Beetle and headed west to start graduate studies at the University of California, Berkeley. The chemical engineers there had decided to take a risk on a mechanical engineer who also happened to be a woman, and I was accepted into the PhD program, beginning in January 1981.  Although my first desire was to work on cellulosic biofuels, interest in that technology had waned: automobiles ballooned again to giant proportions, and the oil embargoes were forgotten. We also forgot how to care for the planet. Funding for alternative energy projects became scarce; the professor I had come to work for retired; and I had to change direction. Professor Harvey Blanch, Australian by birth and recently recruited to Berkeley from the University of Delaware, however, was ready to support a whole new industry on the horizon, the biotechnology industry. A revolution was taking place in California and Boston – new companies with names like ‘Genentech’ and ‘Amgen’ were looking for engineers to scale up their processes for making protein therapeutics using recombinant DNA technology. Someone would have to produce and purify the recombinant proteins that promised to change the face of medicine.  Thus, I took on research in bioseparations, studying affinity chromatography, and developing and validating mathematical models of chromatographic separations. I also developed an appreciation for the challenges of working with proteins: everything was designed around keeping the proteins happy. This was not easy, since proteins are only marginally stable and, it seemed, would denature at the slightest provocation. Furthermore, most protein therapeutics involved highly complex, post-translationally modified structures that are easily rendered useless when manufactured, purified, or stored under the wrong conditions. Process engineers had little experience with proteins, or with biochemistry for that matter, and the standard chemical engineering separation processes were ill-suited to protein preservation.  Graduate school, like college, was another feast of learning, but this time it was organic chemistry, biochemistry, immunology, enzymology, advanced mathematics, and of course the entire undergraduate and graduate chemical engineering curriculum. Organic chemistry made sense to me – making molecules was like building a puzzle. After taking it for credit, I happily audited multiple organic chemistry courses as the official note-taker for the student-run Black Lightning note service (beloved by students who dreaded waking up in time for the 8 am class). The superb biochemists Jack Kirsch and Judith Klinman introduced me to the remarkable catalytic capabilities of enzymes from a quantitative, physical chemistry perspective that I especially appreciated, and Allan Wilson introduced me to molecular evolution of protein sequences. I soaked up new knowledge, taking science and math courses just for the fun of it, something I continued to do decades later.  It was not until my last year as a graduate student that it occurred to me to try my hand at being a professor. I played bridge and went backpacking with some of the young professors in the UC Berkeley College of Chemistry, but had little idea of what a professor actually did for a living, other than teach a course or two. My PhD advisor, Harvey Blanch, however, also started companies and consulted for industry, as did some of the biochemistry professors, and this multifaceted activity made the academic enterprise much more interesting to me. I wanted a connection to the ‘real world’, but also the independence I had not experienced in my various previous industrial and national laboratory positions. I therefore decided to apply for academic positions. The year 1984 was a very good time to do so: U.S. universities were waking up to the fact that while more and more women were interested in science and engineering, there were essentially no women on engineering faculties. At that time, chemical engineers did not do postdoctoral research before starting their academic careers, and I was offered positions at a number of very good places, including MIT. In 1985 I accepted a position at the University of Minnesota, which enjoyed the #1 ranking in chemical engineering, but I also parlayed my many job offers into funding for a one-year postdoc at UC Berkeley with biophysical chemist Ignacio Tinoco, to learn spectroscopic methods of characterizing biomolecules that I thought I would use in my future laboratory. I was 29.  Around that time, I met Jay Bailey, a world-renowned biochemical engineering professor at Caltech, a small, private institute in southern California that I knew very little about. Its chemical engineering faculty was tiny, and its reputation in engineering was for very ‘academic’ research. Caltech’s PhDs tended to become professors rather than industry leaders. Since the University of Minnesota could not absorb someone of Bailey’s stature, I applied to Caltech for an assistant professor position. Jay and I married in 1987, in Macatawa, surrounded by friends and (lots of) family. **Directed evolution at Caltech 1986–2003** I moved to Caltech in mid-1986, where I was given a temporary position as a postdoctoral researcher (my official title was ‘Visiting Associate’, as I was already on the rolls as an assistant professor at the University of Minnesota). I was pleased to have a bench in Jack Richards’s laboratory, where I would learn how to engineer a protein’s sequence, a technology I wanted for my own research. Richards had recently developed ‘cassette mutagenesis’, one of the first site-directed mutagenesis methods for engineering proteins. My first foray into molecular biology and genetic engineering was to make a couple of mutated cytochrome *c* proteins for a collaboration with Harry Gray’s group, who wanted to use them to probe biological electron transfer. Everything was difficult in 1986: synthesizing oligonucleotides, DNA sequencing, cloning, and working with restriction enzymes were all problematic, while my experience with trouble-shooting cloning experiments was very limited. But I persevered, and when my first mutant sequence was confirmed, I was a proud protein engineer.  Auspiciously for me, two Caltech chemical engineering professors moved elsewhere, thus opening a junior position in this new ‘bio’ part of chemical engineering; an offer was extended to me to join the faculty, and I started as Assistant Professor of Chemical Engineering at the California Institute of Technology in January 1987.  Jay Bailey’s was the first, or at least one of the first, chemical engineering laboratories to use molecular biology methods to approach problems in industrial biotechnology. With his own educational and research background limited to mathematical modeling of chemical reaction systems, Bailey ably demonstrated how to use fearless graduate students to bring new techniques into the laboratory. He attracted some of the brightest students from all over the world to Caltech, and I gratefully recruited from that stellar pool to get my own protein-oriented group started. Over the years, I would fine-tune my own ability to remind graduate students and postdocs that they could learn and do anything. The new Arnold lab was going to make sure that protein engineering would become part of chemical engineering, just as Bailey and others were doing for metabolic engineering. These early efforts to genetically engineer biological systems became important and industrially relevant foundations for what is now known as ‘synthetic biology’.  The problem was that no one really knew how to engineer useful proteins. Proteins, especially enzymes, are fascinating and do many things that people find useful, from monitoring blood glucose levels to taking stains off clothes. But many of the problems that chemical engineers (and others) faced with using proteins for industrial applications came from their inability to function under non-natural conditions. Proteins often performed poorly outside their natural environments, and the engineer had to develop Rube Goldberg mechanisms to purify, store, and use them. However, with the advent of technologies for engineering protein sequences, and therefore their properties, it became possible for the first time in the 1980s to consider engineering the protein itself according to the process engineer’s or the industrial biotechnologist’s specifications. My group was going to engineer protein sequences to make them behave in a process or application, rather than design the process or application around the protein.  I also wanted to show that proteins could be engineered for unusual but useful properties that would open up whole new applications. Alex Klibanov of MIT had surprised the world in the 1980s by showing that enzymes could work when suspended in dry, nonpolar solvents. Dissolving enzymes in high concentrations of polar solvents, however, immediately obliterated activity, even if it could be shown that they retained their folded structures. The prevailing view at that time was that proteins could not exhibit highly non-natural properties, such as the ability to function in organic solvents. The argument seemed to be that because Nature never did it, it could not be done. But in fact, that was precisely why it could be done, and why it might even be easy to do so. I therefore took on the challenge of engineering enzymes that would catalyze their reactions when dissolved in polar organic solvents, but no one knew how to alter their sequences for this purpose. My feeble attempts at ‘rational design’ of enzymes for organic solvents were failures, as were most experiments aimed at improving proteins at that time. While it was easy to diminish or even destroy an enzyme’s function, there were very few reports of making better enzymes. And the process was difficult – it required having the enzyme’s crystal structure, of which there were very few, and then understanding the protein’s structure and function sufficiently well to identify not just the sites of useful mutations, but which amino acids ought to be placed there.  In the 1980s, some labs were starting to engineer nucleic acids, peptides and even proteins using phage display and other methods to make huge libraries of biomolecules, which they then sorted using binding assays or genetic selections to find the useful sequences. Appreciating protein complexity as well as the combinatorial explosion in sequence possibilities that comes with targeting multiple sites for mutation and the low frequency of beneficial mutations that could be expected, I developed an alternative and highly general approach suitable for the problems I was interested in, engineering better enzymes. Adopting a simple, newly-developed method for making mutations randomly in a specific gene, the polymerase chain reaction under error-prone conditions, my students and I made libraries of bacteria having genes randomly mutated at just one or two sites and screened them for the properties we wanted using rapid assays in petri dishes or 96-well plate readers. Then we would take the genes for the best proteins and repeat the process to accumulate benefits, evolving the proteins step-wise until we achieved the functional goals.  To my delight, beneficial and surprising mutations appeared in our laboratory-evolved enzymes. Beneficial mutations were not so rare that we could not find them with a carefully controlled screen, and we could accumulate them for further improvements. When we mapped the mutations to the protein structure, we were surprised to see that they often happened on the enzyme surface, where protein chemists at the time argued that mutational effects were mostly neutral. Activating mutations also appeared far from the enzyme active sites, where no one could explain their effects, much less predict them *a priori.* By 1990 we were finally on our way to engineering useful enzymes, using evolution as our guide. Another golden moment was the arrival of my first son, James Howard Bailey, in April 1990. I was 34 years old, untenured, overworked, but had a beautiful baby boy, was full of energy, and knew exactly where I needed to go.  Not everyone agreed with my approach, however. The protein engineering field, with its main roots in biochemistry, was very much focused on ‘rational design’. Protein chemists argued they could predict beneficial mutations and sequences using structure-guided approaches and even computational methods. Some of my Caltech chemistry colleagues, dismissive of the contemporaneous popularity of ‘combinatorial chemistry’, which involved synthesizing and screening large molecular libraries to find drug leads, looked askance at my random mutagenesis efforts as intellectual laziness. I was undeterred, however, because I had an approach that worked.  While I was finally on the right track to engineering proteins, life outside the lab was going off the rails. My marriage was failing, and Jay moved to Switzerland, to become a professor at the ETH in Zurich.  Caltech stepped in to help me financially overcome the difficulty of living on my own with my one-year-old baby in a Pasadena house I could not afford, for which I will always be grateful. Caltech Provost Paul Jennings and President Thomas Everhart also helped me through a difficult tenure process and demonstrated to me what real leadership means: a real leader has a moral compass and sometimes has to make decisions that go against the wishes of powerful people. Tenured, I could do what I loved best, and that was engineering enzymes by directed evolution. I dropped all other projects related to protein-metal recognition, a much more ‘standard’ part of my research that came out of my physical chemistry training, to focus exclusively on evolving enzymes.  In 1992, I met Andrew Lange, a brilliant and charismatic young cosmologist, at the annual meeting of the Packard Fellows at the Monterey Bay Aquarium. We had both received Packard fellowships in 1989, but had somehow never met. It was as close as one can come to love at first sight. All throughout 1993, while we tried to find positions in the same place, Andrew would fly down from Oakland to Pasadena on Thursdays after teaching his freshman physics class and then fly back up in time to teach his Tuesday morning class. He wanted a family, and with me he had an instant one. James adored him. Andrew, an experimental physicist, encouraged James’s natural curiosity of the mechanical world with hands-on deconstruction of everything one could find in the Caltech dumpsters. There were a lot of oscilloscopes in the trash in those days, and I still have cathode ray tubes scavenged from various deconstruction projects. When Caltech came through with a professor position for Andrew in 1994, he moved down from Berkeley. Some of the physics professors genuinely thought they were responsible for recruiting the most promising young cosmologist in the country to Caltech, but that gold star belonged to me. Very soon thereafter we were overjoyed to welcome William Andrew Lange (1995) and Joseph Inman Lange (1997) to our family.  We struggled to raise three little boys while also establishing our careers. Andrew traveled for his experiments and team meetings to Antarctica and to other distant places for weeks at a time. He was a devoted and loving father, but loved his science just as much. He longed to be with his team during the deployments of experiments. His 1998 BOOMERANG experiment, contained in a balloon that circumnavigated the South Pole and collected photons from the early universe, was a huge success and cemented his name in astrophysics and cosmology. He was Caltech’s golden boy and was said to be on track to a Nobel Prize.  I could not have been more proud, or more exhausted. Life would have been impossible without our dear “Mama”, Carmen, who gave my boys her abundant love, along with homespun treatments for minor ailments, delicious food, and practical tips for navigating the vast Los Angeles public transit system. During the 1990s I attended local conferences, sometimes very pregnant, but traveled relatively little. My own work, while not nearly as visible as Andrew’s, was going well, and talented scientists from disparate disciplines came to Caltech to discuss directed evolution with me and my students. During that time, I was pushing enzymes into entirely new directions. The field was expanding rapidly, and directed evolution methods were becoming widely adopted. I took on a few industrial challenges with Proctor & Gamble, Degussa, and Dow Chemical that would allow me to demonstrate the power of directed evolution with ‘real’ problems, not just model systems. I am still grateful to their scientists for introducing me to interesting and challenging problems and for sharing their deep experience with what makes an enzyme useful – or not. I am especially grateful that they invested time and money in a brand-new and still largely unproven technology spearheaded by a young, female engineer. Importantly, Pim Stemmer, who independently published a directed enzyme evolution paper a year after my 1993 paper, visited Caltech for a few weeks in 1996. We planned a new start-up company, Maxygen, to commercialize our shared vision of using evolution to create virtually any protein or gene. Maxygen negotiated a license to all Caltech directed evolution intellectual property, and I served as a founding scientific advisor.  I was elected to the National Academy of Engineering in 2000, at the same age of forty-three as my father was when he was elected. When I came on stage at the induction ceremony in Washington D.C., my father stood up and shouted, to the delight of his many friends in the audience, “That’s my daughter!” I believe we are still the only father-daughter member pair in the NAE. **2003–2004: A sabbatical around the world** Jay Bailey died of colon cancer at age 58 when our son James was eleven years old. Family life at home with Andrew, who was prone to debilitating depression, became increasingly strained. I reasoned that a trip around the world would give all of us much to learn about and pull us together; with my four gentlemen we could share adventures, such as those of my youth, and also quiet times. To his enormous credit, Andrew agreed to this plan. I chose two of our sabbatical destinations, Australia and South Africa, where I had friends but no real work to do. Andrew chose Cardiff, where he had real collaborators and a chance to get some science accomplished.  We arrived in Alice Springs for the Australian winter of 2003 for our first adventure, with Aboriginal people in the Red Center. Our sons immediately went feral. By the third night in Oz, we checked into our million-star hotel, sleeping on the red dirt in swags well-designed to keep snakes and spiders out. We spent the first two magical weeks of our sabbatical with the Southern Cross overhead, the smell of campfire in our nostrils, and our heads filled with the walkabout stories and legends of the native people. My two littlest boys dug for honey ants and grubs and played with the local children, climbing in to join their family groups piled onto old mattresses spread out on the desert floor. We settled into an eight-week stay at Swinburne Tech, in Melbourne, and Joe and William went to kindergarten and first grade in the Hawthorne public school. I secured for James a two-month stay at a fine boys’ boarding school, Scotch College, nearby. Every weekend the family would go visit gold mines and farm stays.  It was winter again when we came back to Caltech for a short stay, and then headed to Africa for the next stage of our voyage, which included Egypt, South Africa, Namibia, and Madagascar, followed by the United Kingdom. It was a fairy-tale sabbatical, and the best year of my life. We were all happy, healthy, and delighted to watch our sons soak up the adventures.  My research group did exceptionally well during this time. I realized they could do more on their own, and that they had developed real leadership skills. From then on, I have given group members as much freedom as I can to pursue their own ideas and mentor others. **2005–2010: Dark times** I returned from this magical year at the end of 2004 to find out that I had breast cancer which had spread to my lymph nodes. I underwent two surgeries and 1.5 years of debilitating chemotherapy and radiation. I took up yoga for physical and mental health, and somehow managed to work every day, from which I derived both pleasure and purpose.  Our science started to focus on a problem I had long been interested in, alternative energy. Oil prices were steadily climbing. Since 2000 we had been engineering cytochrome P450s to oxidize alkanes, one goal being to make recombinant organisms that could convert gaseous alkanes to liquid fuels. In 2005, with Matt Peters and Peter Meinhold, and funding from a prominent venture capitalist, we started what soon became Gevo, Inc., one of the first biofuels start-ups in the new ‘synthetic biology’ space. Undergoing intense treatment for breast cancer, however, I was in no condition to spend much time on that project, and Matt and Peter ran the circus. Gevo, still in business today, makes renewable jet fuel starting from biomass using an engineered yeast and chemistry.  On January 22, 2010 Andrew Lange committed suicide, which shocked the world and left behind grieving family members, friends, students, and colleagues. We had not lived together for more than two years, but I now had to pick up the pieces of our family and cut some sort of path for our three shattered sons, then ages 17, 13, and 11. That year was a blur. Members of my research group continued to take care of each other, and they and Caltech were my rock. My friends helped me throughout. I continuously remind myself that no one is guaranteed an easy life, but we can make it easier for others. **2011–Present: A new stage** In good health, and perhaps just a bit wiser than before, I made a conscious decision to take risks again, in my professional life as well as my personal one. I traveled with my sons, encouraged their own adventures that took them to distant lands, and made many new friends outside my usual circles. I continued favored activities like scuba diving, and hiking to my historic one-room cabin in the San Gabriel Mountains. And for the first time I accepted invitations to give scientific talks to general audiences. I discovered that both scientific and general audiences respond warmly to story-telling and efforts to convey the big picture; they want to be reminded of the wonder and power of evolution, which we see all around us, and to think that science can lead to a better future. I like to end my talks with an open and exciting future full of questions to answer, rather than closing the box on a problem.  Perhaps most important, I felt free, even compelled, to pursue new and more challenging problems with my science. I had always wanted to make enzymes do new chemistry, and catalyze reactions not known in the biological world. I posed to several good chemists in my group the specific question: can you get a cytochrome P450 to catalyze reactions using nitrogen rather than oxygen? They rose to the challenge, and we engineered the first ‘nitrene transferase’ and ‘carbene transferase’ enzymes in 2012. Building on this realization that nature is poised for all sorts of new capabilities, we have been exploring a whole new world of enzyme chemistry.  Today my laboratory feels very much like it did in the exciting days of the 1990s: intense, with a palpable sense of discovery and the knowledge that we are laying the foundations of how molecules will be made in the future, using genetically-encoded biological systems that include enzymes engineered to do chemistry first invented by human beings. I am grateful to experience that excitement and focus for a second time, again shared with a tremendously talented group of young people.  My work with directed enzyme evolution was recognized by the Charles Stark Draper Prize in 2011, the highest honor an engineer can receive in the United States. I was the first and remain to this day the only woman to win this award, which has been given by the U.S. National Academy of Engineering since 1989. My two youngest sons and I were welcomed by President [Barack Obama](https://www.nobelprize.org/prizes/peace/2009/obama/facts/) at the White House in 2013, when I received the U.S. National Medal of Technology and Innovation. (James was serving in the U.S. Army in Afghanistan and could not join us.) And in 2016 I received the Millennium Technology Prize, again the first (and only) woman to be so honored. I did not set out to be the first female engineer to break into this rarefied territory, but I was one of the first to be given the chance to show what she could do. Only the ninth woman to be hired on the Caltech faculty, I am the first female Nobel Laureate there. Many brilliant women have joined science and engineering faculties in my lifetime, and I predict that many more of the highest recognitions of women’s scientific contributions are coming. **Concluding remarks** I am sure the reader will note that I have not commented directly on the contributions of the many students, postdocs, and colleagues I have worked with and drawn inspiration from. Some were called out specifically in my Nobel Lecture, but I have not been able to thank everyone who contributed to the conception and wide application of directed enzyme evolution. I would like now to thank my mentors and those I have tried to mentor, for I learned much from you. I also want to thank Ben and Donna Rosen for all that they have done and continue to do for Caltech; it has been my great honor to direct the Donna and Benjamin M. Rosen Bioengineering Center for the last six years.  My father, William Howard Arnold, died in 2015. I miss him very much. He would have been very proud and would have especially loved the Stockholm festivities. My dear middle son, William Andrew Lange, died in 2016 at the age of 20; his short life was enriched by caring for monkeys in South Africa, for children in Kenya and India, and for his friends. Both Williams are still very much in my heart. I’d like to think that Andrew, too, would have been happy for me. My son Joseph, and my son James and his wife Alanna, and my stepson Sean Bailey came to Stockholm together with nearly sixty friends, family members, and former students to celebrate my Prize. I am very grateful for all that I have and for all the people, and animals, who have enriched my life. |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** | [FA]  Frances Arnold: Hello.  Adam Smith: Oh, hello. Am I speaking with Frances Arnold?  FA: You are, hi.  AS: Hi. I’m Adam Smith from Nobelprize.org. Congratulations on the award of the Nobel Prize.  FA: Thank you.  AS: You sound very calm and collected in the middle of the night in Texas.  FA: I’m not the least – I’m bouncing off the walls but I’m trying to pretend to sound calm and collected.  AS: I imagine … you’re away from home so perhaps somewhat protected from the immediate onslaught that’s going to happen today.  FA: Well, I’m annoyed because I can’t reach my sons. They’re sound asleep [Laughs]. So, yes, I’m protected but I’m also annoyed. They never answer the phone when mum calls.  AS: Well not in the middle of the night at least, surely [Laughs]. You started as a mechanical engineer, and now I suppose you are a protein engineer. Do you think that is part of the secret of your success, that you came from a different field into biology and were able to see things differently?  FA: I think there’s no doubt about that. I was able to look at the problem with a totally a fresh set of eyes. A problem that had challenged people since the techniques were – of site-directed mutagenesis for example, which won the Nobel Prize – were available. And I realised that the way that most people were going about protein engineering was doomed to failure.  AS: It’s a bold move though, to jump fields so radically.  FA: Oh, well, I have four brothers and I’ve jumped into all sorts of things over my life, so learning new things has always been fun for me. Changing fields has been fun, and I still feel that way many years later.  AS: Would it be fair to say that what you do is to sort of manipulate nature’s inventiveness for our human benefit?  FA: I think that what I do is copying nature’s design process. Right? Here … all this tremendous beauty and complexity of the biological world all comes about through this one simple, beautiful design algorithm, and what I do is use that algorithm to build new biological things. And to me it’s not … it’s obvious, it’s totally obvious that this is the way it should be done.  AS: Can you give me an example of one of your favourite things that you’ve been able to evolve?  FA: Well, what I work on now is … someone asked me ‘What’s the funniest thing or what’s the best thing that you’ve ever done?’ It’s always what I’m doing now. So what I’m going now is looking at this question of how do you evolve innovation. How does innovation happen? How do get a whole new chemical reactivity that you don’t know already exists in nature? How can I evolve a whole new species in essence, a whole new species of enzyme? And, so for example, making a carbon-silicon bond. Humans thought only they could do it, but we evolved an enzyme that does it better than humans do.  AS: Absolutely, and I suppose nature’s doing this all the time. It’s coming up with new enzymes itself.  FA: Of course she is! Nature is solving all sorts of problems that we throw at her – how to degrade plastic bottles, how to degrade pesticides and herbicides and antibiotics. She creates new enzymes in response to that all the time, in real time.  AS: And I suppose that should allay the fears of people who say that humans shouldn’t be tinkering with nature. Well nature’s tinkering with itself, so it’s not so different really is it?  FA: We’ve been tinkering with nature for tens of thousands of years – look at a poodle! So we’ve created all sorts of organisms and biological things that wouldn’t be here were it not for us.  AS: That’s true, and poodles haven’t done much damage to us so far.  FA: That’s right. And they solve all sorts of problems. Look at the agricultural revolution and food. Look at our farm animals. Look at our pets. These are human creations.  AS: Humanity needs science to get over the hurdles ahead.  FA: That is really true. We need science and we need the smartest minds to work on these problems.  AS: You are already a member of all three National Academies of Sciences in the US; you have multiple awards. What do you think the Nobel Prize will mean to you?  FA: Oh my goodness! I don’t know yet. I haven’t had it very long.  AS: Let me rephrase the question. What does it mean to you at this moment?  FA: At this moment I’m absolutely thrilled and I can’t wait to get home and tell my sons.  AS: Really couldn’t be a better answer. Fantastic … well we very much look forward to seeing you in Stockholm in December, and thank you very much for talking to me.  FA: Thank you Adam. OK.  AS: Bye bye.  FA: Bye. |
| **Interview** |  |
| Q9 | How did it feel to be awarded the Nobel Prize? |
|  | Frances H. Arnold: I think I was an engineer and a scientist from day one. I was very surprised and overwhelmed, terrified, happy, thrilled and bouncing off the walls. I was in a hotel room so I could bounce off the walls and nobody would see me. I was walking around in circles because I wasn’t allowed to call home and then after I called home, I could. I was walking around in circles because no one answered the telephone. It was a pretty thrilling moment. Then I really had to take a shower because I knew it would be a very long day. |
| Q12 | How did your family react to the news? |
|  | Frances H. Arnold: It’s a bit of a funny story. My first phone call was to my son James and of course he didn’t answer the phone until a couple of hours later and his reaction, when he answered the phone was; What do you want mom? It was five o’clock in the morning and he was tired and so I said; James, I won the Nobel Prize and I can’t repeat exactly what he said here, but he said; Oh, my goodness! That was just … He was so thrilled for me and of course he jumped in the car and drove over to another house, where my other son was sound asleep and woke him up and then the two of them came to meet me at Caltech later that day. So, when I finally got back to Caltech, because all the flights were full from Dallas to Los Angeles, so I made it back about ten hours after the announcement. I made it back and Caltech picked me up at the airport and brought me to campus and all my students were spread out on the campus. They had made big posters. They were wearing their lab t-shirts and they gave me a standing ovation as I walked onto campus. It was really lovely. Then all my colleagues congregated in the chairman’s office and toasted me with champagne. |
| Q9 | What does receiving the Nobel Prize mean? |
|  | Frances H. Arnold: I’m still working on that one. It’s a fairly recent event and up till today, winning the Nobel Prize has meant a lot of work. Putting together schedules and hearing from many friends and supporters, hearing from my old babysitters. I have heard from thousands of people all over the world, many of whom I’ve never met who just want to say how happy they are for me. I’ve heard from many people I have met and have long forgotten, but I’ve heard from many people who I care about, so it seems to be a shared event. It’s not just about me, it’s about everyone you’ve ever touched in your whole life and people you haven’t yet touched but now will, as a result of this prize. |
| Q3 | How did you become interested in science? |
|  | Frances H. Arnold: My father was a physicist, experimentalist, and he loved fixing things and building things. He would allow us in the workshop every once in a while. I had four brothers so we were always competing: who would be better in math, who would be better at building things. I always had a flair for competition. |
| Q12 | How has your upbringing shaped you? |
|  | Frances H. Arnold: Well, for one thing, as I was growing up, I was shaped by the fact that I had all these brothers, some older, one is older and three were younger. So I learned how to hold my own with the bigger boy but also how to boss everybody else around. I ended up organizing the brothers a lot but we’re also very close. In fact, three of my brothers are here with me in Stockholm. And we had friendly competitions for many things. |
| Q3 | Was there a single moment you decided to become an engineer? |
|  | Frances H. Arnold: No, there wasn’t. Of course, as I was growing up, being a scientist was not on my list of things to do. I enjoyed science. I wanted to be a scientist, when I was a kid. I didn’t worry about too much what I would do, when I was going to grow up, but I tried lots of different things. I thought I would be a diplomat. Then I realized I had no diplomatic skills. I wanted to be a CEO of a multinational corporation, then I realized that was a lot of work, and I studied engineering because it was the easiest option and the easiest way to get into Princeton University at the time and I never left. |
| Q3 | What do you enjoy about science and engineering? |
|  | Frances H. Arnold: I love solving problems. I think science and engineering is a fabulous career for people who see problems in the world that need solutions. My talent happens to be in coming up with technological solutions to those problems, but there are plenty of problems for which we will need solutions, so I think that’s a lovely way to use your skills and creativity in identifying problems and then finding clever new ways to solve them. |
| Q7 | What traits are important to be a scientist? |
|  | Frances H. Arnold: The traits, that are important to be successful in science, include an ability to accept criticism. There’s plenty of it to go around and to benefit from criticism. If someone takes enough time to criticize your work in a constructive way and you are able to listen to that, of course you know you have to set aside the feelings of hurt feelings, say, perhaps that what I need to listen to what’s going on, why is this idea not coming across, what is the fault I have in the way I communicate the idea or maybe the idea really is lousy. But we have to be able to join the discussion. |
| Q7 | Is independence an important trait? |
|  | Frances H. Arnold: As a scientist and end engineer, independence of course is extremely important. You have to come up with your own solutions to problems, you have to come up with your own questions, if you’re going to be a scientist and really explore something new. On the other hand, teamwork is important. So this wonderful balance of independent creativity, but then convincing all these dozens of students to take on some of these problems and put their own ideas into it, is the balance that we have to master. |
| Q15 | Should scientists do work that impacts society? |
|  | Frances H. Arnold: I don’t think it’s necessary, that scientists work on problems of societal impact. There’s so many wonderful stories of how just curiosity has led to societal impact and that if you start off saying I’m going to solve climate change, huge problems or figure out how to purify water, you may come up with a solution or you may not. It may not be a particular person’s passion. I think science is beautiful and that those of us who have a passion to understand how the universe works, how communities work, how people work, how our minds work, just to understand that will also contribute to eventually solving the problems. |
| Q3 | What aspect of science do you enjoy most? |
|  | Frances H. Arnold: I particularly like working on problem-solving. That comes from, probably, my personality but also my engineering background. Engineering is all about how do you come up with a solution to a problem but I should say that much of my work has deep science roots where, if we come up with a solution for a problem, what does that tell us about the underlying phenomenon? What do we learn? And evolution is such a great way to do this. I use this process of evolution to create new biological things that no one would know how to design. They’re too complicated but once I have them and I’d solved a problem, I can go in and do the reverse engineering. I can understand or try to understand how they acquired the new traits that they have and that way I can contribute to a more fundamental understanding of how biology works and how evolution works. |
| Q5 | Which scientists influenced your work? |
|  | Frances H. Arnold: I have done a lot of thinking over the last few months about the scientists and philosophers and writers who’ve influenced my work for the last 40 years. I’ve been strongly influenced by Jorge Luis Borges, a writer, by the philosopher Dan Dennett and by a whole slew of really creative scientists whose ideas I recombined in some new way and it’s wonderful to go back and view those ideas and see in retrospect how they were reassembled. |
| Q5 | How important is a diverse background for a scientist? |
|  | Frances H. Arnold: The diversity of background that I have, which runs the gamut from studying Russian literature to aerospace engineering and chemical engineering, and I speak a number of languages, I’ve been interested in many things over my lifetime. I didn’t actually become a professor of chemical engineering until I was thirty years old. I was doing many other things before that including being a taxi driver. All those experiences, even if they were not the most positive experiences, made me who I am, and I think the diversity of experience makes me very different from everybody else. |
| Q1 | What advice do you have for a young person starting their career? |
|  | Frances H. Arnold: I try not to give too much advice because specific advice doesn’t help. My path is different from your path but don’t be afraid of a path, take it. When you come to the fork in the road, take it. Do something, right, even if you don’t know what it is and where it will lead you. Do it. Do something and do it as well as you can. If you don’t like it, take another path. Life is not doors closing, it should be doors opening. |
| Q1 | Is it ever too late to become a scientist? |
|  | Frances H. Arnold: I think it’s neither too early, nor too late to become a scientist or engineer. It may be hard to study that math, but you could do lots of interesting things just by being curious. |
| Q5 | Why do you enjoy mentoring and teaching young students? |
|  | Frances H. Arnold: I work in a remarkable institution, the California Institute of Technology. We have 900 undergraduates and a thousand graduate students. It’s really small and they come from all over the world, just in love with science, and that’s what they want to do. They want to do science and they want to do it at the highest levels. So I’m working with these tremendously talented and motivated people. Their ideas are phenomenal. They haven’t been molded into some hard set piece of clay. They’re completely open and their creativity is just waiting to be unleashed. So I get to spark that flame and watch that creativity just explode. How could you not like that?  It’s very much a privilege to work with them. They’re nice people, they care about others. It’s my job to provide them the resources to do science; the environment that lets them feel free to express this creativity; the support they need when it fails, as it inevitably does; everybody goes through periods of nothing works and then to give them the credit also when everything works and they graduate and go on to form their careers. I have 250 children as a result of this over the years, many of whom are coming to Stockholm and the ones who aren’t, have all, you know, participated in some way in this event. |
| Q10 | How important are your group and colleagues? |
|  | Frances H. Arnold: It’s all about the people. I’m one brain and sometimes there’s one brain that can do everything but that’s not my brain. But what I’m good at is encouraging 20 brains to work together and when you have 20 really good brains you can do a lot. So I like to bring those brains together. We enjoy each other, we’re friends and we like to celebrate our successes, so I have a group of many of those people who’ve gone on to other careers, who are coming back to celebrate this. |
| Q5 | Did you have a mentor when you were younger? |
|  | Frances H. Arnold: I had several mentors as a younger scientist. People, whose work I admired, whose ideas I admired and who encouraged me to go and try wonderful things. People who found me a job in Brazil in the 1970s and people who supported my PhD aspirations. Throughout my career I’ve been lucky to have inspirational scientists. |
| Q5 | How important is it to be a good role model? |
|  | Frances H. Arnold: I think it’s enjoyable to inspire the next generation of scientists. I try to avoid the moniker role model because there are many things I’ve done that I certainly would not want to model for anyone. Life is challenging and we all have to go through ups and downs, but I would love in any way if I can inspire people to keep going through the hard parts. Science is not easy. This is a hard job and you have to be willing to take their criticism and you have to be willing to take those failures, but the joys far outweigh the difficulties in my mind. |
| Q2 | How do you deal with challenges? |
|  | Frances H. Arnold: Well, I keep going because if I don’t solve this problem I’ll go to another problem, right? I love problem-solving but I haven’t chosen any one specific problem. I define my problems and if you define your problems maybe you can even come up with problems people didn’t even know were problems and then, when you’ve solved it, they realized, hey, that was a really interesting problem. So that’s one way to get around the problem of failure. |
| Q1 | How can we encourage and help women in science? |
|  | Frances H. Arnold: I think we’re doing, we’re starting to do that. What I’m finding is, that in my field in chemistry, there are a lot of really bright, strong women doing chemistry and they’re doing great chemistry. It’s a challenge of course to juggle everything. Of course, I think women are the best jugglers. I don’t know anybody who juggles more things than women do but we also take on a lot to juggle, so these are the challenges, to encourage women to take on yet more balls in the air and say you can do this and you can actually enjoy it as well. |
| Q11 | Has being a woman caused challenges in your career? |
|  | Frances H. Arnold: I’m sure there are many challenges that I’ve encountered. I have to say my personality is that I’m blissfully unaware if someone doesn’t like what I do. I’ve always been able to say: Well sorry, that’s who I am and that’s what I like to do*.* I think that having the four brothers helped to dare. So many of the challenges, where people would look at my work and for example disregard its importance or say it’s not science, which is criticism I had early on, I could just say: Well, I’m going to do it anyway. |
| Q11 | [D](https://www.youtube.com/watch?v=ukdZEweNtfk&t=1184s)o you think more women are taking up science careers? |
|  | Frances H. Arnold: I think the progress of women taking on careers at universities in science and technology, the progress has been slow but it has been somewhat steady. It’s still not good enough. I don’t see the 50% parity that I see at undergraduate level, for example at Caltech, 50% of the undergraduates are women but only 20% of the professors. To some extent, that’s a time difference and maybe in ten years that will change but I’m not sure that’s the case. There’s something systemic that is holding women back from wanting to do this job. I think if they want to do the job they could do it and they could get the jobs but for some reason a number of them say early on: Well, I don’t want to be like you, I don’t want to work as hard as you do, I don’t want to have all these responsibilities because I’d like to focus elsewhere. It’s not easy to do everything. |
| Q10 | What can universities do to help women in science? |
|  | Frances H. Arnold: It is something that the system can help with and many improvements have been made. When I had a baby in 1990, my university had no maternity policy because no one had had a baby before, so that had to be developed and now everybody has babies but that was a new phenomenon. And we had to go through the process of how do we support women, so that they can succeed and can have all the other things that everyone wants. |
| Q1 | What is your advice for young women who want to follow in your footsteps? |
|  | Frances H. Arnold: My favorite advice for young women who want to do science and engineering is, by all means do it even if you don’t want to do it. Don’t leave it for the men because it’s so much fun. It’s fun, it’s important, it’s really thrilling to use your creativity to do useful things for people. Don’t leave it for the men. |
| Q1 | Do we need to encourage more people to take up science and engineering? |
|  | Frances H. Arnold: I think everybody needs to know something about science and engineering. Maybe they don’t go and get a degree in it, but we need a scientifically literate population. Science and technology is a future. It’s the future of the planet. Without science and technology we won’t feed 10 billion people, we won’t provide water or we won’t have cities that are even worth living in. It’s science and technology so everybody has to do it and most certainly women are going to play a huge role in the future of science and technology because that’s where 50% of the best minds are. |
| Q15 | What applications from your work are you most proud of? |
|  | Frances H. Arnold: The wonderful thing about evolution is that here is a design process that works at all scales from molecules to ecosystems. One design algorithm that solved everything in life created everything in the living world. What I realized is that we’re just at the beginning of using evolution to move into the future. So what that means is that these processes, that we pioneered many years ago, have started to be used by hundreds of people, thousands of people to do very creative things with real applications. For example pharmaceuticals are being manufactured using enzymes that have been optimized by directed evolution. That’s important because they used to be made using toxic metals and processes that would generate tons, literally tons of waste products. Now they’re made using a clean enzyme process.  I brought here as one of my guests to Stockholm, a young man who started a company. He got his PhD in my lab doing directed evolution and he recently started a company that’s replacing pesticides with insect pheromones; it turns out if you spray a little bit of an insect pheromone in a field, you can confuse males. When you confuse the male insects, they don’t mate. No caterpillars, the crop damage is not there and it’s a wonderful organic replacement for dumping pesticides onto the planet, all made by synthetic biology by engineering biological systems to make chemicals that they don’t normally make. And these applications are thrilling to me because I see a sustainable future for the planet by using some of these design processes and designed molecules that nature invented. |
| Q15 | How can your work help the environment? |
|  | Frances H. Arnold: I started my career back in the 1970’s working on solar energy when President Carter was our leader and the United States had a national goal of 20% renewable energy by the year 2000. It was a shame that that national goal of course went by the wayside when there was a change of administration and I felt that my career path in solar energy might be somewhat limited so I switched out of solar energy and went into biotechnology at the beginning of the DNA revolution. I stayed with renewable energy though, looking at ways we could replace pumping oil out of the ground and using biological systems then and I’ve stayed with that passion for replacing dirty chemical processes with clean biological processes for many years, because I care deeply about our natural world and how we can maintain a beautiful natural world, all these interesting products of evolution, lions and tigers and rhinos and monkeys and even insects. These things are beautiful, they’re beautiful products of evolution and we will be greatly impoverished if we do not make space for all these other things that we admire. |

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| **Chemistry\_2024-2000** | |
| **ID** | 0317 |
| **Biographical** | **E****arly life** I was born March 10, 1941 to Albert Mark Smith II (March 2, 1908 to February 3, 1978) and Jessie Patton Biggs Smith (September 14, 1909 to June 14, 2000). My brother Mark (A. Mark Smith III) was born December 29, 1942 and my sister Helen (now Helen Boyd) was born June 22, 1947.  My father graduated from West Point (the U.S. Military Academy) in 1930, but left the army for civilian life immediately afterward. He had steady employment during the Depression, and he and my mother, who married in 1936, lived in relative prosperity in those years.  The Japanese attack on Pearl Harbor occurred nine months after my birth. My father immediately re-joined the army and continued as a career officer until his retirement in 1965. This meant that our family moved very frequently while Mark, Helen, and I were growing up. By the time I graduated from ninth grade in 1955, I’d attended an extraordinary 11 or 12 schools. Most of the schools were on army bases, where all the kids moved as frequently as we did. That meant that the new kid in school was rapidly assimilated into society, without having to spend a painful year or two as outsider. I learned how to make new friends rapidly, but not how to maintain long-term friendships – a pattern that continues to some degree to the present day.  Mostly my father was posted up and down the East Coast, but during the Korean War he served in Japan from 1951 to 1954. The rest of the family joined him there in April 1952, just as the U.S. occupation was coming to an end. **My career as herpetologist** In the summer of 1949, our family went on vacation for a few weeks at Penobscot Bay, Maine. The place was overrun with snakes. I ran across two snakes eating the same frog or toad from opposite ends (I don’t know how it turned out). I caught a beautiful green snake and carried it triumphantly by the tail into the parlor, where my mother was hosting a tea party for some proper local ladies. There were some “eeks,” and I was ordered back outside. My herpetology career had begun. **HAM radio** I caught the radio bug while we were still in Japan, and continued through high school. I got my novice license (KN4OWA) around 1956, and built a small rig, which included a classy straight telegraph key I got off an army surplus telegraph set. I never got very proficient in Morse code, however, and dropped out after high school. By that time, I’d learned quite a bit about circuitry, and not a little calculus and analytical geometry (without learning their names), from obsessive study of the Radio Amateur’s Handbook. That’s knowledge that has turned out to be of use in the sequel. **High school** My last three years of schooling were at Philips Academy Andover, a private boarding school in Massachusetts founded in 1778. Both President George Herbert Walker Bush and his son President George Walker Bush graduated from Andover. So did 2018 Economics laureate [Bill Nordhaus](https://www.nobelprize.org/prizes/economic-sciences/2018/nordhaus/facts/), a year behind me; he was a fellow member of the Radio Club, though I don’t remember him from then.  Education at Andover was rigorous in a patrician sort of way. Traditional skills like English composition were prominent in the curriculum, while I remember instruction in math and science to be rather old-fashioned. I was attracted to biology, whose head, Harper Follansbee, appointed in 1940, did nothing to discourage my herpetological ambitions. There was a magnificent indigo snake in one of the buildings. An ambitious young biology teacher, John Kimball, was appointed in 1956, and modernized the biology curriculum over the years. I barely remember him from my years at Andover, but have come to appreciate his great contribution to biology education, especially the free online textbook http://www.biology-pages.info/, which he continues to maintain to this day, and which I made liberal use of in my own teaching career.  Apart from Latin, French, and English, which I’ll discuss in the next section, my most memorable course at Andover was senior American history with Fred Allis. Memorable because Mr. Allis assumed a level of sophistication in the analysis of Supreme Court decisions, the economic theories of (I seem to remember) Joseph Schumpeter, etc., that was utterly beyond my abilities. Some of my classmates seemed to thrive on this stuff. I vaguely remember that a few even argued with Mr. Allis! Not me. Long, miserable evenings in the library earned me a (no doubt undeserved) gentleman’s C.  Altogether, though, I graduated from Andover well prepared for college – provided that I didn’t major in history. **Language** Three language classes at Andover were more memorable than American history: Latin, French, and senior English.  My Latin teacher was Frank Benton, who was appointed in 1918 and retired when I graduated in 1958. He looked upon our attempts to “construe” (translate out loud in class) our assigned Latin texts with curmudgeonly good humor. Wisely eschewing Cicero for the pimply teens in his third year Latin class, he assigned an up-to-date subject instead: medieval Latin. I hold our reader, Helen Waddell’s *A Book of Medieval Latin for Schools*, first published in 1931, before me as I write. The verse has understandable meter and clear rhymes that even a teen could appreciate. As I took up choral singing in college and afterward, thus regularly encountering medieval Latin, I came to appreciate Mr. Benton’s class even more.  My French teacher was James Grew, appointed in 1935. Mr. Grew had adopted l*a méthode directe.* On the first day of French I, he briefly explained the rules of the class in English. That was the last English we were to hear from him for many months. He’d talk to us in French, ask us questions in French, sometime right in our faces, and eventually we’d start responding in French – broken French at first, of course, but gradually more and more idiomatic French. It was as if we were toddlers first learning our mother tongue – which is pretty much the logic of *la méthode directe*. French is the only foreign language in which I attained anything approximating fluency (mais maintenant j’ai presque tout oublié).  My senior English teacher was Dudley Fitts, appointed in 1941, who was in addition a prominent and well-respected poet, literary critic, and translator of classical Latin and Greek literature. What I remember most in his class was Chaucer, whose Middle English language we learned to understand and recite with some facility. I can’t say that senior English in general or Chaucer in particular had the same specific influence on my life as did French and Latin. But it did come in handy a few years ago, when our dinner group gathered for a meal whose theme was Spring. Someone had laboriously typed out the first 18 lines of *Canterbury Tales,* and asked if anyone would like to try reading it during the meal. “Sure,” I said, standing up and ignoring the typescript. I rendered those first 18 lines from memory, more than half a century after high school graduation, with (I flatter myself) dramatic flair and a creditable Middle English accent.  My engagement with language – both my own and foreign – has persisted to the present day. I continued to study French during my year in England as an exchange student between high school and college, and I took German and Spanish in college. I have learned to recognize roots in those and other languages, including some in Hebrew and Arabic. The language instinct has declined dramatically with age, of course; language is largely an academic enterprise now. **A year in England** Before going to college, I spent the 1958–1959 academic year as an exchange student at Wellington School, a combination day and boarding school in Wellington, Somerset, England. I was considered a Sixth Former (senior), and was assigned to one of the school’s houses (I don’t remember which one). By then I knew I was going to be a biology major in college, but I decided to take English, French, and History as my A-level subjects. Surprisingly considering what I wrote above about American history at Andover, I did OK in history: I think the History Master, whose name I believe was Victor Finn, was impressed by my writing ability, not my historical acumen. Evidently, I did pretty well in French too, because I have a copy of the *Oxford Companion to English Literature* with an inscription saying that it was the 1959 Modern Languages Prize.  An incident at Wellington School stands out as a shameful embarrassment in retrospect. Two representatives of South Africa’s apartheid government were invited to address a school assembly. For half an hour or so, one of them explained calmly and patiently how reasonable South Africa’s apartheid policy was, then asked for questions. I stood up and asked a respectful question – thank God I don’t remember what – in my Yank accent, which brought forth an amused comment from the speaker before he answered. After assembly, the History Master (again, I think Victor Finn) took some of us Sixth Formers aside and vented his fury that such an outrage had been allowed to occur in the school. I don’t remember him using the word “racism,” but I understand now that that was what he was denouncing. I felt mildly embarrassed at the time, but now I squirm at how unthinkingly I accepted such racist ideology as if legitimate. **Haverford College** My choice of Haverford College, a small Quaker school outside Philadelphia, counts as a sort of rebellion from my Andover background: Andover in those days was still largely a feeder school for Harvard, Yale, and Princeton.  I came just too late (September 1959) for any hope of a career in herpetology. Emmett “Dixie” Dunn, a prominent herpetologist, had been chair of the Biology Department, but he died in 1956. His replacement, Ariel Loewy, was even then (at age 34 in 1959) a prophet-like visionary on campus, whose soft-spoken charisma is still very much in evidence (along with a hacking cough) in an interview he gave in 1996 (Loewy, 1996). Loewy was born to a prosperous Jewish family in Bucharest, but the family fled to England in 1936 and then to Canada in 1941. He went to the University of Cambridge in England for a research fellowship in 1952–1953, and was thus eyewitness to [Watson](https://www.nobelprize.org/prizes/medicine/1962/watson/facts/)’s and [Crick](https://www.nobelprize.org/prizes/medicine/1962/crick/facts/)’s elucidation of the structure of DNA and the birth of the molecular genetics revolution. He accepted a position in Haverford’s Biology Department in 1953, and by the time I arrived had persuaded the college to let him utterly transform the curriculum, abandoning broad coverage of traditional subdisciplines in order to concentrate on cell and molecular biology. This was a unique educational choice at the time. It was also a terrific piece of luck for me: molecular biology was a far better fit to my abilities than herpetology, its math-like style congruent with the mathematical habit of mind I came to discover in myself at Haverford.  Loewy managed to recruit two ambitious young scientists who shared his curricular vision in full measure, and his charisma in some measure as well: Irv Finger and Mel Santer, who along with Loewy taught most of the biology courses I took.  In 2009 I reconnected with Santer, and told him about an incident in one of his courses that significantly influenced my scientific life. In one of his tests, he asked us (as I remember) to reconstruct the logic of an experiment by Howard Dintzis that had been published the year before (Dintzis, 1961), and that was immediately recognized as an important contribution to molecular biology. Dintzis showed that polypeptides are synthesized from amino terminus to carboxy terminus, by adding amino acids sequentially to the carboxy terminal end of the growing chain of amino acids. I was very pleased with my answer: I thought I’d caught on to the rationale of a complex experiment without a teacher’s help – an unusual or perhaps unique experience in my intellectual life to date. As I remember, Santer didn’t agree: he gave me a low mark on the question. Santer didn’t remember any of this in 2009, of course. Nevertheless, the “Dintzis experiment” (as it came to be called) reappeared in my life on several occasions, including in graduate school as I’ll explain below. This incident is emblematic of the many ways teachers can have lasting influences on their students without realizing it at the time.  A core component of Loewy’s curricular reform was the senior research tutorial, in which every senior biology major was required to complete a research project with one of the faculty. My senior year (1962– 1963) tutor was Meg Mathies, who served as temporary replacement for Santer during his sabbatical leave. Mathies was an immunologist who had just earned her Ph.D. under Abram Stavitsky at Case Western Reserve University; it was her influence that steered much of my subsequent research career toward molecular immunology.  My project was nothing if not ambitious: to show that the antigenbinding specificity of an antibody was determined by the messenger RNAs (mRNAs) that encode it. That seems like an obvious truth today, but it wasn’t then. The alternative *template theory,* which I’ll explain later in this essay, implied that the amino acid sequences of an antibody’s polypeptides (thus the nucleotide sequences of the corresponding mRNAs) did not suffice to explain its antigen specificity. My plan was to immunize a rabbit with a phage (phage T4, a virus that infects bacterial cells), extract RNA from the spleen (a primary immune organ) as the rabbit responded to the immunization, add that RNA to the cell-free protein synthesis system reported the year before ([Nirenberg](https://www.nobelprize.org/prizes/medicine/1968/nirenberg/facts/) and Matthaei, 1961), and determine whether the resulting protein included antibodies that could *neutralize* T4 phages (that is, block their ability to infect bacterial cells). The experiment was hopelessly naïve. I failed to demonstrate any T4-neutralizing antibodies; it was Edgar Haber, who turned out to be my Ph.D. mentor a few years later, who defeated the template theory, as I’ll explain below. Still, a few things did work: the cell-free system did synthesize protein when artificial RNA was added in large amounts; T4 infection could be quantified using a plaque assay; the immunized rabbit did produce antibodies with strong T4-neutralizing activity as measured using the plaque assay. I used T4 to immunize rabbits and mice at several points in my later research career, and phage neutralization assays were key in my first phage-display publication (Smith, 1985).  I took a course called (I think) College Mathematics with a master teacher named Cletus Oakley. It explored a handful of carefully selected areas of mathematical analysis. I found this a most congenial kind of thinking, and went on to take the calculus sequence in college and a number of other courses afterward. Elementary math has been a significant component of my science throughout my career. Experimental results can often be presented in a more perspicuous, compelling, and workmanlike manner using simple mathematics. I can’t claim expertise in any area of the discipline, and I’m not an amateur do-it-yourself purist either. I cheerfully outsource challenging integrations or differential equations to online tables or utilities, or to colleagues who are actual mathematicians. My philosophical interest in probability theory, first encountered in Oakley’s class, as the fundamental rules of empirical reasoning (see below) arises from my engagement with math.  Haverford was still a Quaker school when I attended, and I admired the Quaker attitudes and commitment to social justice that I encountered in college. Many of my college friends had come to Haverford from Quaker schools. I participated in a number of Quaker weekend work camps in the inner city of Philadelphia. All this led to a short-lived engagement with Christianity (which had had little importance in my earlier life) during my college years, but religion dropped back out of my life for good after graduation. It has been Quakerism’s social attitudes and commitment to justice, not its devotional dimension, that has stuck with me. **Singing** During one of the summers in my college years, I got a tech job at the Marine Biological Laboratory in Woods Hole, on Cape Cod in Massachusetts. The college students like me spent many evening and weekend hours socializing, and I joined several other young people in an informal madrigal group. I have been singing in choruses ever since, with some interruptions. Years later, in 1978 in Columbia, Missouri, I was a founding member of the Ad Hoc Singers (a name we made up in haste before our first gig in a nursing home), which has evolved through several namechanges to the Columbia Chorale today. I’m still singing in the Chorale, progressing (regressing?) from second bass to second tenor as my low notes disappeared with age.  Engagement with choral singing meshes with my interest in language. I’ve written a number of musical essays for the Columbia Chorale, and I’ve posted an essay on *Jerusalem of Gold* on the Mondoweiss website. It is the language of the lyrics and how it relates to the musical diction that is my chief concern in these essays. **Briefly a high school teacher** I didn’t graduate from Haverford with an academic career in mind. Instead, my experience with the Quaker inner-city weekend work camps inspired me to be a high school teacher in neighborhoods like the ones I’d encountered. I took a few basic education courses in my senior year, and enrolled in the Master of Arts in Teaching (MAT) program at Temple University that summer. A semester of practice teaching in an inner-city school made me change my mind. I told myself that it was a teacher’s personal relations with young students, not engagement with their developing intellects, that was of prime importance, and I had little talent in that area. A more honest assessment might be my realization that teaching was going to be really hard work, and that maybe I should go for an easier life.  In any case, I resolved to apply to graduate school and took a temporary technician job with Martin Nemer at the Institute for Cancer Research (now the Fox Chase Cancer Center) in Philadelphia. Nothing could have locked in my new career choice more effectively than my brief experience there. Every afternoon there was a tea at which the whole institute, including many eminent scientists, were invited to socialize. As I remember, one of the regular participants, a man who made time for lowly techs like me, was [Irwin Rose](https://www.nobelprize.org/prizes/chemistry/2004/rose/facts/) (he was awarded the Nobel Prize in Chemistry forty years later for the discovery of ubiquitin). This was heady stuff for a beginner! **Graduate school at Harvard Medical School and the Massachusetts General Hospital** In Fall 1964, I was admitted, along with about a dozen other students, to a PhD program at Harvard Medical School called (I think) the Biomedical Sciences (BMS) program. During our first year, we took an integrated basic medical sciences curriculum taught by a large team of professors, after which we would choose a dissertation mentor in any of a large selection of departments. BMS was a concentrated and remarkably comprehensive survey of modern biomedical research by master teachers. We students formed our own little society of friends, though in keeping with the army brat pattern of friendship I mentioned earlier I haven’t kept up with them.  I chose a cellular immunologist in the Department of Bacteriology and Immunology, Hugh McDevitt, as my dissertation advisor. I already had a project in mind: to use the “Dintzis experiment” that I had learned about in Santer’s class at Haverford (see above) to determine whether or not the variable (V) and constant (C) parts of an immunoglobulin polypeptide, which had been defined by the first immunoglobulin amino acid sequence results (Hilschmann and Craig, 1965), were synthesized as separate polypeptide chains that were subsequently joined together. (We now know, but didn’t then, that the V and C portions are joined in multiple steps at the chromosomal DNA level.) I didn’t get to embark on this project, however, since McDevitt was recruited to Stanford and I switched to the lab of Ed Haber (already mentioned above) at the Massachusetts General Hospital (MGH). “My” Dintzis experiment was published two years later by other immunologists, who showed that the V and C portions are synthesized as a single polypeptide (Knopf et al., 1967; Lennox et al., 1967). I wasn’t disappointed to be “scooped”; indeed, that established molecular immunologists would consider “my” experiment worth doing seemed to be a personal validation rather than a setback.  Haber, at age 34, was already chief of the Cardiac Unit at MGH (Editors, 1998) and an accomplished protein chemist. He had been born February 1, 1932, to a German Jewish family who escaped to Palestine in 1933 and moved to the U.S. in 1939. He had done his postdoc in the lab of [Chris Anfinsen](https://www.nobelprize.org/prizes/chemistry/1972/anfinsen/facts/) at the National Institutes of Health. Anfinsen was to receive the Nobel Prize in Chemistry in 1972 for showing that a protein’s primary structure (i.e., the amino acid sequence of its polypeptide) sufficed to specify its final three-dimensional (“folded”) structure, thus its biological activity. Haber had used Anfinsen’s methods to demonstrate the same principle in the case of antibodies (Haber, 1964). This put paid to the template theory (to be explained below) that had been the target of my failed senior tutorial project at Haverford.  Haber had a dreary basement lab in a dreary wing of the dreary (but storied) MGH. Sequencing immunoglobulins was a core experimental approach to molecular immunology at the time, and the Edman degradation was the flagship of sequencing technology. Machines called “sequenators” for automating the Edman degradation had been recently introduced. My plan was to develop a new kind of sequenator in which the protein to be sequenced would be exposed to the Edman reagents in the gas phase rather than dissolved in liquids. This innovation could have the important benefit of applying to small peptides that would be washed away by liquids. I had spectacular success at the beginning, but those successes could never be repeated, and the project was ultimately abandoned without any resulting publications.  The foregoing experimental failure wasn’t the end of my graduate career, for I had meantime been engaged in a theoretical study of the problem of “antibody diversity” (as we called it at the time). This problem arose in its starkest form from the work of [Karl Landsteiner](https://www.nobelprize.org/prizes/medicine/1930/landsteiner/facts/), who had shown in the early 20th century that animals were able to mount a specific antibody response to almost any synthetic organic chemical he tested (Landsteiner, 1962). “It is not reasonable that an animal produces predetermined antibodies against thousands of such synthetic substances,” Fritz Breinl and Felix Haurowitz had argued (Breinl and Haurowitz, 1930).  Breinl and Haurowitz’s solution to this conundrum, as elaborated later by [Linus Pauling](https://www.nobelprize.org/prizes/chemistry/1954/pauling/facts/) (Pauling, 1940), was *the template theory.* They proposed that a very limited number of generic antibody polypeptides could suffice for an unlimited number of different antibodies with distinct antigen-binding specificities. Antigen specificity arose (so went the theory) when these generic polypeptides first wrapped around the antigen as a template, then disengaged from the template as an antibody molecule with an antigen-specific binding site molded into its three-dimensional architecture. Antigen templates thus acted catalytically, each template molecule serving to stamp antigen-specificity into many antibody molecules. It’s the template theory that had been the target of my senior tutorial project at Haverford, and that Haber’s work had refuted (Haber, 1964). The great diversity of antibodies was now understood to reflect a corresponding great diversity of antibody-coding genes. And as the amino acid sequences of antibodies accumulated with increasing use of sequenators and other technical advances, it was clear that that diversity was concentrated in the V regions of their polypeptide chains.  My theoretical study focused on the evolution of V genes (the genes encoding V regions). Walter Fitch at the University of Wisconsin and I applied the computerized phylogenetic reconstruction algorithms he and Emanuel Margoliash had just developed (Fitch and Margoliash, 1967) to the increasing number of V region amino acid sequences that were becoming available. This is was the study at the core of my dissertation and a review by me, Leroy Hood, and Fitch (Smith et al., 1971). Two years later I extended these studies in a full-length monograph (Smith, 1973c). I used these analyses in a critical assessment of two competing explanations of V gene diversity: the somatic mutation and germline theories.  The somatic mutation theory supposed that the observed diversity of V region sequences arises through somatic mutation in V genes in individual B-cell clones during the lifetime of each individual animal or person (B cells are the lymphocytes that produce antibodies). According to this theory, the number of V region sequences far exceeds the number of germline V genes. The germline theory, in contrast, supposes that each possible V region an individual can express is directly encoded by a corresponding germline V gene. This theory required a large, though not infinite, number of V genes to account for the large number of different V region sequences. I argued that the evidence favored the germline theory, though not conclusively. Many predictions of, and arguments for, that theory have been confirmed by subsequent findings; in particular, there are indeed large numbers of V genes for some families of V regions. Nevertheless, the central claim of the germline theory has turned out to be completely wrong: extensive somatic mutation in individual B-cell clones is clearly the fundamental explanation for V region diversity.  My dissertation was finished in December 1969 with some help from my father, who used the drafting set he still had from West Point to draw several of the most complicated figures. The dissertation posed a problem for my committee: it reported no experimental results, my attempt at developing a new sequenator having failed. This was, to say the least, unusual, but I passed anyway, and got my degree at the beginning of 1970. Not for the last time in my career did I receive special treatment.  Haber wouldn’t put his name on any of these publications, but he was a very engaged mentor. In particular, he took care that I had a chance to interact with many other leaders in molecular immunology, an advantage that greatly enhanced my career. **War resistance** Between the Gulf of Tonkin resolution in August 1964 and the March on the Pentagon in October 1967, I became progressively more politically active against the war in Vietnam. Although I was too old for the military draft, I turned in my draft card to my local Selective Service board as a symbolic act of resistance. As was usual in those days, I was promptly drafted into the army, but refused induction very publicly in the presence of dozens of inductees in early 1968. This could well have resulted in a prison sentence, which would undoubtedly have greatly altered the course of my life. But as it turned out, I wasn’t imprisoned and suffered no other consequence of my act. The reason may be that the military was coming to realize that its policy of drafting resisters was backfiring. Refusing the draft was a highly visible form of resistance that was being effectively used to recruit young people to the anti-war cause. **Postdoc with Oliver Smithies at the University of Wisconsin** I first encountered [Oliver Smithies](https://www.nobelprize.org/prizes/medicine/2007/smithies/facts/) at the 1967 Cold Spring Harbor Symposium on Antibodies, a landmark meeting at which major issues that were engaging immunologists at the time, including theories of antibody diversity, were vigorously discussed. Smithies presented a creative new theory of diversity, in which V-gene diversity was generated by extensive somatic recombination rather than somatic mutation. Francis Crick was effusive about Smithies’s hypothesis; he castigated the audience for not hailing the solution to the puzzle they had been seeking so long. A less modest person might have been tempted to gloat in triumph at praise from such high quarter. Not Smithies. He responded respectfully to the several participants who objected strenuously to his theory. I was more impressed with his integrity than Crick was with his theory.  I came to Smithies’s lab at the beginning of 1970. My main experimental project there (and completed at the University of Missouri) was sequencing the immunoglobulin light chains from a mouse myeloma tumor that was peculiar in secreting two light chains (Rose et al., 1977; Smith, 1973a, 1978b). One of them consisted of a signal sequence joined directly to the C region. We interpreted this as aberrant expression of an unjoined C gene, but the two light chains were later shown to be alternative splicing products of the primary RNA transcript of a single aberrantly joined light chain locus (Sikder et al., 1985).  Smithies was the one who in 1955 had introduced gel electrophoresis into the armamentarium of biological research in the form of starch gel electrophoresis, which was a regular component of our work in his lab. I’m one of the few living scientists who remembers the art of pouring, loading, running, and staining a starch gel. I say “art” advisedly, because success required mastery of skills that were exceedingly difficult to systematize in a manual: recognizing exactly the right “blurbling” sound as you boiled up the starch in a flask over an open flame, slapping a spatula just so onto the petroleum jelly covering the gel in order to peel it off in one piece after the run was over, etc. When Smithies turned his attention to DNA in collaboration with Fred Blattner toward the end of my postdoc, he devised an absolutely characteristic style of agarose gel electrophoresis. The molten gel was poured directly onto the benchtop, with a comb held in place by lumps of clay. After the DNA samples were loaded into the wells, warm petroleum jelly was poured over the surface to prevent evaporation (as in starch gel electrophoresis), and electrode trays were connected to the ends with paper wicks.  After the run, the petroleum jelly was removed with a spatula (again, as for starch gels) and the gel was lifted off the benchtop and stained with ethidium bromide – the final step being the only one that would be recognizable to today’s practitioners. Smithies was indeed an inveterate improviser. Otto Hiller, who made starch gel electrophoresis apparatuses in his shop in Madison, was a fellow tinkerer and Smithies’s regular Saturday afternoon companion, as he explains in his Nobel biography (Smithies, 2007). I admired but never emulated the improvisational style I witnessed in his lab.  The Genetics Building in Madison, where Smithies’s lab resided, was also home to two doyens of population genetics: Sewall Wright (December 21, 1889 to March 3, 1988), one of the founders of the field; and James Crow (January 18, 1916 to January 4, 2012), a master teacher and author of “Crow’s Notes,” a concise paperback guide for undergraduate genetics students, as well as coauthor with Motoo Kimura of the best-selling population genetics text *An Introduction to Population Genetics Theory.* Crow’s influence added a new dimension to my theoretical studies, which were continuing in Smithies’s lab. The germline theory of antibody diversity that I favored presumed that multiple germline V genes formed long tandem arrays in chromosomal DNA, as was already known for ribosomal RNA genes. Such arrays would be subject to occasional unequal crossover events in the germline, leading to repeated small contractions and expansions of the arrays over evolutionary time. Tandem genes subject to these expansions and contractions could be looked on as a population subject to many of the same principles of population genetics as a population of interbreeding organisms. This idea was included in my monograph on antibodies (Smith, 1973c) and presented at the 1973 Cold Spring Harbor Symposium (Smith, 1973b). My first publication from the University of Missouri was a lead article in Science arguing that any long stretch of chromosomal DNA not subject to natural selection would tend to turn into a tandem array, thus explaining the abundance of repetitive DNA with no obvious function in the genomes of many organisms (Smith, 1976). **University of Missouri and Columbia** In 1975 I was recruited to the newly-established Division of Biological Sciences at “Mizzou” by Abe Eisenstark, its first director. Eisenstark’s remit was a little like Loewy’s at Haverford: to modernize biological research and teaching on campus. I became part of a small coterie of young cell and molecular biologists who together constituted a favored establishment that was resented by the “Old Turks,” my name for a few older faculty who (with some justification) felt devalued in Eisenstark’s *Risorgimento*.  In my first few years at Mizzou I continued my experimental and theoretical study of antibody diversity, including the amino acid sequencing project I described above. My first doctoral student was Jamie Scott, who undertook to count the number of V genes in the mouse l family. A few dozen different V region sequences in this family had been published, but their diversity was severely limited. According to the somatic mutation theory, these V regions could have arisen from only two V genes; the germline theory, in contrast, would require dozens. Counting the mouse l V genes thus seemed a promising way to decide definitively between the somatic mutation and germline theories. Using two independent approaches, high-precision mathematical analysis of hybridization kinetics and denaturing gradient gel electrophoresis (Fischer and Lerman, 1980), Scott demonstrated that two genes accounted for all the V regions in the family, thus refuting the germline theory in this case (Scott et al., 1985). Her trip to Leonard Lerman’s lab in Albany to learn denaturing gradient gel electrophoresis, a lead pig with radioactive hybridization probe in her luggage, and the exciting results that ensued, are still fond memories. Scott’s article was never accepted for publication except as an abstract. One reason for this injustice is that the reviewers and editors believed, without justification, that the problem of antibody diversity had already been settled in favor of somatic mutation – an example of the impatient inattention to detail that is an unpleasant side-effect of the hurried pace of modern science. Scott returned to my lab as a postdoc after medical school, and played a key role in the development of that technology (Smith, 2018). She and her husband Felix Breden have been friends of my family ever since.  A few years after coming to Mizzou, I embarked on an ill-starred developmental biology project with the roundworm *Caenorhabditis elegans*, a model organism that my Biological Sciences colleague Don Riddle had brought from [Sydney Brenner](https://www.nobelprize.org/prizes/medicine/2002/brenner/facts/)’s lab in Cambridge, England. My interest in filamentous phage biology arose from this project (Bauer and Smith, 1988; Crissman and Smith, 1984; Nelson et al., 1981; Smith, 1988; Zacher et al., 1980).  In August 1983, my wife Margie Sable started graduate school in the School of Public Health at the University of North Carolina. This was an opportunity for me to continue research in a prominent filamentous phage lab, Bob Webster’s at Duke University, only 10 miles away from Margie’s school. The first phage display experiment (Smith, 1985) was started in Bob’s lab at the end of my sabbatical year there.  The contribution of four coworkers to phage display was highlighted in my [Nobel Prize lecture](https://www.nobelprize.org/prizes/chemistry/2018/smith/lecture/) (Smith, 2018), and won’t be repeated here: Steve Parmley, Robert Davis, Jamie Scott (mentioned above), and Jinan Yu. But a number of other coworkers have undertaken phage-display projects that lay outside the scope of the lecture. Prominent among them were Valery Petrenko and Leslie Matthews.  Petrenko arrived as a visiting professor from Russia in 1993. The late professor Richard Perham of Cambridge University had run across his phage-display work in Novosibirsk (Minenkova et al., 1993a; Petrenko et al., 1991), and mediated an invitation to a Banbury Center conference in April 1992 (Minenkova et al., 1993b). Petrenko introduced an entirely new line of research in my lab: fashioning innovative “new materials” by engineering the major coat protein of filamentous virions (Petrenko and Smith, 2000; Petrenko et al., 1996; Petrenko et al., 2002); he has continued this research after moving to Auburn University as a professor in 2000. Petrenko and I have also collaborated on reviews and more conventional phage-display projects (Kouzmitcheva et al., 2001; Petrenko and Smith, 2005; Smith and Petrenko, 1997; Smith et al., 1998). Petrenko and his wife Natasha Petrenko have become friends of my family.  Leslie Matthews came to the lab as a doctoral student and stayed on as a postdoc. She and another postdoc, Melissa Nevils, were the lead scientists in the “epitope discovery” (ED) project that was my lab’s main research initiative for about five years starting in 1999. ED’s goal was to use phage display as a new gateway to discovery of promising synthetic vaccine candidates, especially for difficult diseases like malaria. After an auspicious start (Matthews et al., 2002), the project suffered a severe setback when Matthews’s and Nevils’s demonstration project with a malaria-like model, babesiosis of cattle, was not accepted for publication. Despite multiple attempts, I was unable to secure funding for applying the ED concept to human malaria.  My closest colleague in the Division of Biological Sciences has been Miriam Golomb. She is a gifted science writer who was one of the chief architects of the university’s Campus Writing Program – an endeavor to which she recruited Matthews, also a gifted writer. I myself taught many writing intensive courses. Golomb embraces an inspiring approach to undergraduate teaching that emphasizes strong student engagement, including regular extended conferences with students and lab courses with hands-on experiments that she’s constantly updating – recently adding a yeast CRISPR module, for instance.  For the final six years of my university career, my chief endeavor was a teaching initiative called Mathematics in Life Sciences (MLS), directed by math professor Dix Pettey. The program included a campus learning community called a freshman interest group for which I was faculty co-facilitator; and an alternative beginning biology lab that integrated elementary mathematics more intimately into the curriculum. Golomb and I developed the first MLS lab in Fall 2009, and I took charge of the Fall lab for the succeeding five years. The program was funded by the National Science Foundation for its first five years. Two of its lab modules have been published in a biology education journal (Smith, 2017; Smith et al., 2015).  I have had a long-standing philosophical and technical interest in probability theory as the fundamental guidebook for making rational scientific judgments about the world in light of the available evidence. This viewpoint goes by the name Bayesian statistics or philosophy because of the central role of Bayes’s theorem as the rule for updating our assessment of contending theories in the light of new evidence. Bayesian principles were included in a presentation I gave at a university genetics symposium in 1978 (Smith, 1978a), and in an article I co-authored with Hans Lehrach and his coworkers in Germany using Bitnet to exchange drafts (Michiels et al., 1987). I continue to talk and write informally about the subject.  My brother Mark and sister-in-law Lois Honeycutt also live in Columbia, where they’re history professors at the University of Missouri. My wife Margie was director of the School of Social Work until her retirement in 2016. Nepotism evidently isn’t a thing of the past at Mizzou.  Margie is Jewish, and since our marriage (next section) I’ve become increasingly engaged in Jewish culture. I’m not technically a Jew, however; that’s because for a non-believer like me, religious conversion would be dishonest. As I learned more and more about Zionism, I came to understand it as a great ongoing injustice against the Palestinian people, as well as a threat to Israeli Jews and to the wider Jewish society that I value as one of my most important adoptive communities. I helped organize Mid-Missourians for Justice in Palestine, a community organization that supports the global boycott, divestment, and sanctions (BDS) campaign against Israel until it ends its regime of subjugation and dispossession. **Tanksuit very much** I met Margie in October 1979 during a faculty/staff swim at the university’s natatorium. She was wearing a green tank suit, which lives on in our basement as an affectionate memento of our encounter. Soon after our romance began, she sent me a card with the title of this section as the printed message inside. We married October 10, 1981.  Our older son Alex Sable-Smith was born July 15, 1985 – the result of many plane trips between Columbia and Chapel Hill, where Margie had stayed on to continue her doctorate in public health after my sabbatical leave ended. I was the only solo male student in a child-birthing class in Columbia. Alex’s birth was a personal watershed, as fatherhood and family life in general grew to occupy at least as central a place in life as science. Alex is now a family physician, working in hospice and palliative medicine at the Veterans Administration Hospital in Palo Alto, California. Our younger son Bram Sable-Smith was born April 1, 1988. He’s now a freelance journalist in Madison, Wisconsin, where he lives with his wife Emma Brown. |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** | [GS]  Adam Smith: May I speak to George P Smith please?  GS: Yes, yes, this is he.  AS: Oh hello, my name is Adam Smith. I’m calling from Nobelprize.org, the official website of the Nobel Prize in Stockholm. Well, many congratulations on the award of the prize.  GS: Thank you very much.  AS: It’s, what, coming up to 5am there. Did the call wake you?  GS: No, actually had just woken up. You know, elderly people have a difficult time sleeping sometimes so I got up really early at about 4.  AS: What was your first reaction on hearing the news?  GS: Great surprise. Actually I thought it was one of the, sort of, numerous jokes ‘Call coming in from Stockholm’ [Laughs] which is kind of like a mean … that’s really what I kind of thought it was, but there was so much static on the line I knew it had to be real.  AS: We’re going back to 1985 when you had this idea to get viruses that infect bacteria to display peptides for you. Did the idea come to you suddenly or was it a long process?  GS: Oh no, no, no, certainly not suddenly, no. It was an idea from … with many sources because I had all these streams that were very much in my background at the time. So it was definitely not something that just popped into my head.  AS: But so much a case of being the right person in the right place at the right time.  GS: It is very much the right person and the right time. I mean I was trained in immunology, but I also knew a lot about this phage, and classical, you know, molecular biology, that’s what my basic training was in college.  AS: You never know which pieces of information are going to be useful and what you’re going to need to combine to make something happen, I suppose.  GS: Well I think that’s very, very true. It’s like evolution, you really don’t know which mutation is going to be the one that, you know, that flourishes.  AS: Were you surprised by the rapidity with which it was all taken up?  GS: You know, it was, as I say, all those precedents that were in the air, so no I wasn’t that surprised actually. And I certainly wasn’t surprised … I mean, another … I’m sharing my half, our half with Greg Winter, so he came out of this Cambridge group that had been, as they were calling, a cloning … cloning the immune system at the time. So that was very similar, very allied, line of reasoning, line of research. And I was very aware of that too, so I actually wasn’t surprised that people would catch onto it because it was something that was … it was a way of thinking very much in the air at the time.  AS: And did you dream that it would lead to, for instance, the therapeutic antibodies that came out of Winter’s work?  GS: Well, that’s a good question. I don’t think that, certainly in ’85, that I thought in those terms, although I was very much interested in antibodies and very much aware of the work in the Cambridge group. But the first publication of single-chain antibodies … single-chain antibodies are sort of paired down antibodies that have the central feature of binding specifically to an antigen that are missing a whole bunch of other things and are single polypeptide chains. At that point it became quite obvious that, well I won’t say quite obvious, but it seemed very plausible that not just small peptides but larger folded domains like single-chain antibodies could be displayed on phage just like small peptides. And of course the Cambridge group realised that at the same time, and independently, so …  AS: What an exciting journey to be part of.  GS: Well, I guess it seemed so at the time, I mean, you know … so many years later it seems a little bit old hat.  AS: And I know you haven’t had long for it to sink in, but what do you think the prize means to you?  GS: You mean, what does it mean personally?  AS: Yeah.  GS: I don’t know. That’s a really good question. I have no idea! I’m completely unprepared for this. I mean I’ve been retired for three years, and I have very different interests now. And so that remains a question to be answered. I don’t know what this will mean for my life.  AS: Well you’ll have plenty of time to find out, and plenty of time to mull over it before you come to Stockholm in December.  GS: Well apparently I have, you know, like a few minutes before reporters are going to be ringing the phone off the hook.  AS: I’m afraid I think the day is going to take a very different turn, so …  GS: [Laughs]  AS: It’s been a huge pleasure speaking to you. Once again, many, many congratulations.  GS: OK, bye. |
| **Interview** |  |
| Q3 | Where do you get your passion for science? |
|  | George P. Smith: Originally I would say that I had a passion for nature, especially animals. Apparently I broke my parents in going to the Bronx Zoo and stood for like half an hour watching alligators and crocodiles that never moved and they needed to have a lot of patience with me. In 1949, when I was eight years old, we went on a vacation in Maine in the northeast of the United States. The place was like alive with snakes and I caught my first snake, a green snake, and paraded into the living room where my mother was entertaining a tea party of the very sort of like proper ladies of the neighbourhood who appropriately screeched and so on. I became very interested in snakes at that point. In fact, our family lived in Japan during the Korean War from 1952 to 1954. I and a friend, whose name I’ve long since forgotten, were both lovers of snakes and there were so many wonderful snakes in Japan at the time. So I thought I was going to be a herpetologist when I grew up and I would have, I think, except that my college, Haverford College, had only three biology professors and all of them were cellular molecular biologists and no-one was, you know, anything like a herpetologist so actually, professionally I abandoned my herpetology and I became a molecular biologist. |
| Q12 | How did your family influence your decision in science? |
|  | George P. Smith: Oh, my parents are relevant in many ways. Scientifically I would say my father was very influential because he was an army officer. He was in the branch we call ordnance which is like supplies. It’s kind of like the business part of the army, but he was curious about everything. For example when we lived in Japan, every weekend he would be taking us on an adventure in the neighbourhood out off the army base where we lived and using sign language and expressions and so on to converse with a farmer like a peanut farmer or something like that. We’d so many times be invited for tea inside someone’s house. He was just extremely outgoing and curious about everything and especially about …  He went to West Point which is our military academy and that’s kind of like a technical education, it’s like an engineering education. And he was particularly interested in science engineering, things like that. I think that that was very influential in my upbringing as far as my science upbringing and being something that really encouraged that kind of curiosity and interest in how the world works, like how things work. That was one of his big things he would understand how, you know, gadgets worked and I think I inherited, or not genetically, but I was encouraged to have that kind of habit of mine from my father. So that was certainly a big part. Also my father was in the army. As I became politically active or politically aware in the 1960s, the war in Vietnam was a big part and my parents, despite the fact that they were an army family, turned against the war in Vietnam and this is a very, I think, perhaps unusual upbringing and in the army so that had quite a bit of influence on me. |
| Q3 | What do you enjoy most about being a scientist? |
|  | George P. Smith: You know, if I had to say the thing that has given me most pleasure over the years, is kind of like workmanship in the laboratory, like gel electrophoresis. Actually my postdoctoral advisor who was also a Nobel laureate, Oliver Smithies, invented gel electrophoresis as well. Any molecular biologist uses it all the time so, but to me designing exactly how you would load the samples, in what order, trying to design it so that the results would be really striking, that was really important to me. I took such great pleasure in the little tiny triumphs of two hours of work. I would say that was really important to me. Of course it was very exciting when sometimes I might have some insight that I thought was a breakthrough or thought it was an ‘aha moment’, those were very exciting too. Those were rare and the delight in workmanship in the laboratory was a constant pleasure to me, a constant scientific pleasure to me. |
| Q5 | Is it important for scientists to have mentors? |
|  | George P. Smith: I think it’s very important in many ways. For one thing mentors help students, and early career scientists make their thoughts sharper, more concrete. They can also be a force of conservatism about their science so they also have to learn from their mentors, not to worship their mentors and not to pay attention, you know, not to think that their mentors’ word is gospel because sometimes the mentors are going to give them advice that’d be probably in the long run better to ignore. I think that’s something that, it’s very important for a mentor to get across to an early career scientist, a student, a postdoc etc. that you know you should … A scientist needs to be skeptical about everything. That I think is a very important lesson for scientists to learn. They have to be skeptical about everything, not to the point that it immobilizes them, but to a point where everything has to be looked on as provisional. Everything in sciences has to be looked on as provisional. I think this is a habit of thought that is really important in science.  A mentor also of course serves as a role model. It would be good to be a mentor that upholds standards of decent behaviour and morality and the conduct of science. I mean that for example … Don’t be a role model that’s like a cut-throat that cuts down in competitors /—/ looks on science as fundamentally a competitive enterprise because I don’t think it is. I mean science flourishes by a community of scientists, communicating their ideas with each other. Fundamentally, that’s the nourishment of science and I think that mentors owe it to their protégés to value this above all else in science. So how about me, am I a good role model? Well, you know I’d said that I think that a scientist need to foster the attitude of being skeptical about everything, so I think everyone should be skeptical about his or her own behaviour. So I think that maybe I’m a harsh critic of myself and I don’t value … valorise my own behaviour as a role model. I aspire to be a good role model but no one really reaches his or her aspirations. |
| Q9 | How did you discover you were awarded the Nobel Prize? |
|  | George P. Smith: I heard the news about the prize, well, it came at 4:30 in the morning in Columbia Missouri where we live and actually I have sort of a difficulty sleeping through the night that many old people do have and so I actually had come downstairs around ten after four to start the coffee for the morning and the phone rang and my wife answered it upstairs in the bedroom and apparently the call was, well, stand by for a very important call from Stockholm at which point the line went dead and then the call came through again. She answered it again and the same message and she called downstairs: “This is a call from Stockholm, I think you’d better get it!” So I did, that’s how I learned about it.  When I get this call I was very surprised. I do want to say that I knew that I was one of the hundreds of people that was on the radar of the Chemistry Committee and that’s because I was invited to a conference in the hundredth year anniversary of the Chemistry Prize in 2001, to a conference in honor of that anniversary. There were very few participants in the conference, maybe 20 or 30 or something like that, and all of us were invited to the ceremony and to the banquet afterwards. I kind of know what the ceremony is going to be like, although not from the point of view of an actual laureate. But that also alerted me that it was pretty likely that I was on the radar of the Chemistry Committee. It did come as a surprise 17 years later because I thought the time had long since passed. It wasn’t an, you know, a bolt out of the blue but is was a big surprise because I had long since thought that the time had passed. |
| Q9 | What does it mean to receive a Nobel Prize? |
|  | George P. Smith: To be a prize winner when you’re retired, because I retired from my university three years ago and I’m not doing much science anymore, so it is something to look back with, with pleasure and pride that this award has come. I’m going say in my lecture that I feel that I’m taking it, I’m accepting the prize as a representative of the science community that I belong to because many people in this community could equally get this prize but it certainly is an honour that I look upon with pleasure. Also, I think that my family looks on it with even more pleasure than I do and I should add that this is the first Nobel Prize for my university, a public university, the University of Missouri, and it is a great honour to my university. I think that all three of those are things that give me pleasure, my own pleasure, and the vicarious pleasure on the part of my family and my university and my science community. |
| Q10 | What is needed to create a supportive environment for research? |
|  | George P. Smith: In countless ways the science community is nurtured … it depends for its support on the wider community of society as a whole. It depends crucially of course on the schools that educate our children, some of whom will eventually end up in as part of the professional scientific community, their teachers. It depends crucially on our colleges and universities, especially the public colleges and universities including my own university, the University of Missouri, where children get their further education and that support the local science communities of which I was a member at the University of Missouri for 40 years. These are very important and also science, the well-being of science, depends critically on institution, public institutions, like in the United States, the National Science Foundation, the National Institutes of Health which supported my research and similar institutions in other countries, for example the Medical Research Council in the UK. Our science communities depend on public institutions supported by the people as a whole for critical financial support and for being … If we’re persuading people as a whole, that this is really an important part of our culture and the economy. That’s what we absolutely depend on, that kind of broad society support and university support is part of that. |
| Q1 | What skills do young scientists need? |
|  | George P. Smith: It’s a perpetual problem in science education, really in education in general, but specifically in science education is: What do we teach our young people to try to ensure as well as we can, that they could be successful in science afterwards? Do we teach them the specific technical skills that we ourselves depended on? That’s a question that teachers often have to grapple with and there are two sides of that, one thing is, I think, that students really need to understand specifically and concretely: What physical things support our theories about nature? What results? What concrete results are behind what we think of as our knowledge about nature so … The students really should learn about some of the nitty-gritty of experimental science, how we carry out experiments and how we look at the data and how we deal with the fact that inevitably data are messy and it’s not so clear-cut as if it were in a textbook. We have to, I think, educate students to be sophisticated about the relationship between physical findings and the interpretations that we give about those physical findings. I think that’s really critical.  I think also that students should learn about the fundamental ideas, the fundamental theories, theoretical understanding that underlies the science that they’re learning. They need to be educated in the science culture in which they are, in which they are learning and as I’ve tried to say before, also they need to learn to be skeptical about that culture, that it is not the last word and nothing in science is the last word about anything. They need to be skeptical about that culture as well. These are all things that I think a teacher has a sacred duty to pass on, to help to pass on to students as well as he or she can do it. |
| Q15 | What are your favourite applications of your research? |
|  | George P. Smith: I’m often asked about the applications of my work and what their meaning is and my co-winner Greg Winter went on to use the phage display idea in very imaginative ways, not just him but of course his whole group and other groups that are similar groups carrying out similar research, use this in very imaginative ways that have turned out to be important for developing new medicines. A good example and a commonly cited example in the context of this prize is the Humira, which is a medicine developed partly using phage display technology, not buy me, but … that’s an example of something that has come from this.  I’m not sure, that I would say, that I myself, am most proud of that. To me a phage display, the technology that I developed, I saw that my vision at the time, as it matured over a few years, was that it would make a technologically very productive technology available broadly and cheaply and without a very strong technical background required, without the high demands, technological demands, available widely to researchers all over the world. I think that it is an aspiration that has been partly met because certainly many people have used phage display in ordinary laboratories, not in heavily funded industry laboratories or academic laboratories but in very ordinary laboratories as my laboratory was itself. It didn’t have a lot of money to spare but this was a technology that could be carried out by such a laboratory. That was a big aspiration of mine. I think it is one that has been partly fulfilled. |
| Q8 | What do you do in your free time? |
|  | George P. Smith: I mentioned before that I’ve been retired for three years and I haven’t abandoned science altogether, I still go to lab meetings for a couple of collaborators at the University every week or most weeks. And I go to many of the seminars in my former department which wasn’t chemistry by the way. It was biology, I’m a biologist. It’s not that I’ve abandoned science altogether, but I also have continued a long-standing interest in my life, in I would say social justice and human rights. I would say that it started in the 1960s when I was a war resister during the Vietnam War and has continued on and off since then, so that’s become a very important part of my life, human rights and social justice in the United States for example. A major effort that my wife Margie Sable and I are involved in is the fight for a just health care system in our country, one that is universally available to all citizens and that does not bankrupt people that happen to get sick. So that would be an iconic social justice issue and that kind of issue is what engages me more now in my retirement life. |
| Q9 | How does it feel to be a biologist who has been awarded the Nobel Prize in Chemistry? |
|  | George P. Smith: It would be funny to me, except that I’ve known many Nobel Laureates and I know about many of the prizes. I told you that I was at the ceremony in 2001. There was no Nobel Prize in biology, yet clearly biology is an iconic scientific enterprise and especially ever since Darwin really, it is a landmark scientific enterprise in the 20th century right from the beginning of the 20th century when Darwin was fully accepted by the biological community. And since chemistry is deeply involved in biology, it is pretty natural that many of the … that the prizes in chemistry that involved biological subjects are awarded to people who would identify themselves as biologists and also that really applies to physics as well because several of the physics prizes, I think, owe their salience to the fact they have led to applications in biological sciences. So yes, I think that it’s pretty natural that prizes go to biologists from both chemistry, especially chemistry, but also physics, not just to make up, but to the fact that there’s no biology prize and also Barbara McClintock who was a maize geneticist got the prize in physiology and medicine and who could be more of a biologist than Barbara McClintock? So the prize don’t fall into the neat categories that Nobel envisioned in his will and I would imagine that Alfred Nobel would be very pleased that that’s the case. |
| Q4 | Can you summarise your Nobel Prize awarded discovery in 30 seconds? |
|  | George P. Smith: A phage is a virus that infects bacteria and grows to huge numbers and can be grown to huge numbers very cheaply, so it is a very convenient laboratory organism for experimenters to work with. Phage display tries to harness this natural device for searching through huge libraries of structures, tens of billions of structures, for structures that have a particular activity that the experimenter wants for some experimental end. As for example something that would … some structure that would bind to a receptor involved in cancer or autoimmune disease or something like that and might be used as an intervention for that disease. So it’s a technologically pretty simple and yet powerful way of searching through enormous collections of structures, for very rare structures, that have a desired activity. |

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| **Chemistry\_2024-2000** | |
| **ID** | 0318 |
| **Biographical** | **S****ummary**  I was born (14 April 1951) in Leicester, England but spent most of my childhood in the Gold Coast (later Ghana). The family returned to England in 1964, settling in Newcastle-upon-Tyne. There I went to the Royal Grammar School, which developed my interests in chemistry and biology and set me on a path to Cambridge University (Trinity College), a BA in Natural Sciences (1970–1973) and PhD in protein chemistry (1973–1976).  Most of my research career (1973–2012) was based at the Medical Research Council’s (MRC) Laboratory of Molecular Biology (LMB), Cambridge. I undertook my PhD and postdoctoral work at the LMB. I was appointed to the MRC’s scientific staff at the LMB in 1981, and became Head of the Division of Protein and Nucleic Acid Chemistry (1994–2008) and Deputy Director of the LMB (2006–2011). I was also Deputy Director of the MRC Centre for Protein Engineering (1990–2010), and held Fellowships at Trinity College, Cambridge (1976–1980; 1990–2012; 2019–). I was appointed Master of Trinity from 2012–2019.  My research developed from my interests in the chemistry and structure of proteins and nucleic acids. After a period (1973–1982) sequencing proteins and nucleic acids, I developed genetic engineering as a tool to analyse protein functions, applying it to a study of the binding and catalytic mechanism of an enzyme (1982–1988). I also developed genetic engineering strategies for the design (1984–1988) and evolution (1988– 1997) of antibody pharmaceuticals suitable for treatment of cancer and immune disorders, helping to spearhead the development of antibodies as a new class of powerful biologics. Subsequently I have contributed to the development of bicyclic peptides and their conjugates as medicines. In the course of my academic research, I have worked with industry as a consultant, and also as a founder and director of two start-up companies based on antibodies, Cambridge Antibody Technology Ltd (founded in 1989, listed on the London Stock Exchange in 1997, sold to AstraZeneca in 2006), Domantis Ltd (founded in 2000, sold to GlaxoSmithKlein in 2007), and one start-up company based on peptides, Bicycle Therapeutics Ltd (founded in 2009) and listed on Nasdaq in 2019. **Enzymes** I started my PhD studies at the MRC Laboratory of Molecular Biology, Cambridge (LMB) in the autumn of 1973, funded by an MRC studentship and supervised by Brian Hartley, a protein chemist. With LMB colleagues David Blow (protein crystallographer) and Alan Fersht (enzyme kineticist), Brian aimed to compare the amino acid sequences, crystallographic structures and catalytic mechanisms of an ancient family of enzymes, the aminoacyl tRNA synthetases, and to gain insights into the early evolution of proteins. For my PhD, I was supposed to determine and compare the sequences of the tryptophanyl (TrpTS) and tyrosyl tRNA (TyrTS) synthetases by protein chemical methods, in the hope of identifying a sequence motif involved in catalysis. During my PhD studies, Brian was appointed to the Professorship of Biochemistry at Imperial College, and I had to follow him to London in the autumn of 1975 and help set up the protein chemical facilities. Nevertheless, I managed to complete the sequence of the TrpTS by the summer of 1976, the work forming the core of my Cambridge PhD thesis and a successful application for a Junior Research Fellowship at Trinity College.  In the meantime, David Blow had obtained good crystals of the TyrTS and needed the amino acid sequence to solve its three-dimensional structure. I postponed my return to Cambridge for over a year, trying to complete the sequence, but without success. Nevertheless, I was able to provide large segments of TyrTS sequence to David and to compare it with the TrpTS sequence. This revealed a cysteine (Cys 35) in the N-terminal region of both enzymes, a region identified by David as part of the tyrosyl adenylate binding site and hinting that Cys35 might have a role in catalysis.  After hearing a lecture from [Fred Sanger](https://www.nobelprize.org/prizes/chemistry/1958/sanger/facts/) on his new DNA sequencing methods, I concluded it would be easier to deduce the amino acid sequence of a protein from the DNA sequence of the corresponding gene than by direct chemical sequencing of the protein. Accordingly, I decided to learn DNA sequencing, and taking advantage of the salary provided by my Trinity Fellowship, applied to join Fred back at the LMB. In turn he passed on my application to his colleague George Brownlee.  George was planning to sequence the genome of influenza virus to help understand the mechanisms underlying influenza virus epidemics and pandemics. He had also taken on a PhD student, Stanley (Stan) Fields. We first had to grow the virus in eggs, isolate the viral RNA and then make cDNA copies. Instead of cloning each of the individual genome segments, we used an M13 shotgun strategy to sequence all the segments together, working closely with Fred’s group. During this work George was appointed to the Professorship of Chemical Pathology in Oxford, but Stan and I were allowed to stay at the LMB to complete the sequence. By 1981, we had completed the sequence, and Stan left for a postdoctoral position in the USA.  Although the sequence of the influenza genome was now available as a framework for further understanding of the epidemiology and biology of the virus, I couldn’t shake off a longing to return to a world of proteins, structure and mechanism. Now thoroughly familiar with recombinant DNA technology, I saw huge potential in the application of this technology to the structure-function studies of proteins. Although my Trinity salary expired in the autumn of 1981, Fred Sanger offered me a short-term MRC position to explore these ideas.  Fortunately, an opportunity soon materialised: a former colleague at Imperial College, David Barker, had cloned the gene for TyrTS, and joined me for a couple of months in Cambridge to learn DNA sequencing and to help sequence the gene. The gene was soon sequenced, and David Blow (now at Imperial College) provided with the sequence information necessary to complete his model of the three-dimensional structure of TyrTS. David Barker also sequenced the methionyl tRNA synthetase (MetTS), revealing a constellation of residues (Cys35…His 45… His 48) conserved with the TyrTS, again implicating Cys35 in the catalytic mechanism.  To obtain experimental evidence for the role of Cys35, I decided to mutate the Cys35 to a serine residue in the cloned TyrTS gene, and to express and characterise the mutant enzyme. For this purpose, I used oligonucleotide-directed mutagenesis, travelling to Michael Smith’s laboratory in Vancouver for six weeks to learn the latest methods from his postdoctoral worker Mark Zoller.  On my return from Canada, I collaborated with Alan Fersht (now at Imperial College) to understand the effects of this and other mutations on the enzyme mechanism. We confirmed that Cys35 was a key catalytic residue, but also found that the Ser35 enzyme was weakly active. In due course, by exploring other mutations around the active site, we established that the catalytic mechanism of the enzyme involved the preferential stabilisation of the tyrosyl adenylate transition state by multiple non-covalent bonds (including bonds from a mobile loop involving His 45).  As we improved our methods for site directed mutagenesis and synthesis of oligonucleotides, we started to undertake larger scale mapping projects. In particular we mapped the path of the tRNA across the enzyme, and later, by the same approach, mapped the binding site for complement C1q in antibodies. With site-directed mutagenesis established as a powerful analytical tool for studies of protein structure and function, I started on the next phase of my career. **Antibodies** In October 1983 Fred Sanger retired and [César Milstein](https://www.nobelprize.org/prizes/medicine/1984/milstein/facts/) took over as Head of Division. César’s passion was antibodies – particularly the mechanisms underpinning their diversity. He agreed to my tenure but suggested that I use site directed mutagenesis to study the structure and function of antibodies. In January 1984, I was attacked on the way to work, and my shoulder dislocated, leaving my right arm temporarily paralysed. No longer able to work at the bench, and as a distraction from the pain caused by the nerve damage, I immersed myself into a virtual world of protein structures using the LMB’s Evans and Sutherland PS300 computer graphics system. I was particularly interested in the architecture of binding sites. In the light of César Milstein’s suggestion, I started to look carefully at antibodies.  At that time, only the three-dimensional structures of human and mouse myeloma proteins were known. Human myeloma proteins are a species of antibody produced in myeloma patients and for which we do not know the cognate antigen. Nevertheless, it was supposed that the antigen binding sites were located in regions of hypervariable sequence in the loops of the variable (V) domains; indeed Elvin Kabat had called the hypervariable regions “complementarity determining regions” (CDRs), and the regions outside the CDRs he called Framework Regions (FRs).  Inspection of the antibody architecture suggested to me that if Kabat was right, the antigen-binding activity of one antibody might be transferred to another by CDR transplant. This offered the prospect of endowing human myeloma proteins with the binding activities of rodent monoclonal antibodies, and so creating “humanised” [see Note 1] antibodies with predetermined binding activities for treatment of human disease, particularly non-infectious diseases such as cancer. I was aware that rodent monoclonal antibodies were seen as “foreign” in patients, provoking a blocking immune response, and anticipated that “humanised” antibodies (up to 95% human), might provoke a lesser response.  Accordingly, I designed a synthetic gene encoding an antibody variable domain in which the CDRs from a mouse monoclonal antibody with known binding activity were stitched into the framework regions of a human myeloma protein. César Milstein allocated a post for a research officer, and was joined by Peter Jones, who acted as my right hand man until my retirement. We set about creating the gene by the chemical synthesis and assembly of oligonucleotides and produced the humanised antibody in myeloma cells using expression vectors kindly provided by Michael Neuberger (LMB). This took us some 18 months of work, and to our relief we found that the humanised antibody bound to the same target as the original mouse antibody, and with similar binding affinity.  We followed up with two more humanised antibodies; in these cases, we had to engineer mutations into the packing contacts between FR and CDR residues to fully restore binding affinities. One of these antibodies, a rat monoclonal antibody against a lymphocyte marker, was humanised in collaboration with Herman Waldmann’s group (Cambridge Department of Pathology). This antibody had been chosen for its therapeutic potential and within months, the humanised antibody was used to destroy a large tumour mass from the spleens of two patients with non-Hodgkins lymphoma.  On the advice of César Milstein, I had filed a patent on the humanising technology, but then found myself embroiled in discussions with my employers, the MRC, in formulating the best licensing strategy. Fortunately, the MRC finally agreed to adopt a largely non-exclusive licensing policy, similar to that used for the licensing of the Cohen Boyer patents on recombinant DNA technology, with a small upfront payment and a low royalty. Later the MRC’s Collaborative Centre for Industry at Mill Hill offered a service to industry for humanising antibodies. These strategies encouraged the uptake of the humanising technology by companies, and led to the development of several therapeutic antibodies, marketed mainly for treatment of non-infectious diseases such as cancer and immune inflammatory disorders.  In the course of our work in humanising mouse hybridomas, we developed a set of PCR primers to amplify and clone the genes encoding the antibody variable domains from hybridomas. As explained in more detail in the [Nobel Lecture](https://www.nobelprize.org/prizes/chemistry/2018/winter/lecture/), this technical advance also opened up the prospect of making human antibodies from V-genes harvested from human lymphocyte populations. However, we soon became aware of competition: the Scripps Research Institute and the biotechnology company Stratagene appeared to be working together along similar lines. We had yet to develop a screening method of sufficient power and realised that with our limited resources we would be outgunned. **Companies** At that time the MRC was unable to offer more resources, and so I sought external collaborations with industry. We had filed patent applications on our work, but industry saw the ideas as too “blue sky”. I therefore mused about starting my own biotechnology company and using it as a vehicle to develop the screening methodology. After a lecture at Amersham International in the summer of 1989, one of the Amersham employees, David Chiswell, offered to help me set up such a company. Around this time, I also had a visit from an Australian friend, Dr Geoffrey Grigg, who had already founded his own company (Peptech) in Sydney. He loved the “blue sky” ideas, and offered to help with funding, but we first had to bring together all the various interested parties. After two months we had a deal: the MRC agreed to license the patents to a new company, Cambridge Antibody Technology (CAT), in return for an equity stake and a product royalty; Peptech agreed to provide CAT with a draw-down loan convertible to equity; David Chiswell agreed to become the Managing Director of the company and set up the laboratory facilities; and I agreed to split my time between my academic studies and the company for several years. The deal also included the provision that CAT would fund an employee to work in my group at the LMB to explore strategies for mass screening of antibodies, including the use of filamentous bacteriophage.  Credit: Gregory Winter.  In early 1990 John McCafferty (formerly Amersham and now a CAT employee) joined my group. He soon discovered that antibody fragments could be displayed on filamentous bacteriophage and that binders could be enriched by factors of one thousand-fold in each round of affinity selection. More good news followed – in the autumn of the same year the MRC offered me further space and posts in a refurbished building adjacent to the LMB. This was the MRC’s new Centre for Protein Engineering (CPE), a species of research institute originating from a government initiative to encourage academic and industry collaborations. Alan Fersht (now back in Cambridge at the Chemistry Department of Cambridge University) was appointed as Director of the CPE, and I became the Deputy Director.  Credit: MRC Laboratory of Molecular Biology.  The antibody work flourished in the CPE, and the explicit link with industry facilitated our collaborations with CAT. We isolated “binders” from human phage antibody libraries, explored methods for mutating and selecting antibodies with improved affinities, and showed that high affinity human antibodies could be isolated directly from very large libraries. The CPE became a hub of antibody expertise, with projects to develop new antibody formats (including diabodies and later single domains), and to clone all the human germline antibody segments which we used as building blocks for synthetic human antibodies. Most importantly we isolated human antibody fragments against human self-antigens from the antibody libraries.  Credit: MRC Laboratory of Molecular Biology  In CAT the scope for rapid expansion was more limited due to the limited cash reserves and the difficulties of finding further investors. Fortunately, a collaborative contract with Knoll Pharmaceuticals (later acquired by Abbott Laboratories) was successful and led to the development of the antibody adalimumab (Humira) against the inflammatory mediator TNFalpha. This later became the first human therapeutic antibody to be approved for marketing by the US Food and Drug Administration (2002) and the world’s top selling pharmaceutical drug. By 1996 the company had started to prepare for an initial public offering (IPO) on the London Stock Exchange and was floated in 1997. However, the preparations for the IPO brought out tensions between investors and split the Board. As most of the antibody technology was by now well established, I stepped down from the Board and left CAT before the IPO.  I was also interested in developing some antibody technology that had not been established in CAT. In 1989, at the LMB we had isolated single antibody variable (VH) domains with excellent binding activities, but prone to aggregate. With improved properties, these domains had potential as small protein domains for topical applications, or as building blocks for bispecific antibodies. As CAT decided not to develop this technology, I helped to establish a new company, Domantis (originally named Diversys) to do so, with the MRC taking an equity stake. Ian Tomlinson, a former PhD student and group leader at the LMB, was a scientific co-founder, and as with CAT, Geoffrey Grigg and Peptech Ltd played a key role as seed investors. Domantis was founded in 2000, the company focusing on the selection of aggregation-resistant domains against potential pharmaceutical targets. The company established several research partnerships with pharmaceutical companies and in 2007 was acquired by GlaxoSmithKline, shortly after AstraZeneca acquired CAT. By 2018, the MRC had received more than £1 bn in royalties, sales of shares and other commercial payments in respect of the therapeutic antibody technologies we had created at the LMB, CPE, CAT and Domantis.  My next enterprise emerged from work with peptides. I had always been interested how proteins evolved and was much taken by a suggestion that proteins had evolved through stitching together multiple peptide segments by RNA splicing, a process termed exon shuffling by [Walter Gilbert](https://www.nobelprize.org/prizes/chemistry/1980/gilbert/facts/). We tried to mimic this process by randomly shuffling together peptide segments, displaying the combinatorial libraries on phage, and using proteolysis to select for those that folded. We found that the folded peptides were stabilised by forming multimers (dimers and/or tetramers), and/or by incorporation of a prosthetic group (heme). This led us to consider making small proteins by folding random peptide libraries around a prosthetic core, and to a postdoctoral worker, Christian Heinis, stapling peptide libraries to the core through three cysteine residues. These libraries, comprising highly constrained bicyclic peptides, proved to be a source of high affinity ligands against a range of protein targets. Indeed, we came to think of the bicyclic peptides as small antibody mimics, in which the b-sheet protein framework had been replaced a chemical framework. The “bicycles” were expected to have some advantages (and disadvantages) over antibodies; unlike antibodies they could be chemically synthesised, and on injection would penetrate deep into tissues.  The technology seemed ripe for development, and a start-up company the best vehicle to deliver this. Christian would soon depart for an academic post at the EPFL Lausanne. One of my previous seed-phase partners, Geoffrey Grigg had passed away, and Peptech had merged to form Arana Therapeutics (swallowed in turn by Cephalon, then Teva). Fortunately, one of my former postdoctoral workers, Regina Hodits, was now with the Atlas Ventures and liked the technology. In 2009 she helped set up the company Bicycle Therapeutics, bringing in other venture capital partners and John Tite (formerly GSK) as CEO/CSO. The company industrialised the selection and synthesis of bicycles, and later with Kevin Lee (formerly Pfizer) as CEO, pressed ahead with the development of bicycles and bicycle conjugates for use in oncology. Bicycle Therapeutics was listed on the Nasdaq stock exchange in 2019. **Institutions** Gradually I found myself becoming more interested in the possible applications of my work and more detached from the academic focus of the LMB. However, the LMB was my scientific home and where I had done most of my scientific research. I had worked my passage from PhD Student, to Postdoctoral Worker, to Group Leader, to Head of Division and finally Deputy Director. In the course of my career Brian Hartley, George Brownlee, Fred Sanger and César Milstein had acted as scientific mentors; Alan Fersht, Michael Neuberger and Terence Rabbitts had proved excellent collaborators, and Hugh Pelham, [Richard Henderson](https://www.nobelprize.org/prizes/chemistry/2017/henderson/facts/), [Aaron Klug](https://www.nobelprize.org/prizes/chemistry/1982/klug/facts/) and [Sydney Brenner](https://www.nobelprize.org/prizes/medicine/2002/brenner/facts/) had been supportive as LMB Directors. The LMB was a wonderful place, acting as a magnet for brilliant PhD students, postdoctoral workers and technical staff – all too numerous to mention here [for names see Note 2].  In 2013, the LMB moved from a cramped 1960s building on one side of the Cambridge Biomedical campus into a large and superb new building on the other side. The case for funding the new building had been fortified by the revenues generated for the MRC and HM Treasury by the antibody technologies and the expectation that further revenues might follow from such opportunistic translation of curiosity-driven research. However, throughout my time, the LMB itself had limited space, resources or appetite for translational work. To see my work applied I had to “privatise” the more translational aspects outside the LMB, whether through the CPE, CAT, Domantis or Bicycle Therapeutics. The move to the new building weakened the spell that had bound me to the LMB.  When in 2012 I was offered the Mastership of Trinity College, I accepted it – I was very grateful to the College (and its Fellows) for their catalytic role in my life. Brian Hartley had been my undergraduate Director of Studies at College, and had persuaded me, through his infectious enthusiasm, to build a research career in molecular biology. David Blow, also a Fellow of the College, had taken me as a summer student to build a display model of the enzyme trypsin, igniting my interest in the structure and mechanism of proteins. Another Trinity man, Michael Neuberger, had provided me with the expression vectors that got me started in the antibody world; Michael had also sent me one of his Trinity undergraduates, Ian Tomlinson (later Domantis) as a PhD student.  As a Fellow of the College, I already had some idea of the changes in store for me as Master. I was installed in the Master’s Lodge, a Tudor palace, and expected to “exercise a general superintendence over the affairs of the College.” My main role was to maintain the good order of the College by attending or presiding over its meetings and activities, making speeches and representing the College externally. However almost all powers were reserved to the College Council, which generally aimed to reach a wide consensus before agreeing any change, delegating matters of substance for deliberation by sub-committees, which might only meet once or twice a year. The pace of change was glacial, but the effect of small tweaks here and there seemed to work, and the College continued to perform well academically and in its investments.  I did nevertheless preside over some changes, including the development of better relations with the College’s alumni and the provision of more space and a higher profile for early stage companies at the College-owned Cambridge Science Park. I also continued with my involvement with Bicycle Therapeutics and some other biotechnology companies and started to advise venture funds in biotechnology investments. At the time of writing, as I come to the end of my tenure as Master, I expect that some combination of science, medicine and start-up companies will underpin my future activities. |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** | [GW]  Gregory Winter: Hello.  Adam Smith: Hello. My name is Adam Smith from Nobelprize.org, which is the website of the Nobel Prize in Stockholm.  GW: Ah, yes.  AS: Many, many congratulations on the award.  GW: Thank you very much.  AS: Your work using phage display to engineer antibodies that became medicines is really a perfect example of how translational research would work, wouldn’t you say?  GW: Yes, because I suppose I started … I wasn’t actually thinking about doing translational work at the time I started the work so it was much more an interest in how one might create new molecules in general. I didn’t actually … in my earlier work with protein engineering I’d just been more interested in understanding how enzymes and things work, and then I started moving to antibodies again to try to understand how antibodies worked. And then I realised the power of evolutionary technologies to create large repertoires of them and to select them, and of course I think there are two components to the work that were really very important. The first was the generation of repertoires, and making sure those repertoires were efficient, fully folded proteins. And then secondly the way of displaying them on the use of the phage which George Smith had provided pointers to. So, so … and of course having … so it wasn’t as if I’d thought at the very beginning ‘right, I need to create pharmaceutical antibodies’. You kind of start working along a different route and then you find yourself gradually being, you know, seizing opportunities as they come up, and those opportunities were opportunities to actually overcome a really difficult problem which was how to make human antibodies against human self-antigens. And so realised that we could create this by using evolutionary technology. In some sense, it’s a bit like how the immune system works – you could also regard it as … I mean, you could think in terms of early evolution, but if you think about the way in which the immune system works, that is an evolutionary system. So we effectively … what we did is we started to rationalise it in terms of how can we mimic the immune system, which is an evolutionary system, to make human antibodies, but without all the checks and controls the immune system would have that prevent you from making anti-self antibodies.  AS: Quite, so how can you mimic and then direct.  GW: Correct.  AS: Yes, well there’s a very important message in all of that isn’t there – that one doesn’t really know where the opportunities are going to arise. You have to do lots and lots of basic research in order to be in a position …  GW: I certainly agree with that. I mean it’s … so my strategy, my personal strategy has been to do the basic research and let … and, but to be mindful of opportunities that may arise. In other words not to say ‘that’s applied, I’m not going to do it’. My own view has been actually if I just did the basic research and I came up with a, you know, a very interesting method and I didn’t take it any further then people would say ‘well that’s just a curious … you know, it’s very clever little system he’s got there but you know it’s a bit of curiosity really’. So I thought actually one needs to prove it, you need to drive it all the way through and so I certainly enjoyed that …  GW: I’ve just had the university people trying to coordinate all the incoming calls. It’s like a siege. We can’t actually get any … all the phonelines are blocked. Yep.  AS: I can imagine. You’re a scientist, you’re an inventor, you’re an entrepreneur, you’re an administrator. Where do you get the energy to do all this?  GW: Well it’s rapidly fading I can tell you! [Laughs] I mean, again I suppose, I don’t necessarily do all of them terribly well. I’ve done each of them well at different stages in my life, because in the end you have to say ‘why does the public give … is willing for large sums, I mean billions per year, to go into supporting science?’. It doesn’t agree to put the same amount into humanities, and the reason for that is that the public believes that some good will come of it. And if we want to maintain credibility with the, you know, public in general, we have to show that from time to time, yes indeed, exciting things will happen, and particularly things that are in the … for the public good. So I think it’s terribly important that scientists don’t ignore the opportunities that may come from their work. That doesn’t mean to say … some people say ‘well, applied research, that has no place in academia’ and I’m not sure I agree with that. But, yeah, there is a bit of an obsession now that you put the focus on application and you write projects for application. And I’m not saying that’s a bad thing, but I think that sometimes if you want to make big leaps it’s sometimes more effective to be a little more defocussed, so that you actually focus on some basic research and you give the people the freedom to … and perhaps expect them to be responsible, and if they don’t want to take up the opportunities themselves, at least alert other people to them, so that these, the opportunities latent within whatever their inventions are can actually be exploited. So I think we kind of have a duty as scientists to do that. That’s my personal view.  AS: I must just very briefly touch on the LMB [MRC Laboratory of Molecular Biology]. It’s yet another Nobel Prize from that environment, much has been said, but what is it that makes it so particularly special?  GW: People refer to the ‘LMB culture’ as the thing, one of the things, that makes it special. It’s an attention to people who are willing to tackle very big problems. I mean problems that are so big that you couldn’t just solve it in a grant. The kind of problem that you could devote your life to. I was very fortunate in having mentors of Fred Sanger and César Milstein who exercised a kind of very benign mentorship but encouraged us to think big.  AS: Well, I should leave you to your amazing day that’s unfolding.  GW: That’s right, yes, indeed.  AS: Thank you so much.  GW: Thank you very much, thank you. |
| **Interview** |  |
| Q3 | When did you decide that you wanted to become a scientist? |
|  | Sir Gregory P. Winter: I started to take an interest in chemistry because I think I was very good at it. I found it logical but it wasn’t absolutely mathematical. I liked the way it was taught which was very much based on evidence. We had a historical approach going through how all the scientific experiments were done that led us to our understanding of matter and the way elements came together, and I found that evidence, that trail of evidence, very satisfying, always thinking about what evidence you needed to justify any particular statement. But in fact, my real interest was also in biology as well and when I went to university I hadn’t been sure whether I’d be a biologist or a chemist but what happened was, about in my second year in university, I still preferred chemistry as a subject but I thought that, for research, the biologists just had the more interesting questions.  So chemists seem to have got themselves lost, in my view. They were exploring things that really didn’t interest me. They were kind of more mathematical, so endless dealing with equations, which I could do, but I didn’t get any pleasure out of them. To me a mathematical equation is just a tool for solving a problem. I had no interest in the beauty of mathematics as such. I was much more interested in some of the big problems in biology and I became particularly excited by … There was a book by [Melvin Calvin](https://www.nobelprize.org/prizes/chemistry/1961/calvin/facts/) about early evolution and which was published around that time, which was the late 80s, perhaps early 70s, and in that book was a description of how the prebiotic soup was formed and the way in which that is thought to have bootstrapped its way into life as we know it and I thought, now that’s really interesting, it’s all combined my interest in molecules. At the same time it made me think about the bigger biological question of evolution. In a way that theme has underpinned everything I’ve done at some level since then. It’s that deep interest in evolution, but also interest in the chemistry of how that evolution is achieved. |
| Q3 | What is it that you love about chemistry? |
|  | Sir Gregory P. Winter: We had a couple of very good teachers at school but, they were very good at teaching, neither of them were role models in the sense that they explained the subject in very different ways. The chemist was very competitive. We were always making us compete against each other to get the top grades, to answer faster than the next person. The biologist was more measured but again he would go out of area, he would get us to look at things that weren’t on the syllabus, went much wider than the standard school syllabus. So from both of them I learned quite a lot in very very different styles but they weren’t people I myself wanted to emulate, I had no model early on for the kind of scientist I might like to be. Only later when I started doing research did I start picking up ideas of the kind of people I’d like to be, the style I’d like to follow. |
| Q5 | Who has inspired you? |
|  | Sir Gregory P. Winter: It’s a combination of role models. My own PhD supervisor was a northerner and he was very blunt and I’ve borne in mind some little teachings that he’s given from time to time. One of them was I happened to say that an experiment I was proposing to do or a subject I can’t remember the exact issue, was really interesting and he said: “Bugger interesting. Is it important?” And actually that got me thinking, yes, he was right, it was interesting to satisfy your curiosity about something but no, he was right, it wasn’t important and so actually that was a guiding principle I incorporated to try to work on things that were important. Of course you have to judge what you mean by important and as my own research developed I realized the importance was very much in the eye of the beholder but for me importance started to become increasingly utility, in other words the ability to use certain things for the common good and to my mind, that’s what I started to think about as being important and that’s what I nailed my colours to in the end. |
| Q9 | How did you react finding out the news of being awarded the Nobel Prize? |
|  | Sir Gregory P. Winter: When I first got the news I was very tired and I didn’t really take it in. It wasn’t expected and it didn’t really compute. I just felt it was a bit unreal and I think that continued for quite a long time actually, so people said: “Didn’t you feel elated?” No, I didn’t feel remotely elated. I felt just in shock. I’ve had other prizes and I felt elated but this didn’t fill me with joy, it filled me with an unease. I think the unease being that actually inevitably I would become much more of a public figure which is not something I really wanted. |
| Q15 | What are your favourite applications of your work? |
|  | Sir Gregory P. Winter: The applications I get the most pleasure from are the applications that where people have benefitted. There was a big impact from a patient that … I’d made an antibody against a mark on white cells and this antibody was given to the patient and I wasn’t involved in making a decision as to whether to give it to her, but we did not know what was going to happen. In fact, there was some unease that it might be so powerful it could give very unpleasant side effects. In fact, there were very few side effects it turned out, and in fact the large accumulation of tumours she had in the spleen started to regress and on about the fifth day I was taken round by the scientist to meet her and I was told: “Well, to get in there, you’ll have to look like a junior doctor, put on a white coat, it shouldn’t say medical research council on it because it looks like you’re going to experiment on people, just a white coat. There’s a stethoscope, put it round your neck! Everyone will think you’re a junior doctor!”  So I went round and I got to walk straight in, no-one challenged me at all and went up to this lovely old lady, she was sitting knitting, and talked to her and I remember at the time, she asked me if I’d got any idea of how long this therapy was going to last and I said that we think you won’t react to the antibody because it was our first humanized antibody, but we don’t know for sure. And it, you know, frankly we’re just very glad to see the tumours disappearing but we don’t know just how long it’s going to go on for, you know, maybe it’s going to buy you a few days, a few weeks, a few months, a year or two. I simply don’t know. She said “Well, you’re very honest”, she said “It’s actually a pleasure to talk to scientists”. She’d been talking to medics and I suppose they were a little bit more circumspect, and she said “But all I really need is a couple of months.” I was startled: “Why do you need a couple of months?” And she said: “Well, my husband’s dying and I want to be with him when he dies.” I still feel choked up when I think about it now and I thought, this poor woman, there’s nothing she can do and yet we’ve done something that we can make a difference and you know we just have to … It actually gave me an increasing feel of worth for the kind of science I was doing and at that moment I decided I’d really got to make much more of an effort to focus my work on the practical application of those molecules. |
| Q15 | What happened to the patient? |
|  | Sir Gregory P. Winter: Her husband died and she was with him and she’d also mentioned that the other two months, the rest of the time she wanted to acclimatize her granddaughter to the fact she was going to have two grandparents dying very quickly. But she lasted a year and then, unfortunately what happened is, the tumour came back. We had no more antibody to treat her, well, we only had one lot of antibody to treat her and it was all in the hands of medics and they decided to give it to a child who they said was more important or it was the ethical thing to do. As a scientist I didn’t agree with that, because I actually felt that this woman was valuable experimental material. She’d also been the first person to have it. It had worked well in her case and I actually felt that we owed it to her to give her another shot of the stuff. But they said: “Well, I’m afraid you know you’re taking the scientist’s perspective, we have to take the clinical perspective and the ethical thing for us to do is to give it to the child.” And they gave it to the child and the child died and so did the lady.  It was all very sad and it made me realize that one of the issues that we hadn’t dealt with, we simply couldn’t make enough of this antibody on the laboratory scale where, I say we, it was really my colleagues, Herman Waldmann in the Department of Pathology, they were making this antibody and just the amounts we could make of suitable grade to go into patients wasn’t suitable and it wasn’t sufficient and I realized that we will have to work with industry to do it. So I thought, well, we’d just better grasp that nettle. I need to find ways of working with industry so anything I get in the lab can be taken through and we don’t end up with these situations where we’ve got antibody and we just simply can’t. We’ve not got a route forward. |
| Q10 | Why do you think scientists shy away from working across science and industry? |
|  | Sir Gregory P. Winter: Other scientists, I think they do their best but they probably … and it’s perfectly legitimate to say: Well, this is what I can do. I can do this bit and I need other people to take it forward. It’s true in my case. There’s a limit to how far I can go, but on the other hand I feel I should go as far as I can to make sure it is actually used and once it’s been picked up by industry that then, in fact, I don’t have to do anymore. I don’t have to keep to following it through. I don’t have to continue doing industrial stuff. So I actually would step back at that point. It’s quite exciting to see something going all the way through and I have always kept tabs on it but actually the most important thing for me has been to get involved to the point at which … If you’ve done something novel, you’ve got a new technology, then I can assure you industry doesn’t run over and seize it off you. You’ve really got to work quite hard to cross that gap to make them feel it’s worth picking up and running with. |
| Q14 | How do you stay focused on your research? |
|  | Sir Gregory P. Winter: I realize now my research has gone in phases so what tends to happen is I’ll have a period where I make some discoveries. I try to apply that, I take it forward, then having done that, I step back and try and go back and think of something else I want to try and in fact, that’s happened two or three times. So I’m now working on, or trying to take forward something we invented in the lab in 2009 which was development of mini antibodies which we call bicycles, bicyclic peptides, and we’re lashing on toxins to those and also trying to use them in immuno-oncology so those are things which again, it wasn’t possible to take those forward in academia, you know. To get into patients and well, to do all the preclinical and to get into patients has consumed tens of millions which is the kind of money you don’t get from granting bodies. You have to go to the market to get that and so therefore I’ve tried to, least sell the technology to people, to investors so they will come in and we try to take that forward with a company to a point at which we can see these things applied and in patients. And we’ve now got in the case of the bicyclic peptide, so it’s 2018, we founded the company in the end of 2009 and so it’s nine years but with technology development plus developing individual molecules, we’ve actually got a molecule in a patient now in the clinic in London which we hope will work out well. I mean so far, they don’t seem to have any side-effects but who knows. The kind of things we’re using potentially could be very toxic. |
| Q3 | How can we get more young people interested in science? |
|  | Sir Gregory P. Winter: I think a lot of things have happened, certainly in the UK since I grew up. I think one of the problems is there’s much less focus on experimental work. With my own children, I was astonished to hear them say that chemistry was boring and I said, “How can it be? It’s a wonderful subject, it’s so exciting all these things you can do.” And they said: “Well, dad, don’t you realise, the most exciting thing we saw was a nail rust.” I said: “You what?” It turned out for whatever reason virtually everything is frowned on for health and safety reasons and possibly other reasons as well, maybe there aren’t the teachers to do it but in the state schools there just isn’t this culture of experiment.  In fact I remember going back a few years later to my old school where I’d done chemistry, and this was probably about five years after I’d left. I’d gone through Cambridge and I went to see my old chemistry teacher and he was surrounded by a class of 14-year-olds with Bunsen burners and things leaping out of the ends of tubes and things going pop and he was sitting there unconcernedly marking things and all round him there was kind of mayhem of boys doing this and that and adding things they shouldn’t have added and I realised you probably have to be quite brave if you’re a chemistry teacher but he kind of presumably knew all the various kind of serious risks. Occasionally a boy would burn their fingers or singe their hair and you know he’d quickly administer first aid and tell them to do what he told them to do in the first place, but I remember thinking this is what chemistry was. The room was full of smells, probably all toxic, it was full of boys doing things off stage and playing little jokes on each other but actually it got them excited and they really looked forward to chemistry and I remember thinking, what a shame that we’ve destroyed that. |
| Q5 | Is education in experimental science too timid? Is the focus on safety concerns legitimate? |
|  | Sir Gregory P. Winter: I’d like the things I’d like to see people taking … Well, it depends on what you mean by legitimate. I mean I think providing that, you know, I think people should wear safety glasses and obviously you make sure that you couldn’t actually blow anybody up in a lesson but I think people are far too safety conscious, is my impression, but I can’t say I’ve been in lots of schools and I’ve seen lots of things. All I can do is to report back from my own children in state schools and I can tell you that there was a reaction I had many years ago to a biological experiment I did in school. I got invited to my children’s primary school many years ago to show them, you know, parents were asked to come and say something about their work and so for example it was easy for a carpenter to come in and show how they did, carved a piece of wood or whatever. But I went in and I thought I’ll show them an experiment but I needed to make it a couple of days’ worth.  So what I did was, I took petri dishes on one day and I agreed I’d go in the next day and I took samples of bacteria and we had a great time because it was a school in the country and we went round taking samples from the bottom of people’s shoes, from down their ear, up their nose, round the back of a young boy’s neck, on the school climbing frame by swabbing these different areas. I then also mixed this in some school disinfectant to see how that worked and then we plated the bugs out. We plated out the cultures and I’d done some initial ideas of titrations myself earlier on something, so I had an idea of the kind of dilutions you might need to make and anyway took the things home, put them in the bottom of the Aga oven which is a nice 37 degrees or so. The following day they were colonies on these different plates so I wrapped the plates up carefully in cling film and took them in and we scored the plates and we had a sort of big chart on the blackboard with the different sites, named the bottom of Johnny’s shoes, who always used to come from a sheep farm and he’d always trod on sheep shit, that’s just why the girls wanted to have that back of someone’s neck, someone’s hands, the school climbing frame, the school, the effect of the school disinfectant and there were certain things that ended up being very unexpected. First of all the school climbing frame was not the filthiest thing which I had assumed it would be. Nor was it the bottom of Johnny’s shoes, which clearly did have discernible pieces of sheep shit on them. It was the back of the boy’s neck and these things came up. I just couldn’t believe the number of colonies that came up. The other thing was that the school disinfectant had no effect on anything. So we produced this chart and I have to say the children loved it, particularly the boys. Two of them cut out: “Can I be a scientist when I grow up, sir?” They were transfixed by the idea that you could discover things that you didn’t know because they said: “We didn’t know what the answer would be because we’d had a bet and we realised everyone was wrong.” They’d all bet it was actually the bottom of this boy’s shoes and it wasn’t.  Of course the next thing that happened is, I have a nasty letter from the headmistress saying apologizing for the school disinfectant but saying the mother of the boy Johnny had been humiliated by this and this poor boy was going to get his neck thoroughly scrubbed and furthermore there was a hell that I should have done a health and safety assessment on the possibility that there could have been pathogenic organisms on these plates which children had scored and I said: “Look! The plates are sealed.” I had sealed them all round so they couldn’t open them and I thought to myself, these poor little children under that kind of culture. You know, this shows the dead hand of health and safety and bureaucracy in schools. It was such a shame because those boys were really enthused. I thought it was actually quite a good experiment, relatively harmless. |
| Q1 | What would be your advice for young researchers starting their career in academia? |
|  | Sir Gregory P. Winter: My tips for a career in academia: Work on something important that matters. That matters to you but also most preferentially will matter to other people as well and that someone’s going to put some money into it. I would say you will have to work extremely hard, harder than you have ever known before. You need to forget about work-life balance, you will have none. |
| Q4 | Could you explain your prize awarding discovery in 30 seconds? |
|  | Sir Gregory P. Winter: The prize was given for making antibodies using a filamentous bacteriophage and I’m going to explain it by analogy and I’m going to explain it by the analogy of a master thief. Let’s imagine that we want to make an antibody against a cancer cell. Imagine the cancer cell is being the lock and the antibody is being the key. If you’re a master thief, what you would do would be to create a huge number of different keys and then you would try those keys out on that lock and that’s effectively what we did. We found ways of generating a huge number of keys and then we found an automated way which was the use of the phage to be able to do many locks in parallel. |

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| **Chemistry\_2024-2000** | |
| **ID** | 0319 |
| **Biographical** | My curriculum vitae has been on my personal page of the University of Lausanne’s website for a long time. Few people had looked at it so far. Suddenly, with the news of the Nobel Prize, it became a worldwide buzz almost overnight. All of this because people found it, let’s say, “unusual”. But why is it so unusual? Of course, there is little place for creativity in a resume sent to apply for a position in some political institution or international firms – but why not being a little bit imaginative when presenting yourself on your own, personal web page?  This old CV has been rejuvenated to fit recent developments and has been enriched with commentaries. It is presented below. **October 1941** Conceived by optimistic parents.  *This was a bad time. The Germans were approaching Moscow. Switzerland was encircled by countries under the Nazi or Fascist regime. My father, a civil engineer, was building fortifications for the army. My mother Liliane was taking care of my sister Michèle, 3, and my brother Emmanuel, 2.* **Born June 8, 1942****1946** No longer scared of the dark, because the sun comes back; it was Copernicus who explained this.  *To make it simple – too simple almost – two solutions were offered to me: prayers with my Protestant mother or logical explanation from my atheist father. As time passed, the second option seemed more and more alluring.* **1948–1955** 1st part of an experimental scientific career in Wallis and Lausanne (instruments: knives, needles, strings, matches).  *My father was building a dam, high in the mountain. We were living in a small village where electricity was recently brought in. At school, there were two classes for the boys, each with a wooden stove in the middle. The good boys were allowed to sit close to the stove, while the bad boys had to sit by the window. Since we were the engineer’s children, our place was by the stove of course! We spent the six-month-long summer holidays in a chalet further up, closer to Dad’s work. We had no electricity, and no shops close by. Rye bread was getting hard after a few weeks. There was a big rock, too big for me − but not so big as I realized when I came back as an adult – on which my brother and sister were spending hours climbing and playing. There were thousands of other adventure grounds and experimenting places all around and down by the river.*  *Then we went to the big city of Sion and to the even larger capital of Lausanne where I had to find my way – with difficulty – through a more standard education system. I succeeded somehow in passing the college examination (normally passed at 11, but I was already one year late).* **1955** First official dyslexic in the canton of Vaud − this licensed me to be bad at everything … and allowed me to understand those with difficulties.  *It didn’t take long for my parents to find out that my grades were not promising, but they noticed that my spelling mistakes – as those of my brother – were unusual. They drew the attention of the college’s director to this. He decided to take the case further and this is how I became the first recognized dyslexic child of the Canton. This meant that I was allowed to pass from one class to the next in spite of more and more catastrophic grades. This was a bad time. From being bad in spelling I soon became very bad in everything, because dyslexia was my “laziness pillow”. Not completely though; following the instructions of the book by Jean Texereau, I was building a 15 cm aperture telescope. My handwork teacher spent more time helping me than he spent with all my classmates put together. The college director retired shortly before I reached the end of the compulsory school program. It didn’t take long until I was dismissed. Still optimistic, and creative, my parents sent me to the boarding school of Kantonschule Trogen, deep in Swiss-German speaking central Switzerland. The message was clear: either I move on, or I get stuck. One year later, the German teacher asked me to give a talk to the class. I spoke about rockets, and it was good. I knew I was on my way to becoming a scientist. And that was the end of the central-Switzerland episode.* **1962** Federal maturity exam.  *After the salutary shake-up in Trogen, my parents sent me to a private school in Lausanne where I could prepare the examination for entering University. It was a time of intense catching up. I am still surprised by how much a teenager or young adult can learn when he is motivated. My cultural background of poetry, music, history, and geography is still strong − but it’s not as much about language and spelling. The maturity examination went well.*  *Shy and polite, but socially unskilled, I gained preliminary social experience in homes for disabled children where my sister – a work therapist – brought me during the holidays. Then it was the military service. I still have nightmares from this time, but I benefitted there from meeting regular human beings. I became an officer, even though I wasn’t exactly fit for the job.* **1967** Physicist-engineer at EPUL, with the intention to become a biologist.  *I wanted to understand more about the world, the living world in particular, and to become a scientist. It was a time during which Physics were shaping Biology.* [*Watson*](https://www.nobelprize.org/prizes/medicine/1962/watson/facts/)*,* [*Crick*](https://www.nobelprize.org/prizes/medicine/1962/crick/facts/)*,* [*Kendrew*](https://www.nobelprize.org/prizes/chemistry/1962/kendrew/facts/) *and* [*Perutz*](https://www.nobelprize.org/prizes/chemistry/1962/perutz/facts/) *had won their Nobel Prizes. Quite obviously, I chose to study Physics at EPUL, École Polytechnique de l’Université de Lausanne (now federalized as EPFL), where my father had studied Civil Engineering. I found calculus difficult during the first year and, contrary to some of my admired classmates, I never became a skilled mathematician. Nevertheless, I tremendously enjoyed everything I learned. I felt more and more at home in Physics, mostly thanks to my professor Jean-Pierre Borel and to the three volumes of* [*Feynman*](https://www.nobelprize.org/prizes/physics/1965/feynman/facts/)*’s “Lectures on Physics”.*  *During my second year I went up to my preferred professor and I asked him for advice. ”Where shall I go for a PhD in Biology when I am finished with my diploma?” He had the answer: ”Prof. Édouard Kellenberger, at the laboratory for Biophysics in Geneva.” So there I went. Édouard was very friendly and he offered me a position as a doctoral assistant. ”Oh, not so fast,” I replied, ”I have 3 more years to go with my studies in Lausanne.” ”OK, come back in 3 years.” Three years later, I was there again. In the meantime, Édouard had been to the States and married Cornelia, and he had forgotten me. I got the doctoral assistant position anyway.*  *The Laboratory for Biophysics at the University of Geneva was a remarkable place (Strasser, 2006) – one of those in which Molecular Biology was introduced in Europe. Science was practiced there in a most enthusiastic, creative, and open way. Mountain touring and climbing the Salève were the only limitations on the long working hours in Biology courses and in the lab with my electron microscope – an old RCA EMU2.* **1968** Very important.  *Then came the student revolution. We couldn’t escape. We didn’t. Unprepared, I played along the game of being politically active in the midst of big turmoil. We were left-oriented of course, but our group 2002 (that was its name) was not along the general line. We had a strong involvement in environmental protection. I cherish the memory of the moment when, having climbed high on a pole to plaster a poster against a car exhibition, I saw, down below on the street, two smiling policemen waiting for me to come down. That stunt cost me a major part of my meager salary.*  *A friend, more committed to the revolution than me, gave up his studies and rejected his family. His father, a banker driving a big black car, told me – perhaps because I still looked a bit reasonable − “Don’t worry, he will soon become normal again.” I told myself, “For sure, I’ll never be ‘normal again’ as he means it”.* **1969** Certificate of Molecular Biology in Geneva to become a biophysicist. Began to study electron microscopy of DNA, which remains my main topic.  *My diploma in Physics didn’t bring me much in Biology. The certificate was designed to bridge the gap in order to form this new kind of scientist: the biophysicist. Namely: those who are biologists but with the spirit of a physicist. I took courses with Biology students and, more importantly, I discovered the strange way of living of those dedicated to the observation of natural life. With them, I woke up at dawn for bird watching and digging the soil to count earthworms.* **1973** Thesis in biophysics at Geneva and Basel with Édouard Kellenberger who taught me Biophysics, ethical responsibility and durable friendship.  *Édouard Kellenberger was called from Geneva to lead the final construction and early operation of the new Biocenter at the University of Basel. He took with him a group of colleagues and students. Most of us were still politically active. My bias was still towards environmental protection and durability, but the work in the laboratory was my major activity. I became the first Philosophy II graduate from the Biocenter with a PhD entitled ”Contribution to dark-field electron microscopy”. In fact, dark field was a minor part of the PhD and the conclusion was that it is not very useful for biological observation. However, I learned how to operate an electron microscope and a lot about the strange behavior of matter at small dimension.* **1970–1976** Very classic psychoanalysis.  *As it should be, my affective life was quite intense during my psychoanalysis. Toward the end of this period, I met Christine. Our second encounter was during a manifestation against a planned nuclear power plant near Basel (the plant was never built). Christine is an art historian from Basel and Paris. She was teaching art at school. We settled in together and got married when she decided to move with me to Heidelberg.*  *What did I get from the unreasonable effort of a Freudian psychoanalysis? I asked myself this question, walking along the Rhine after my last session. The answer I gave to myself was ”I don’t know yet, but in ten years’ time I will come back to this”. Ten years later, I thought the decision was pretty good. Ten more years later, I thought it was very good. At present I do believe that it was the best decision of my life, together with the other one – living with Christine.* **1978** Group leader at EMBL (Heidelberg); how to deal with water in electron microscopy. Discovery of water vitrification and development of electron cryo-microscopy.  *The newly formed European Molecular Biology Laboratory, hidden in a beautiful forest above the old city of Heidelberg, was a kind of paradise for research. John Kendrew, the initiator of the laboratory and first General Director, appointed a host of young scientists with ambitious projects. Everything was arranged for us to work freely under the best conditions, with the sole expectation of producing knowledge of significance. My project consisted in learning how to deal with water in electron cryo-microscopy. It didn’t start well but we have been lucky for the rest. The story has been told elsewhere (Dubochet, 2011).*  *At this time, we were living in a small village in a vineyard south of Heidelberg. Christine gave birth to a boy, Gilles, and 18 months later to a girl, Lucy. I was used to working early in the morning and coming back in the middle of the afternoon. I had the opportunity of participating closely in family life. We also had a good group of parents sharing the care of the children as well as their education. It was a great time!* **1987** Professor at the University of Lausanne (UNIL), Department of Ultrastructural Analysis.  *I was among the lucky few who had a permanent contract at EMBL. Nevertheless, I was attracted by teaching and I doubted that I could be creative all my remaining professional life in pure research only. I didn’t hesitate to accept the offer for a professorship in Lausanne, which involved the management of the well-established Electron Microscopy Center with its service duty, and the chance to install a brand new Laboratory for Ultrastructural Analysis where I could pursue my own research under favorable conditions.*  *During the 20 years as professor in Lausanne, I also had the chance to extend my research work in the field of science and society. We developed a compulsory curriculum whose aim was to make sure that our students are as good citizens as they are good biologists.* **1998** President of the Biology section with the chance to perform this assignment with Nicole Galland and Pierre Hainard, and to live at a moment when interesting things were happening in Biology in Lausanne.  *Yes, interesting things indeed. This was the time when a major rearrangement took place between UNIL and EPFL. The principle was simple. At that time, Biology was the exclusivity of UNIL but departments of Mathematics, Physics and Chemistry existed both at UNIL and EPFL. This seemed unreasonable. It was decided to concentrate these three activities exclusively at EPFL and to reinforce Biology accordingly at UNIL. The continuation was more complicated. I discovered what real politics were. The result was, indeed, the move of Mathematics, Physics and Chemistry to EPFL but, in an unexpected twist, EPFL also developed a strong department of Life Sciences and, at UNIL, what was left of the Faculty of Sciences merged with Medicine into the new Faculty of Biology and Medicine. The result is probably better than the original plan, but what a stir it all was!* **2002** End of the assignment. Sabbatical in Australia, Germany and Paris. **2004–2007** Maturation of CEMOVIS (cryo-electron microscopy of vitreous sections).  *The success of electron cryo-microscopy relies on the observation of very thin specimens, in the sub-µm range. This is even too thin for the observation of a single normal cell, without speaking of a tissue or of a complex organism. From the start, our electron cryo-microscopy project included the observation of bulky specimens. For that aim, the strategy consists in vitrifying a volume as large as possible and then cutting it into vitreous sections that can be directly observed in the electron cryo-microscope. The method faces a number of difficulties that we summarized with the acronym SIVEMCATOR (Al-Amoudi, Studer and Dubochet, 2004) which, for some, is the symbolic expression of the hopeless task that I imposed on a number of my collaborators. I think they are wrong. The need for electron cryo-microscopy of bulky specimens is obvious and CEMOVIS is the most direct avenue to solve it. My guess is that the success of the thin film vitrification method applied to macromolecular complexes or small organels has depleted the group of those ready to accept the most challenging task of studying large objects. This will change. The future of CEMOVIS is bright.* **2007** June Retirement Colloquium. **2007 =>** Host of the Department of Ecology and Evolution. Science and Society for the elderly.  *Retirement in Swiss universities is compulsory at age 65. Some try to find a solution to continue the work they are trained for and good at. I thought that, with a bit of luck, 65 years would not prove to be so old. Statistically, it leaves you with about 20 years of creative life. I decided to cultivate my 4 “S”. The first S stands for Self, taking good care of oneself. The second S is for Social, living together. I started teaching mathematics − that is 2+3 – to young migrants; the effort broadened and I went into politics in my small city and, back like in the old days, to the movement for environmental protection. The 3d S stands for Science, because I love it. I have the chance to keep my mind on it, through direct contact with my colleagues at the university, where they generously left me an office desk. The last S means Service, because the fruits of the quince tree are better as marmalade than rotting on the ground, and because dishes must be placed in the dishwasher. My sister gave me the advice to devote the first year of retirement to learning this new job. At the end of the year, I found that a second year of training was necessary. Ten years later, the work is still in progress.*  *The children are grown up. We have a son-in-law from India. They are all working for the common good or development help. They have not yet made us grandparents, even if we are active members of the association “Grandparents for the climate” (*[*https:/www.gpclimat.ch/fr/*](https://www.gpclimat.ch/fr/)*).* **October 4, 2017** Ouch! A Nobel Prize  *Christine says: “It’s a good thing for us that you got it late and that you had 10 years of retirement to broaden your scope.”* |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** | [JD]  [Adam Smith]: Hello Professor Dubochet?  [Jacques Dubochet]: Yes, I am on the phone!  AS: My name is Adam Smith, calling from Nobelprize.org and congratulations on the award of the Nobel Prize.  JD: [Laughs]. Thank you very much.  AS: It must be quite a day you’re suffering.  JD: Yes, it’s quite a day but you see I’m still at the University of Lausanne and somebody is taking care of me, *voilà*, so there … I just follow what I have to do.  AS: That’s nice.  JD: Yes, that’s nice.  AS: Ok just a couple of quick questions. You have been awarded, in part because of your development of vitrification of water and people.  JD: That’s right.  AS: So people know about liquid water and they know about ice, but I guess most people don’t know about vitrified water.  JD: Yes. If you cool water it becomes ice. It would be great if you could cool the water and immobilise the molecules, though keeping the structure because when it’s frozen, when it’s immobilised you can have it in the electron microscope and the water will not evaporate because in the electron microscope it must be under vacuum, and water at normal temperature evaporates. So that, when it was possible to vitrify biological material, you could have it in the microscope in the vitrified state and observe it quietly in the electron microscope. This was the beginning and so, if you have it in ice, or if you have it without water, the molecules, like fish, are dead.  AS: Yes, beautifully said. And the Nobel Prize will put a lot of attention on you. How do you feel about that and about the responsibility of scientists who interact with the public.  JD: That’s interesting. I’ve been, during the twenty years I was at the University of Lausanne, I have devoted a lot of effort to the curriculum – biology and society – and Lausanne at that time was unique in developing this curriculum for all our students. It was not the kind of additional piece of education, it was a core programme in the study of biology and it still continues. Tomorrow morning I give a talk at that course and the idea of this course is to make sure that our students are as good citizens as they are good biologists. I can tell you that this is very close to my heart.  AS: How wonderful. So in a way for twenty years you’ve been preparing for this role. [Laughs]  JD: Well, ok. You can guess that today I have a lot of journalists and I do not miss to speak about that.  AS: No, good. Lovely. Can we look forward to welcoming you to Stockholm in December?  JD: Oh I think so. [Laughs] *Si Dieu me prête vie.* If God is good enough, but I don’t mind God.  AS: Good, well we anticipate your arrival with great excitement. Thank you very much indeed and once again congratulations.  JD: I thank you, of course. Goodbye.  AS: Goodbye.  JD: Thank you. |
| **Interview** |  |
| Q3 | Where does your passion for science come from? |
|  | Jacques Dubochet: I heard frequently this term, passion, and it is not quite correct for me. It is just a requirement, it is a need. The need for understanding was my way of finding my way in life. You know as a young child I don’t think that I was a very special child, but sometimes you are afraid, life is sometimes threatening, the night, and understanding was my way out.  I was in Wallis, in a very catholic region, my mother was also protestant, actively protestant. There are two solutions in the world, one is the guardian angel, the other one is understanding. I will not say that the guardian angel is nothing, but my way was understanding. Then I continued and it is not just by accident that I became a scientist. |
| Q17 | How do you think that having dyslexia has shaped your life? |
|  | Jacques Dubochet: In fact I think I thought more about this point since two months than all the time before. I got a lot of contacts with other dyslexias and with the association of dyslexic parents and so forth. But at that time it was complicated so I could continue during the college from, well say, eleven to sixteen, I was at school and I was still accepted at that school while I had marks which were not acceptable. In some sense this saved me but also its make that, it was you know laziness below. So instead of working hard I did nothing, relaxing on dyslexia.  But at sixteen then the director who gave me this chance not to be thrown away, went into retirement and I was thrown away within three weeks. But my parents made a courageous move, they throw me to Swiss Germany in a college there and within one year it was too late I would say. I had other methods to understand and to progress in life. It was a big shake-up and then from that moment it went well. The time before was a hard time, a sad time. You know, a young boy who does not know where to be in life. In this sense I feel quite happy to speak with young people who has trouble. And I like to say, to society, that there are a lot of young children who are lost because we feel they are out of the frame. But what can happen later is enormous, I am an example for that. |
| Q1 | What words of advice would you give your younger self? |
|  | Jacques Dubochet: Really, we all have something valuable in us, so cultivate what you have in you. When you are young you don’t know what it is, but you know what you like so go on with what you like. We don’t know to be good in everything, we just know to be good in something. On this stone you can build a life, I think so, or you need a bit luck and in order to bring me to Nobel Prize you need a lot of luck. |
| Q5 | Tell us about your passion to teach science and mathematics to young refugees. |
|  | Jacques Dubochet: Imagine you have a Somalian girl who came here, abducted by some terrorists. Was brought away and could come home again and then her father could send her away because she could not stay there and come in Switzerland and she is fourteen and a half. She come in a home for young refugees without parents. There she grows and she was supported. Then I work with this person and I teach her mathematics, two plus three and so forth. Then you have this two person, this person and the future Nobel Prize speaking for one hour in front of the other, just about trying to understand, trying to understand each other. That is impressive! Perhaps she learned something in mathematics, but I learned very much about human being. First of all, of course, what to say? There are so many words, the basic word of course … We are as different as possible, but we love each other. You see, this word is a complicated word, but there is in human beings the capability to love each other above all the difference. That is a big thing! The thing we should cultivate and make great! |
| Q5 | How can we interest the younger generation in knowledge and science? |
|  | Jacques Dubochet: I think that it is in human, in the biology of human, to be interested, not in science, but in knowledge. Understanding what is coming on. If I dream, if I walk, and just think about nothing. I think about what will happen, what is going to happen. I want to know what is going to happen. For that I need to understand a lot of things. The more I understand, the more I am prepared to go my way in life. This is the way the homo sapiens developed and became this powerful object which is making the world, for the best and for the worse. |
| Q9 | How has life been since you were awarded the Nobel Prize? |
|  | Jacques Dubochet: Of course it is a shock but I thought I don’t want to change. I thought I managed that, but my wife and my children noticed that no, no, it is visible that you are quite shocked. Indeed, two days ago I was sick, I didn’t understand what happened, but the Nobel Prize is a big shock. |
| Q9 | How did you celebrate the announcement? |
|  | Jacques Dubochet: At the first minute, the first afternoon, I was at my university campus. Everybody was celebrating, and they wanted signatures and photographs. I thought, what do they want with that? Then a young person gave me a packet of chocolate, a box of chocolate. And I told her ‘*Allez*, keep it, I don’t want chocolate’. And she took it again and she put it on me vigorously and said ‘But no, *ça me fait plaisir’* – it is a pleasure for me! And so I realised so many people just are happy because I got this Nobel Prize. And this is surprising, all this people, I got now about 2,000 messages, the overwhelming majority you have the impression, the people are happy to be happy with you. |
| Q9 | How has your discovery benefitted humankind? |
|  | Jacques Dubochet: We got this Nobel Prize for our progress in imaging of molecules and we see now atoms therefore we are in chemistry and more chemistry is extremely powerful with that we can develop drugs to cure I don’t know what, understand how the brain working, conscience. I don’t know where we go. It is knowledge. Knowledge is our best common good. We should keep that as a common good. Any knowledge in the world should belong to everywhere. Which is not so obvious. Now the second question is what will you do with that? We are very good in producing knowledge, I am the testimony of that. But are we so good in using it, in using our knowledge for the best of all mankind? We have clearly very big progress to make on that. |
| Q8 | What do you like to do in your spare time? |
|  | Jacques Dubochet: I am retired since 10 years. I am still in my university, I have my small office there. I try to learn, I continue, I read. The best way to learn is to discuss with colleagues. Because instead of reading hard difficult scientific papers you just discuss and you get the explanation. That is a big advantage. As you understand I spend time with refugees or with people with less chance. We walk a lot, *voilà*, we are doing things that make us quite happy. |
| Q2 | Do you feel that the day has enough hours? |
|  | Jacques Dubochet: No, no, that is the big trouble. Twenty-four hours a day is very much too short. *Oh, là là*. You see I am 75 and I still do not know how to restrict myself. Probably this has something to do with Calvinism. I am not at all Calvinist of course but nevertheless every minute you get, every minute is so precious you want to do something out of it. “*Les minutes, mortel folâtre, sont des gangues. Qu’il ne faut pas lâcher sans en extraire l’or*.” Baudelaire! |
| Q2 | Do you enjoy reading? |
|  | Jacques Dubochet: Reading, yes of course. Ishiguro, very good! All the family is reading him know. My daughter read him before, but we discovered him only since the Nobel Prize. It is a very remarkable thing! |
| Q2 | When do you get your most creative ideas? |
|  | Jacques Dubochet: Morning, but no no! The right way, and I am not first one to say that is, is while walking. Before it was while jogging, now I am not jogging anymore, but walking in the forest. I think Nietzsche was saying things about that. Do not believe my great thing that I am writing on my desk are coming like that, no, they are coming while I am walking and from time to time I am able to keep them until I can write them down. That is exactly my feeling. Or under the shower! All my genius ideas are coming under the shower, but unfortunately, the minute after, they are no more genius. |
| Q4 | When did you get the idea for your Nobel Prize-awarded discovery? While jogging? |
|  | Jacques Dubochet: No, but the jogging was very important, yes. At that time I was jogging nearly every day, my ten kilometers. We were not numerous too. The institute was in the forest, it was a beautiful forest. It was ideal for that and we frequently went in a group. It was psychologically interesting, those who always want to be a bit quicker and those who are running three meters behind or three meters in front and those who are just running alone. |
| Q4 | What would you say is your greatest achievement in life? |
|  | Jacques Dubochet: I have tried all my life, I think now I can say it, to live harmoniously. Big, big, big, hard task, and to decide to make my life and I have had the chance to be able to do it relatively well as I wanted. I have given this recent time frequently for the young one and for the students and also I said it already to my students. There are two kind of fishes, the fishes going with the stream, they are the dead fish and there are the fishes going against the stream, they are the living fish. So I try to be a living fish. I was lucky and I feel that it went quite well. So my biggest achievement was that I think I could do that a bit correctly. |

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| **Biographical** | I was born on September 12, 1940 in Weidenau/Sieg, Germany. Since 1972 the town has been part of Siegen, a city with currently some 100,000 inhabitants, situated at the southern tip of North Rhine Westphalia. The mountainous area around it is called *Siegerland*, for centuries home of the iron mining, processing and manufacturing industry. Mining of iron went all the way back to the Celts, two thousand years ago. After mining and processing moved to the Ruhr area, only the iron manufacturing part remained − boilers, metal pipes, railroad tracks, buckets and many other parts made of iron and steel. Weidenau’s most prominent landmark is called the Fujiyama, a giant heap of slag from iron mining, matching the shape of the famous mountain in Japan. Siegen was also the seat of the House of Orange Nassau, related to the Dutch royal family.  The city of Siegen prides itself of being the birthplace of Peter Paul Rubens. However, the only reason he was born there and not in Cologne, his parents’ place of residence, was that his father got arrested as he was passing Siegen in a carriage with his pregnant wife, in a case of mistaken identity. The dispute between three cities claiming Ruben as their son – Siegen, Cologne and Antwerp – is immortalized in a fountain sculpture at Siegen’s Upper Castle showing three mothers holding, and fighting over, baby Peter Paul.  My father Wilhelm Frank was a judge (*Amtsgerichtsrat*) at the District Court in Siegen. He was born in 1896 in Weidenau. His study of law was interrupted by the draft to fight in Verdun in WWI where he was wounded, losing most of his left hand. His mother came from a wealthy local family, the Schleifenbaums, that owned a flourishing iron-manufacturing business, and his father was a high school teacher who came from a rural family in Banfe, in nearby Wittgenstein. My mother Charlotte came from the distinguished Manskopf family that traced its origins in Siegen back to the 15th century. A branch of her family settled in Frankfurt in the 18th century and gained wealth and notoriety from international wine trading. They were friends with Johann Wolfgang von Goethe’s family around the beginning of the 19th century.  My mother, educated in *Stift Keppel*, a high school for girls with a history going back to the 13th century, stayed at home, taking care of her four children – myself, my four year younger sister Renate and two older siblings: Ingeborg and Helmut. Our house was large and stately, solidly built from red double-glazed bricks by my grandparents in 1905. It was set on a good-sized plot bordered from the street by a wrought-iron fence. The house had verandas on the first and second floor overlooking the backyard. Walking paths were seamed with boxwood and covered with ornamental gravel. **The war** As I was born during WWII, my whole childhood was marked by the war. Siegen’s iron manufacturing industry made the city a target of the Allied raids, and eventually, by the end of the war, led to the destruction of 80% of all buildings. My first memories, at age four, were of houses in the neighborhood going up in flames. In one of the early raids in February of 1944, my parents’ house was fire-bombed. Since the roof and upper floor of our house were destroyed, and the rest rendered uninhabitable by extensive water damage, we had to move for over a year to Hilchenbach, a town 20 kilometers to the north, where a colleague of my father offered us room in his large apartment. This apartment was located in the *Williamsburg*, an 18th century water castle that served as the court building at the time. The memory of sitting in the bomb shelter, in the basement of the large building, surrounded by crying babies, and listening to the sounds of planes, air raids, and radio announcements were the stuff of nightmares well into my adolescence.  The time immediately after the war was one of great hardship. My mother went on “hamstering” trips into the country by train, traveling with zinc-plated buckets, manufactured by the company of her in-laws and much treasured by the farmers. She bartered them for butter, ham, big loafs of bread, flour, and eggs. Back home, she would mix “real butter” with margarine in a large bowl to stretch out the experience of tasting traces of real butter into weeks. We had a good-sized garden with apple, pear and cherry trees. For a while we grew sugar beets to make syrup and tobacco plants to support my father’s smoking habits. We kept chickens in the backyard, and even kept a pig at one time in the space under the veranda. Helping my 10-year older brother with the garden work and spending time with the chickens made me appreciate nature from a close range.  The sight of rubble of houses burned and collapsed in our neighborhood had a peculiar effect on me, a mixture of fright and fascination. The fright was the natural reaction to the sights of chaos and destruction, which implied to a child that nothing still standing is safe. The fascination part came from the experience of playing, together with other boys my age, on desolate lots filled with bricks, pots, twisted wires and Bakelite insulators. Here and there we uncovered a family of mice with pink stillblind babies. **School years** My elementary school, where I spent my first four years, was right across the street from our house. I was eight years old when I started my first experiments in the dark place underneath the veranda where our little pig once roamed. It was natural curiosity that made me do it, before I had any concept of science. I built a shelf, collected little *Magenbitter* liqueur bottles and filled them with every liquid I could get hold of: oil, water, gasoline and, when I was a little older, hydrochloric acid. In bouts of intuition I mixed the fluids, exposed metals to them and recorded the results. I watched calcium carbide dissolve in water and enjoyed watching the violent reaction and the smell of the escaping gas. I watched zinc dissolve and bubble up in hydrochloric acid. I heated up coal in a metal container connected to a tube since I’d heard that a flammable gas would escape.  My parents’ house contained one amazing treasure that would accompany me through all of my boyhood and adolescence, as soon as I was able to read: Meyers *Konversations-Lexikon*, an encyclopedia in 20 volumes published in 1905. Each volume measured about 1000 pages, filled with scholarly articles, technical drawings, colorful photogravures, and maps from all over the world. Quite possibly I read them all over the course of the years. As a whole, this large encyclopedia reflected the belief that all that ever needed to be studied was known already, and that progress from then on would be at most incremental. Ironically, 1905 happened to be the exact year when [Albert Einstein](https://www.nobelprize.org/prizes/physics/1921/einstein/facts/) published a paper on the photoelectric effect, with its evidence for the quantization of energy, the precursor of Quantum Mechanics. It would leave little of the old wisdom untouched. I would later claim the collection as my only bid for a tangible heirloom in my parents’ house.  Starting with fifth grade I went to the *Fürst Johann Moritz Gymnasium*, named after one of the prominent Orange Nassau dukes. I was one of only four to step up from my elementary class of twenty students. In the Gymnasium, which in the German system combines middle and high school, I immediately took an interest in science classes, particular physics. Meanwhile my tinkering at home had migrated from the place under the veranda to the attic of our house and expanded to include radios, which I rebuilt from used and mail-ordered parts. This obsession with radios started after my brother showed me how to build a crystal radio. I constructed several fancy miniature radios fitting in soap boxes. Most of my savings went into the purchase of valves, transistors, resistors, and capacitors. The attic was filled with the exciting smell of vapor from the soldering rosin. I made a friend in school who shared my hobby and lived across the street.  I should add at this point that all three of my siblings went to the same Gymnasium.  After receiving his Abitur (high school diploma) my brother finished his Ph.D. in Engineering and became a civil servant for Occupational Safety. Both my sisters left at the “Einjaehrige,” an early departure point from high school for a switch to a trade school, in their case a school for physical therapists. My elder sister finished her Abitur many years later after she married and her kids had grown up, proceeding to college and obtaining a Ph.D. in Biochemistry. My younger sister, after working as a physical therapist, became an artist and made many beautiful quilts until her early death in 1998, from cancer. **College** For me the choice of physics for study in college was always a foregone conclusion, though my father needed extra reassurance, as he doubted this would lead to a career that would ever earn me a living. In 1960, after finishing my Abitur I went to the University in Freiburg. The move into the little quiet university town with its large Gothic cathedral and charming medieval buildings was nevertheless a huge step for me coming from the provincial town I grew up in. I took Calculus and Linear Algebra, and learned how to write rigorous mathematical proofs. I also took courses in Special Functions of Mathematical Physics and Statistical Mechanics.  Following the example set by my brother, who had studied Engineering in Aachen, I joined a fraternity, Corps Suevia, and made several friends there. Later, though, influenced and enlightened by the political upheavals in the sixties, I decided to quit the Corps since I recognized the nationalistic, right-wing roots of German student organizations. Freiburg was also the place where *Martin Heidegger*, as rector of the university, had infamously aligned himself with the Führer. During my time there I saw the aged Heidegger, a little man, give one of his rare public speeches in front of the University, barely visible as a throng of students surrounded him.  Based on my performance in the Vordiplom (B.S. equivalent) exam, I was nominated for the *Studienstiftung des Deutschen Volkes*, a special fellowship that would prove instrumental in widening my horizon to include other fields of science and humanity. The Studienstiftung fostered interdisciplinary discourse by organizing meetings at the forefront of science. In one of these meetings, in 1964, I first learned about the tenets of the Central Dogma and the structure of DNA. I was also here that I met Wolf Singer, a neurophysiologist, starting a close friendship that would last until today. With him and like-minded students, I founded a discussion group focused on Cybernetics, the hot subject of the time. **Graduate studies** I went to the Physics Department at the University of Munich to do work toward my Diploma thesis, the equivalent of a Masters degree. The thesis project had to do with the back-scattering of electrons on gold in the liquid phase, an esoteric subject vaguely related to the then-emerging technology of machining with high-intensity electron beams. My mentor, Ernst Kinder, had done early work with the electron microscope, tracing the colorful patterns of butterfly wings to light interference created by submicroscopic arrangements of tiny scales. He still kept an ancient electron microscope in his office.  After finishing my diploma, when it came to choosing a Ph.D. thesis mentor, I was therefore prepared and open to the idea of working on a project that involved electron microscopy. The mentor I chose was Walter Hoppe, an X-ray crystallographer-turned electron microscopist at the *Max-Planck Institut für Eiweissund Lederforschung* on the Schillerstrasse in the center of Munich, which later relocated to Martinsried and became the Max-Planck Institute for Biochemistry. Hoppe looked for ways to use the electron microscope for imaging biological molecules in three dimensions. My thesis focused on an exploration of the properties of electron micrographs using methods gleaned from other fields, such as Statistical Optics. My first paper, in the journal Optik, examined the optical diffraction patterns of micrographs affected by specimen drift, and interpreted the stripes observed in terms of Fourier theory (Frank, 1969). I was proud when Hoppe refused to put his name on it, recognizing it as a totally independent piece of work.  My first experience in computer programming was with the programming language ALGOL, and involved a 20-minute walk to the Technical University for every compilation and every run of a newly written program. I later learned to program in FORTRAN on an IBM 1130 machine tucked in a little basement room of our Institute, where I sometimes worked late into the night. The Institute, located just minutes’ walk away from the *Wiesn*, the site of the *Oktoberfest*, had its own social life with distinct Bavarian color. Early-morning mushroom picking raids were organized when they were in season. The porcinos and pfefferlings brought back by the teams of three or four students – always including at least one expert – wound up boiling in Erlenmeyer flasks in the exhaust hood. They were sprinkled with salt and served with pieces from a big loaf of Bavarian bread. We celebrated the acceptance of papers with a keg of beer and big hunks of meatloaf in the library room.  Munich at the time, as now, was a city rich with cultural events. There were so many venues; it was possible to go to a classical concert every day. One of my friends, who also made the move from Freiburg to Munich, was a classical music aficionado and lured me to many outstanding performances. It was then that I learned to recognize many classical symphonies from a few opening notes. Little experimental theaters were abounding. The Munich Opera House offered a grand experience for affordable ticket prices. I spent my time with two circles of friends, one around Wolf Singer, whom I’d met through the Studienstiftung, the other around Jan Groneberg, a firebrand college dropout with utopian ideas who lived in a little cottage outside of Munich. It was in Wolf Singer’s circle of friends where I met my first wife, Cathy Engelberger. We married in 1969, but the marriage would last less than 10 years.  During this time, a meeting in Hirschegg, in 1968, gave me the opportunity to meet several people who later became important in the field. The workshop (as well as later ones) was co-organized by Walter Hoppe and [Max Perutz](https://www.nobelprize.org/prizes/chemistry/1962/perutz/facts/) from the Laboratory of Molecular Biology of the MRC in Cambridge, known for his pioneering work in protein X-ray crystallography. Among the people I met there were Harold Erickson, Richard Henderson, Ken Holmes, Hugh Huxley, and Nigel Unwin. With afternoons free for skiing, and both mornings and evenings reserved for the lectures and discussions, the format resembled that of the Gordon Conferences. Two papers (in German) related to my thesis were later published in the proceedings of the meeting, in a special issue of *Berichte der Bunsengesellschaft für Physikalische Chemie* (Frank et al., 1970; Langer et al., 1970). **Postdoctoral studies** After my thesis defense at the Technical University Munich in early summer of 1970 I was awarded a *Harkness Fellowship*, which allowed me to spend two years in the USA at labs of my choice. I chose the Jet Propulsion Lab (JPL) at Caltech in Pasadena, the Donner lab in Berkeley, and Cornell University. Coming from Europe, the culture shock of being placed into the Hollywood-like landscape of Pasadena with its restless freeways and little houses with palm trees and little old ladies with tennis shoes could not be greater.  In hindsight, all three labs gave me important impulses toward my future direction. The JPL at the time had the world’s best image processing equipment, and had developed a modular image processing system, VICAR, that I could hook my own programs to. This package would later serve as a model for developing my own system, SPIDER. At Donner lab, which was part of the Lawrence Berkeley labs on the hill, I spent time with the group of Bob Glaeser, who focused on two quintessential problems faced by structure research with the EM: radiation damage, and the need for a hydrated environment. He and his student Ken Taylor were already experimenting with the preparation of frozen-hydrated samples, but the decisive invention of the vitrification technique in Jacques Dubochet’s hands had yet to come. At Cornell University, in the group of Benjamin Siegel in Clark Hall, I made the acquaintance of Ken Downing and William Goldfarb. I later asked William to join me in Albany as part of my team.  While in Ithaca, in 1972, my son Hosea Jan Frank was born.  Returning from the USA, I spent a brief time back at the Max-Planck Institute, in the winter of 1972/73, working on the theory of partial coherence in electron microscopy. This work brought me in contact with Peter Hawkes, a world expert in Electron Optics. In 1973 I joined the group of Vernon Ellis Cosslett at the Cavendish Laboratory in Cambridge, still at its old location in Free School Lane, as a Senior Research Assistant.  Among the people I interacted with were Owen Saxton and Peter Hawkes. During my years at the Cavendish I worked further on partial coherence and found a way to obtain the signal-to-noise ratio of electron micrographs by computing the cross-correlation of two successive images of the same field.  This was the time when the vision of single-particle averaging and reconstruction took hold in my mind – the idea of spreading out electron dose among multiple “copies” of a molecule randomly arranged on the grid. In 1975 I published a concept paper presenting the idea that the structure of a molecule could be retrieved by taking advantage of multiple occurrences of this molecule in solution (Frank, 1975). Together with Owen Saxton I analyzed the conditions under which bright field images of biological molecules can be aligned with sufficient accuracy for the image average to reach a given resolution. The result of this study, which we jointly published in 1977 (Saxton and Frank, 1977), gave me confidence that the single-particle approach would work even under weak native contrast (i.e., protein vs. water) conditions. **Albany, and the Wadsworth Center** In 1975 I received a job offer from Don Parsons at the Division of Labs and Research (later renamed Wadsworth Center) of the New York State Department of Health in Albany, New York. While the original mission was tomographic reconstruction of cell sections, I focused on the implementation of the single-particle approach. In both areas I recognized the need for a workbench of programs to gain flexibility in the design of programs, and started on the development of SPIDER, an image processing system of modular design (Frank et al., 1981). As the single-particle techniques developed, SPIDER became the vehicle for disseminating the technique to the community. It was initially distributed under a license agreement, for a one-time fee, and later became available for free under a creative commons license.  It would still take a few years until proof of concept would be available with actual images of biological molecules. These were glutamine synthetase, provided by David Eisenberg at UCLA, acetylcholine receptor, by Peter Zingsheim in Goettingen, and ribosomes, by Miloslav Boublik, at Roche in New Jersey. Martin Kessel, an early convert and close friend, helped me in some of these studies as he took a Sabbatical leave from Hadassah University Medical Center. In each case, reproducibility of two-dimensional averages demonstrated that the approach was sound. Still, there was a lot of skepticism among practitioners of electron microscopy. A turning point came with the addition of a method addressing the problem of heterogeneity, which I developed jointly with Marin van Heel, a student visiting from the Netherlands in 1980 (van Heel and Frank, 1981). Looking for other suitable challenging molecules to try the technique on, I started a collaboration with Jean Lamy and his student Nicolas Boisset in Tours, France, to image a variety of arthropod hemocyanins. (I stayed in touch with Nicolas over the years until his untimely death in 2008. He had a meticulous way of record keeping and developed beautiful slides for teaching the principles of single-particle reconstruction).  Albany is the capital of New York State but has a distinctly provincial character, especially lying as it does in the shadow of New York City. The town is surrounded by beautiful countryside, and hikes into the Adirondack mountains are not far away.  The move to Albany not only gave me my first independent position, it also unleashed an urge in me for creative expression in areas not associated with science. I joined an artists’ collective, called WORKSPACE, founded by Jacy Garrett. At the time, performance art was being redefined across the country, and artists’ collectives were springing up everywhere. The FLUXUS movement directed attention to the peripheral, the accidental. I enjoyed being accepted by the collective without formal credentials, just by virtue of my creative contributions. I participated in mail art correspondence and, for several years, either edited or co-edited a small literary magazine called PROP.  At the end of the 70s my first marriage ended. The divorce agreement gave us joint custody over our son, an arrangement that would keep me in town for quite some time, as I would see Hosea grow and become a multitalented artist who renamed himself Ze. I was to meet my present wife, Carol Saginaw, in Albany in 1982. Carol worked initially at the New York State Office of Mental Health, then over the years was executive director of several statewide non-profit organizations in mental health and later in early care and education. Carol was from Michigan, from a Jewish family that had lost many of their members in death chambers constructed by the country I was from. Although our diverse backgrounds presented a challenge, we were married in 1983, and we have been happily together ever since. In good part it was Carol’s continuous support, and her faith in me, that made me prevail and come to the present point in my career.  At that time, I also started writing fiction in English and was quite flattered when William Kennedy, and later Steven Millhauser and Eugene Garber, gave me very positive feedback on my manuscripts. To me the idea that I might be able to express myself creatively in my second language was thrilling as I was unsure at this stage if I would ever return to live in Germany. After a course in fiction writing with Eugene Garber at SUNY Albany, the participants of his class, myself included, decided to continue meeting as a writers’ group. Constructive criticism by this group, and other groups that I joined later on, honed my writing and helped me recognize “my voice,” and writing became part of my life (*www.franxfiction.com*).  Looking back now, I see that my early contributions to single-particle EM were made possible mainly by three factors: the peace and quiet of the place where I worked, the absence of any teaching requirements, and the steady support by the National Institute of General Medical Sciences, of NIH, which lasts until the present day. I was quite fortunate to have Michael Radermacher join my team in 1982, a German student who had also trained under Walter Hoppe and had a special background in three-dimensional reconstruction with arbitrary geometries. Michael was the one who single-handedly designed the random-conical reconstruction programs in my lab that, in 1986, yielded the first three-dimensional reconstruction of a totally asymmetric molecule, the large subunit of the *E. coli* ribosome. By adopting the novel plunge-freezing and vitrification technique of Jacques Dubochet, we were soon able to reconstruct biological molecules in their hydrated, native state as well. From that point on, in the late 1980s, the technique we had been working on so hard was evidently headed for success, though it was still uncertain if it would ever be able to compete with X-ray crystallography in resolution and propensity to yield atomic structures.  Meanwhile, in 1985, our daughter Mariel Beth was born and became the center of our life. When she was two years old, I received the invitation for a Sabbatical stay at the Medical Research Council (MRC)’s Laboratory for Molecular Biology (LMB) in Cambridge, England, with Richard Henderson as host. We rented a charming little home, King’s Cottage in Little Shelford, with a flower garden where Mariel played with other children. We made punting trips on the river Cam and walked in the beautiful parks in the surroundings of Cambridge. Most of my interactions in the lab were with *Wah Chiu*, whom I first met as a student during my visit at Bob Glaeser’s lab, and who visited the LMB at that same time. With his help, and using his data on two-dimensional crystals of crotoxin, I developed and demonstrated *patch averaging*, a method of structure recovery that made use of “local” averages of a crystal divided into small areas – essentially the single-particle approach applied to pieces of a crystal.  Back in Albany, among the first molecules we reconstructed in 3D were hemocyanins, in continuation of our collaboration with Jean Lamy’s group in France. Another collaboration, with Sydney Fleischer of Vanderbilt University, gave me the first opportunity to work on the structure of the ryanodine receptor. Still, the work on the structure of the ribosome continued to fascinate me most. As early as 1990 I became convinced that my lab would be able to contribute significantly to the structure and function of the ribosome, and I started hiring biochemists with ribosome background. Rajendra Agrawal, trained in the Burma lab at the Baranas Hindu University, was the first to bring real “ribosomologist” expertise into the lab. Others would follow later, among these Christian Spahn, trained in the lab of Knud Nierhaus in Berlin.  A major factor promoting discussions in the growing cryo-EM community and the dissemination of the new technologies of sample preparation, instrumentation and data processing has been the Gordon Conference on three-dimensional electron microscopy (3DEM). Established in 1985, it met every two years initially and later switched to the present annual cycle. My election in 1987 to be Vice-chair in 1989 with David DeRosier and to be Chair in 1991 was a big step marking recognition of the single-particle techniques by the whole community.  A Humboldt-funded Sabbatical stay in 1994 at the Max-Planck Institute for Medical Research in Heidelberg, hosted by Ken Holmes and Rasmus Schröder offered me the first opportunity to work in Germany again. Through the efforts of my graduate student Jun Zhu and my postdoc Pawel Penczek, the first detailed map of the *E. coli* ribosome emerged, well before the X-ray structures came out. The putative placements, by Raj Agrawal, of tRNAs and mRNA into this map of the ribosome have stood the test of time. It was also in Heidelberg that I completed writing my book on 3D electron microscopy, which would be published in 1996 and, in a second edition, in 2006 (Frank, 2006).  In 1998 I was appointed a Howard Hughes Medical Institute (HHMI) investigator, a position that would last for 19 years and was only recently terminated. The funding by HHMI during these years was absolutely crucial for my lab to continue development of cryo-EM and realize very challenging biological projects with several collaborators. At about that time the Wadsworth Center joined eight institutions in New York City to form a consortium for structural research, called the *New York Structural Biology Center,* which supports NMR, X-ray crystallography, and cryo-electron microscopy. This connection provided entrées for me at Columbia University and other leading institutions in New York.  In 2000, on my 60th birthday, I organized a meeting in Rensselaerville, in continuation of a series of conferences started by Anders Liljas in Sweden on the Structural Basis of Translation. The conference site in Rensselaerville is set in a beautiful park, an hour driving distance from Albany. As I spent time during this meeting with Måns Ehrenberg we made concrete plans for collaboration on ribosome structure and function. This turned out to be the beginning of an exhilarating journey that has lasted until now, as we investigated the structural basis for initiation, decoding, mRNA-tRNA translocation, termination, and the recycling process, thereby contributing to the rich knowledge base on the mechanism of translation available today.  My children at this point were grown and on their own. My son Ze Frank had majored in neuroscience at Brown University and started a band, playing the guitar. His special talents for music and the arts had been in evidence early on. He subsequently moved to New York and began doing web design. Through a fortuitous route, which he recounted in his first TED Talk, he became an internet personality virtually overnight. Most recently he was a media executive at Buzzfeed. He now lives with his wife and two children in Los Angeles. My daughter Mariel Frank majored in linguistics at Barnard College. Speaking multiple languages, she taught English in Japan, worked for a Latinx non-profit organization and is now a programmer and curriculum developer at Code academy. She is married and lives in Brooklyn. **Columbia University** In 2008 I joined Columbia University as a faculty member of both the Department of Biochemistry and Molecular Biophysics, and the Department of Biological Sciences. After more than 30 years, this move from pastoral Albany to New York City was quite exciting as it offered many opportunities for collaborations. I brought the HHMI-owned FEI Polara microscope with me and, together with the FEI F20 microscope purchased as part of the startup, established cryo-EM at Columbia University. One area of collaboration I was immediately attracted to was single-molecule FRET, which had just been set up by Ruben Gonzalez coming from the Puglisi lab at Stanford.  For the first four years at Columbia, progress with our cryo-EM projects was slow as it was still limited by the poor quality of recording media. The situation changed radically when direct electron detection cameras were introduced commercially, transforming the field profoundly and opening up many new avenues in my lab for exciting collaborations, particularly on channel structures. A Columbia-wide cryo-EM resource facility has been recently created and, thanks to generous gifts by donors and the cooperation by the deans of all three campuses, Columbia is now headed toward becoming one of the world’s leading centers for cryo-EM.  Beyond the benefits to Columbia and the USA, looking at the way the new technology has recently spread across the entire industrialized world, I’m gratified to see that single-particle cryo-EM is now able to fill a huge gap in molecular structure research as membrane-bound channels and receptors, and also many large molecules with flexible regions can be tackled, promising to add significantly to the war chest of human medicine in years to come. **Acknowledgments and final note** The emergence of many near-atomic structures in the last five years in several labs has drawn the world’s attention to the many preceding years of work not just by the Nobel Laureates now honored and their groups, but by the whole cryo-EM community. Because, for perspective, it is necessary to note that since about 1990, when the technique started to receive recognition within the cryo-EM community, there have been major contributions by many groups to every aspect: sample preparation, automation of data collection, computation, validation and atomic model building. These contributions are too numerous to list, but instead I refer to a recent review of the whole field (Frank, 2015).  I have been very fortunate throughout the journey that has brought me to this point. I would like to express my gratitude to my family, particularly my wife Carol, for their steady support over this long time. My sister Ingeborg Berg, with her training in biochemistry, was the one person in my family who could appreciate the enthusiasm I expressed in letters to her early on. Among my friends I need to single out Martin Kessel for his early encouragement and support and Jose-Maria Carazo for so many brainstorms along the way.  As a final note, the recognition by the Nobel Prize is an experience both extremely thrilling and humbling. A lifetime achievement benefiting the whole of humankind – in the words of Alfred Nobel’s will − seems an idea so grandiose that only few can live up to it. [Ernest Rutherford](https://www.nobelprize.org/prizes/chemistry/1908/rutherford/facts/)? [Linus Pauling](https://www.nobelprize.org/prizes/chemistry/1954/pauling/facts/)? [Marie Curie](https://www.nobelprize.org/prizes/chemistry/1911/marie-curie/facts/)? Their shoes are difficult to fill. The event is also transformative since all of a sudden my life is defined, or confined, by the perceptions of many people I have never met. It dawns on me that there is no way back – for better or worse − to the life I was living before. This is why I’m grateful for this opportunity to tell my own story, in my own words. |
| **Autobiographical** |  |
| **Podcast** | No scirpt |
| **Telephone**  **interview** | [JF]  [Joachim Frank]: Hello  [Adam Smith]: Hello my name is Adam Smith calling from Nobelprize.org, the website of the Nobel Prize in Stockholm. Congratulations of the award of the Nobel Prize.  JF: Thank you very much.  AS: Göran Hansson mentioned that he woke you up with his phone call.  JF: Yes, although it’s, it’s sort of a race because we have a new dog and she wakes up very early in the morning. So this time it was the Nobel prize! [Laughs] Normally it’s the dog that wakes us up.  AS: That’s nice because that will ground you today. While everything else is rushing around she’s still …  JF: [Laughs]  AS: The committee have singled out the fact that you developed the image analysis methods to allow ensembles of biomolecules to be put together and produce 3D images from many 2D images. You’re interested in images generally. You’re a photographer I know. Is there something special about the way you view images that allowed you to do it do you think?  JF: I don’t know I’m just, I’m just very visually oriented. So I see patterns, I see structures, I see patterns very, very fast in a background and so forth. So I have a view when I walk around, sometimes I take pictures. I’ve had photographs in exhibitions and so forth.  AS: Yes indeed. Was there one moment where you suddenly realised how to put these ensembles together?  JF: Regarding the three-dimensional reconstruction, first of all the whole step of averaging, that was one step. But these are two-dimensional averages and how to get to three-dimensions requires two steps. One was to find relative orientations between the molecules which is difficult if you don’t know the structure. So it’s like a chicken and egg problem.  AS: Yes.  JF: And the other one is putting all that information together once you know the angles. So these are essentially different moments, so in terms of how to find the orientations there was an ‘aha moment’ in 1977 or something like this where I conceived of the random conical method.  AS: What does this technique allow us to see that we haven’t seen before?  JF: We now are able to see molecules in their free unconstrained functional states. If you have a molecule and you have a system *in vitro* in which you have all these different ligands and all the factors present. If you have a system in which the molecule actually can perform work. These systems exist, for instance for the ribosome, you can do *in vitro* translation of a messenger RNA if all the different ingredients are there. Or you can do something like transcription, all this. But you have molecular machines, and there you have a certain work cycle. Now the x-ray approach would be to try to get a particular state in a crystalline form. And so that would be one of the many states. And you don’t even know whether this is an important state. Whether it’s very populated because in forming a crystal you’re imposing some energy constraints. You want to minimise the energy of aggregating the molecules that has nothing to do with the functional conformation. Whereas in cryo-EM the molecules are actually there, they are frozen in the process of doing their thing. And since we have the capability of classifying all the views that exist in the same sample and extract all the corresponding 3-dimensional images we have a whole inventory of the molecular machine in its various states, and then we can connect them in some kind of a narrative.  AS: Yes you’re capturing it behaving naturally.  JF: Yes, yes. So that’s the important distinction.  AS: Lovely, thank you. Beautifully said. Now I’ll let you go but just one thing. Because you’re a photographer is there a possibility, do you think, that somebody around you or yourself could take a photograph and send it to me for Nobelprize.org? Possibly with your new dog?  JF: I do have a great image which actually has to do with… We were in Central Park and I took a picture of the dog sitting there and it was illuminated from the back, in a sunlit place, and one sees the projection of the dog on the ground. And me photographing the dog also.  AS: That would be absolutely splendid.  JF: This is a fantastic illustration of 3D, 2D, projections and so on.  AS: The whole Nobel Prize in one picture.  JF: Yes, yes. [Laughs]  AS: We look forward to welcoming you to Stockholm in December. You will be coming I hope.  JF: Yes, I’ll be coming with my family.  AS: Lovely. Well we look forward to the celebration. Thank you very much for speaking to me.  JF: Thank you.  AS: Thank you. bye |
| **Interview** |  |
| Q2 | When was your scientific interest first sparked? |
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| Q2 | Do you find that science and your art are related in any way? |
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| Q6 | When did you become interested in photography? |
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| Q6 | What do you remember of the war, growing up in Germany? |
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| Q18 | What are your thoughts on social media? |
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| Q18 | Does science and research still get the respect it deserves? |
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| Q1 | What do you learn from your meetings with young people? |
|  |  |
| Q9 | What were you doing when you received the call? |
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| Q9 | How has life been since you received the prize? |
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| Q2 | How well do you know your fellow Chemistry Laureates? |
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| Q5 | Have you been inspired by any Nobel Laureates in your field? |
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| **Chemistry\_2024-2000** | |
| **ID** | 0321 |
| **Biographical** | **Early years**  I was born in Edinburgh, Scotland, on 19th July 1945. My mother Grace Goldie, after two weeks convalescence, took me back on the train to Berwick-upon-Tweed, England, to re-join my father John Henderson, who was a baker at Bryson’s in Berwick. My mother was born in Edinburgh and my father in Tadcaster, North Yorkshire. They met in Edinburgh and started their married life in Berwick, where my father had been brought up. We lived in several rented flats in Berwick before moving when I was 3 years old to a council house across the river in Tweedmouth, where my father kept pigeons and then budgerigars. My mother persuaded Tweedmouth primary school to let me start early when I was four years old. I have no idea why she was so keen to get me out of the house. Just before my sixth birthday, my parents moved to the small rural village of Newcastleton, 2 miles north of the border between Scotland and England. My father was one of four bakers working in the local bakery, Oliver’s, graduating from baking bread to cakes. I attended Newcastleton primary school for 5 years (aged 6 to 10). Towards the end of primary school, the four most academic pupils in our class of 19 (Figure 1) were selected to attend Hawick High School, which is about 20 miles north of Newcastleton and was at that time accessible by a 45-minute morning and evening journey by steam train. We would set off at 8am every morning and get back at 5pm each evening. The total travel time of over an hour per day meant we were able to complete any homework during the train journeys. At Hawick, the classes were “streamed” by academic ability, with the entry year having 13 classes of about 35 pupils per class. The four of us from Newcastleton were in the most academic A stream (see Figure 2) and thrilled to be taught Chaucer, Shakespeare, Latin and French as well as Science, Mathematics and my favourite Metalwork. I also remember being delighted to find that mathematics lessons were subdivided into algebra, geometry and trigonometry.  My great aunt, who owned a corner shop in Edinburgh, sent me every week copies of all the children’s comics that were published in the 1950s, so I did read but definitely not literature. Although my mother tried to persuade me to read when I was young, I did not succeed in completing any novel until the compulsory school English syllabus forced me to read Walter Scott’s “Heart of Midlothian”, which I managed by reading 12 pages each night. When my paternal grandmother died, she left me a set of Arthur Mee’s “Children’s Encyclopedia”, which kept me occupied, especially on “Things to make and do”. Most children left school aged 15 at that time, so in our fifth and sixth form examinations, then called Highers and Lowers in Scotland, the entry year of about 400 pupils had dropped to about 55. For my final two years, at age 15 in Hawick and 16 in Edinburgh, my parents received a £50 family allowance to encourage them to encourage me to continue into higher level education.  When I was 15, the bakery where my father worked in Newcastleton ran into financial troubles. My father resigned and took a new job in Edinburgh about 3 months before I would sit my first national school examinations in June. My mother and younger brother Ross moved with him to Edinburgh, but it was decided that it would be best if I stayed on for 3 months with our next-door neighbours in Newcastleton, the Zurbriggens, so that I could sit the examinations without having to move to a new school. For my final (6th) year of High School, I moved to Boroughmuir in Edinburgh, following a recommendation by John Low, the headmaster at Hawick.  During that final school year at Boroughmuir, we were all asked whether anyone would like to apply to Oxford or Cambridge University, for which extra lessons geared to their entrance exams would be given, but only one Latin and Greek scholar decided to apply, unsuccessfully. Everyone else decided to apply to Edinburgh University, so when I started a Physics degree course at Edinburgh, I had four or five classmates from Boroughmuir and a similar number from Hawick. Our fourth and final year in Physics at Edinburgh University had a class of 45, including 4 others from Boroughmuir and one other from Hawick. Our final year Physics class photo is shown in Figure 3. The large representation from Boroughmuir arose from the enthusiastic teaching of our Boroughmuir physics teacher Bill Cow, or “Bilko”. Bill once played a recording to the 6th form physics class that he had made of a lecture by Dr Jack Dainty, Reader in Biophysics at Edinburgh University, in which he talked about his work on ion fluxes in *Nitella*, algae with giant cells. Bill’s view was that biophysics was an important developing area in the future of physics. Although it did not make a deep impact on my thinking at the time, it is possible that my later decision to follow a career in biophysics derived from this initial exposure to Bill Cow’s enthusiasm.  My mother, Grace, and both grandmothers were my strongest supporters; my father and grandfather were very busy working and often tired after working all day. My mother had to leave school at 14 to help earn money for her family (her father had been unemployed from 1930–1938 in the Depression), but had really wanted to continue in school, so my higher education allowed her vicariously to fulfil some of her aspirations. She was very supportive and delighted when I did well academically.  The following are some brief memories of the four schools I attended.  1. My first school was Tweedmouth West First School (at age 4–5), which was a 10-minute walk from our house. I can remember even then being fascinated by numbers, and less interested in literary topics. There was a strong emphasis on learning arithmetic skills, and I can remember reciting the “times tables” while walking to school. My paternal grandmother, Jinny Henderson, lived next door to the school, and a great aunt on my father’s side a few doors farther down the same street, so occasionally I would visit my grandmother for lemonade and a biscuit on my way home.  2. When we moved to Scotland, I attended Newcastleton Primary School. Newcastleton is a small village midway between the Scottish and English towns of Hawick and Carlisle, each about 20 miles away in opposite directions. Its population then was about 800, but this has since dwindled to about 600. The two teachers I remember were Miss Russell and Mrs Fleming (when I was aged 6–10). During the summer when we moved, my mother realised that the Scottish schools were ahead of the English schools in their syllabus, so I was set some exercises by Miss Russell during the summer holidays, so that I could catch up. One difference was that my new classmates had all graduated to writing with “joined up” letters, whereas in Tweedmouth everyone was still writing using separate “printed” lettering. In those days also, the UK currency consisted of pounds, shillings and pence. So, when our class was set some problems involving the long-division of money, which my new schoolmates had already been taught, I remember having no trouble completing the task from first principles and getting the correct answer. However, I was told that my procedure was not correctly laid out and that I should not make up my own method. Towards the end of primary school, our class was subjected to a series of tests or qualifying exams that were used to decide on the type of secondary school education each pupil would be offered. Scotland had introduced universal free education up to age 15 in 1945, in a parallel reform to follow the 1944 Butler Education Act in England and Wales. I realised much later that the tests were the Scottish equivalent of the 11-plus exam, although, having started school earlier, I was only 10 years old at the time. The outcome of this testing was that 4 of us from a class of 19 were sent off to Hawick High School, leaving the remainder of the class to continue for another 3 years of secondary education in Newcastleton, which had a separate wing for older pupils.  3. At Hawick High school, when I was aged 11–15, the teachers I remember were “Jeemie” Allen, an excellent maths teacher and dahlia fancier, and Bill McLaren, who taught us for gym and rugby. One of my Hawick classmates, Myra Thomson, wrote to me after the 2017 Nobel Prizes were announced to remind me of the occasion when I was told off by Jeemie for simply writing down the answer to a maths question without bothering to write out the working. I remember being quite surprised when I was 14 to receive a school book prize, valued at 5 shillings, for being placed 3rd in maths, 3rd in science and 3rd equal in geography, having in earlier years always been nearer the bottom of the class. I chose a paperback book called “The Cockleshell Heroes” about a daring kayak raid to sink some German battleships in the French river port of La Rochelle during the second world war. This may have led to my later enthusiasm for kayaking. Although I gradually worked my way up in maths and science at Hawick, my language skills were always poor, and I was the only one in the class to fail the “Lower” in French. In Hawick, there was a shop I visited in the school lunch hour along with one or two friends, which sold ex-WD (War Department) electronics, so we would acquire very inexpensive components and build our own valve radios.  4. At the end of my 5th year of secondary school, the headmaster at Hawick recommended three schools in Edinburgh for my final (6th) year of secondary school, namely Royal High, George Heriot’s or Boroughmuir. The first two had (nominal) school fees whereas Boroughmuir was free, so we chose Boroughmuir Secondary School. My final year of school, at age 16, was spent at Boroughmuir, with Bill Cow, an excellent Physics teacher, and Dr Young our chemistry teacher, who had a Ph.D. and had worked on explosives during the war. Since we had already finished our science “Highers” examinations at the end of the 5th form, the 6th form science had no special curriculum. One difference between Hawick and Boroughmuir was that the sciences were taught in an integrated class by a single teacher at Hawick, whereas there were separate physics, chemistry and biology classes at Boroughmuir. Boroughmuir also had selective entry, so that the overall academic level and teaching standards were higher than at Hawick, which was an all-inclusive comprehensive school. A few of us expressed an interest in biology and studied some plant biology in our free periods. Dr Young also allowed us to choose any chemistry experiment we wanted to do on Friday afternoons, when we had a double period of Chemistry. One member of our class decided to take advantage of our teacher’s wartime experiences to test a different explosive each week, so every Friday at around 3.30pm we all had to crouch down below the bench while that week’s test explosive was ignited. Only once was the explosion strong enough to leave marks on the walls. My abysmal performance in French was rectified by having tuition in the 6th year in a class that had only two pupils. I had failed Lower French at Hawick and my classmate had failed Higher French at Boroughmuir. After an entire year of individual tuition, I scraped through the French exam with a bare pass and was thus able to meet the entrance requirements for the University of Edinburgh.  In my academic education, I thus benefitted greatly from the post-war education reforms, which opened new opportunities for working class children and brought in free secondary school education for all. At one stage aged 13, I tried to drop French in high school, but our headmaster called me into his office and told me that I should not do that if I wanted to keep open the option of going to University, because a language at O-level (Scottish Lower) was an entry requirement. I don’t think I even knew of the existence of Universities at that point. **University of Edinburgh (age 17–20)** I pursued a B.Sc. in “Natural Philosophy” which was the traditional name for Physics. This consisted of 4 years of physics, maths and mathematical physics. [Peter Higgs](https://www.nobelprize.org/prizes/physics/2013/higgs/facts/) was our mathematical physics lecturer in 1962–64, at just about the time he was writing his famous paper predicting what came to be known as the “Higgs boson”. I was delighted finally to be allowed to focus entirely on the subjects I found most interesting.  During my undergraduate years, I took many jobs during the Christmas, Easter and Summer breaks, partly to earn enough money to pay for running a car, and partly to get direct experience of different working environments. With two school friends, we bought a car (£10 each) when we were 17. The car, a 15-year-old Morris 8 Series E, was very unreliable, so the three of us learned a lot about car engines, clutches, gearboxes, back-axles and half-shafts, since they all seemed to need frequent repair or replacement, mostly from scrapyards. Although only one of us had passed his driving test, he taught the other two. During the three summers from 1963 to 1965, I worked in the technical drawing office at the electrical engineering company Ferranti designing a slide projector, at the UK Atomic Energy Authority (UKAEA) at AWRE Aldermaston in a small group evaluating lithium-drifted germanium detectors for gamma rays, and with Dr John Muir in the Physics Department on a summer project using microwaves to analyse the dielectric properties of kaolinite clay, with support from a Carnegie Trust Vacation Scholarship. Each of these three positions exposed me to different cultures. In the company, it was very hierarchical: the man in charge of the drawing office did not cope well with the more competent students. At UKAEA, a science campus operating as part of the civil service, there were many brilliant scientists who were a pleasure to work alongside, but their research was part of bigger projects, so their enthusiasm was muted. In contrast, those carrying out research in the university were enthusiastic, highly motivated and clearly excited about their work. I therefore decided that an academic research career would be my best option. **Decision to choose biophysics for graduate research** During my final year as an undergraduate, I spent a long time trying to decide which of the many exciting directions that physics was taking would be most interesting for me in a future research career. I can remember considering fusion research which promised to provide unlimited power generation, solid state physics which has transformed our lives through development of a multitude of semiconductor devices, high energy particle physics which has led to a deep understanding of nuclear structure, or astrophysics which has transformed our understanding of the universe from the big bang to black holes, neutron stars and gravitational waves. In the end, I decided that biophysics had great potential in bringing the power of physics to understand biological phenomena. One of the most important factors in making this choice was that I was keen to do individual hands-on research either myself or with one or two close colleagues, rather than to work as part of a large team, which would have been essential for some of the other directions. The final year physics exam in Edinburgh consisted of 6 papers on successive days on different topics ending with a final essay paper with a broader scope, and encouragement to be somewhat light-hearted. I wrote an essay on “Time”, in which I explained that time consisted of the past, present and future. Since the past and present could simply be looked up in a history book or encyclopaedia, only the future was interesting. This then led into a consideration of where physics was heading, with a discussion of the above range of topics and ending up with the conclusion that biophysics had great potential and might offer rewarding opportunities for the individual.  Having decided on biophysics, the question was then where to go for a Ph.D. research project. Since, at the age of 20, I had no desire to do any more studying, attending lectures or sitting exams, this ruled out all American Universities, and on further investigation also ruled out Leeds (R.D. Preston, successor to Astbury) and Norwich, where Jack Dainty had moved to a Professorship, his promotion having been turned down by Edinburgh. Both those biophysics departments had compulsory M.Sc. degrees that took at least a year before they would allow students to pursue research for Ph.D. That left only King’s College London, which I visited in November 1965. I talked with many people at Kings (Randall, Wilkins, Jean Hanson, Jack Lowy, Watson Fuller, Struther Arnott), and eventually wrote back after my return to Edinburgh asking whether I might be allowed to work on surface forces with Dr Anita Bailey. King’s did not offer me a place immediately but said they would let me know next Spring. Having made my plan after a lot of investigation, I thought it might be tactful to go and tell our new Professor, Bill Cochran, who had arrived from Cambridge in 1964 and quickly built up an outstanding solid-state physics group, about my decision to go into biophysics. Without hesitation, he quickly advised me that I should write to his friend [Max Perutz](https://www.nobelprize.org/prizes/chemistry/1962/perutz/facts/) at the Medical Research Council (MRC) Laboratory of Molecular Biology in Cambridge (MRC-LMB). Somehow, in spite of all my efforts to talk to many other people in Edinburgh and to contact and visit other places around the UK, I had not managed to identify the MRC-LMB. This was primarily because most research in UK universities at that time was listed in the Science Research Council (SRC) Handbook. The MRC-LMB in Cambridge was listed only in the MRC Handbook, which was not available in the Physics Department. In contrast, King’s College Biophysics was both a Biophysics Department in the University and an MRC Biophysics Unit, so was listed in both handbooks.  I therefore wrote to Max Perutz in January, received a reply in February and visited the MRC-LMB on a Saturday morning in March for the student Open Day, arriving on the overnight train from Edinburgh and returning on the same evening. There were about 20 students visiting, almost all from Cambridge. David Blow gave an informal talk about some of the research. I was also interviewed individually by Max Perutz and [John Kendrew](https://www.nobelprize.org/prizes/chemistry/1962/kendrew/facts/). Kendrew simply asked whether I had any questions. I said I was concerned that I had studied no biology or chemistry, only physics and maths, but he said I should not worry: I could easily pick up biology and chemistry as I went along. The laboratory was a hive of activity with more people at work on a Saturday morning at MRC-LMB than in other places I had visited midweek.  On my return to Edinburgh I therefore immediately wrote to say I would be very interested in becoming a Ph.D. student at MRC-LMB. Perutz wrote back two days later accepting me. That year two physics students started as Ph.D. students at MRC-LMB. Peter Gilbert who was a Physics undergraduate from Cambridge was the other. I had also learned from Cochran that another physics student from Edinburgh, Keith Moffat, had gone to MRC-LMB the year before to start a Ph.D. with Max Perutz, so I also wrote to Keith and asked him to tell me a bit more about Cambridge, especially the College system, about which I knew very little. Keith very kindly replied with a 4-page letter giving a thumbnail sketch of the positive and negative aspects of each college. Keith recommended Darwin and Corpus Christi, largely because Corpus had just opened new postgraduate accommodation in 1964 in the George Thomson Building. I spent a year living in the George Thomson building, and later became a fellow at Darwin and an Honorary Fellow at Corpus. **Cambridge (age 21–24)** I carried out research for my Ph.D. at the MRC Laboratory of Molecular Biology in Cambridge (MRC-LMB), with a thesis on “X-ray analysis of chymotrypsin: substrate and inhibitor binding”. With David Blow, my supervisor, and [Tom Steitz](https://www.nobelprize.org/prizes/chemistry/2009/steitz/facts/), who was a Jane Coffin Childs postdoctoral fellow at that time, we worked out the mechanism of action of this enzyme, which was the first serine protease to have its structure determined. It was also the third or fourth protein structure to be determined at atomic resolution, after myoglobin (1959) and lysozyme (1964). The structures of chymotrypsin, ribonuclease and carboxypeptidase were all determined in 1967. By 2018, there were atomic coordinates for 140,000 macromolecular structures deposited in the Protein Data Bank (PDB).  Before I started my postgraduate work in Cambridge, I applied in June 1966 to attend a 2-week Summer School in Molecular Biology and Biophysics in Oxford, which was held to mark the inauguration of the Laboratory of Molecular Biophysics in Oxford, under Professor David Phillips. My application had arrived after all the places had been filled but Max Perutz had also written to Phillips in support of my application. Consequently, I received another letter a few weeks later from Oxford to say that “due to a withdrawal” I could now be offered a place. Thus, after a week or two at MRC-LMB, I spent 2 weeks in Oxford listening to 50 superb lectures by 25 outstanding scientists, including David Phillips, Max Perutz, [Fred Sanger](https://www.nobelprize.org/prizes/chemistry/1958/sanger/facts/), [Maurice Wilkins](https://www.nobelprize.org/prizes/medicine/1962/wilkins/facts/), [Aaron Klug](https://www.nobelprize.org/prizes/chemistry/1982/klug/facts/) and Mark Bretscher. The only lecture for which my notes were almost a blank, save for the word “supercilious”, was by [Sydney Brenner](https://www.nobelprize.org/prizes/medicine/2002/brenner/facts/). Brenner was arrogant but also very clever, and shared the 2003 Nobel Prize in Physiology or Medicine for his work developing the nematode as a model organism. One of the highlights of life at MRC-LMB in the 1960s was the Saturday morning coffee meeting in the “Molecular Genetics” kitchen where Brenner would entertain six or ten weekend researchers with his wide-ranging, acerbic comments, phenomenal memory and ability to provide an integrated overview of all aspects of molecular biology as it was then.  Having learned only a limited amount of chemistry at school, since the syllabus for Scottish Higher Science at that time stopped with inorganic chemistry, with only the briefest mention of organic chemistry, I attended Cambridge University Part IA organic chemistry in which Peter Sykes was the most memorable lecturer, and also spent one term doing ten afternoon laboratory practicals in synthetic organic chemistry, the most memorable of which was the synthesis of methyl orange.  Towards the end of my Ph.D., I spent some time thinking about what to do next. I had realised by then that MRC-LMB was a superb laboratory with many truly outstanding scientists, and that its success depended on a very deep investigation and understanding of a few very narrow research topics. However, with my own very narrow training in physics and mathematics, I also realised that I would need a much broader grasp of a wider range of problems if I were to be able to choose a productive research topic and research direction, following the philosophy of [Peter Medawar](https://www.nobelprize.org/prizes/medicine/1960/medawar/facts/)’s description of scientific progress as “The Art of the Soluble”. I therefore looked around for a postdoctoral opportunity where I would be able to get a much broader overview of the importance of different research areas across biology. I had been impressed by two scientists at Yale. One was Fred Richards (1925–2009) for his work on the structure and mechanism of ribonuclease, where his broad knowledge and insight had allowed him to provide the definitive explanation of the mechanism of action of the enzyme ribonuclease; although his structural work lagged significantly behind that of another US group at Buffalo led by David Harker, who had determined a better structure for ribonuclease, Richards was much more successful at explaining its importance and in relating structure to mechanism. The second impressive person at Yale was Jui Wang (1921–2016) in the Chemistry Department, who had proposed a hydrolytic mechanism for chymotrypsin that was appealing and showed deep insight into the chemistry of catalysis. I therefore wrote to both enquiring about the possibility of postdoctoral work. Wang replied immediately offering me a place, whereas Richards’ reply, although equally encouraging, did not come for 6 weeks: he was a keen yachtsman and was away sailing. I therefore decided to join Jui Wang and wrote two postdoctoral fellowship applications to the Helen Hay Whitney Foundation (HHWF) and the Jane Coffin Childs (JCC) Memorial Fund. Maclyn McCarty, the chairman of HHWF came to interview Jonathan Greer and me in Cambridge, and we were both subsequently offered HHWF fellowships. Since the HHWF stipend was higher than that of any other postdoctoral fellowship at that time, I accepted their offer, withdrew from JCC, and went to Yale accompanied by my wife Penny and our new-born daughter Jennifer, arriving in New Haven on 20th June 1970. It was Jennifer’s first birthday on the day we arrived at Yale. **Postdoctoral (age 25–27)** I thus ended up as a Helen Hay Whitney Foundation Postdoctoral Fellow at Yale University, in the group of Prof. Jui Wang for 2 years in the Chemistry Department, then spent my third year with Prof. Fred Richards in the Department of Molecular Biophysics and Biochemistry, with a bench in Tom Steitz’ lab. I tried to work on voltage-gated sodium channels in nerve and muscle membranes with the goal of determining the structure, but after 2 years decided that this goal was premature because the methods were inadequate, so then decided to tackle a simpler membrane protein, which was the light-driven proton pump bacteriorhodopsin, which had just been discovered by Walther Stoeckenius in 1971.  When I first arrived at Yale, based on my postdoctoral fellowship application and my own thinking at that time, I had planned to embark on two projects. The first was to label a peptide substrate of chymotrypsin with 13C at its carbonyl carbon and to carry out 13C Nuclear Magnetic Resonance (NMR) analysis to explore the chemical environment in the active site. The second was to choose another enzyme, perhaps slightly more interesting than chymotrypsin, and to purify, crystallise and solve its structure. I had written to David Blow to tell him about my plans and he replied to say that he thought Bob Shulman, then at Bell Labs in Newark, New Jersey might be already trying the 13C experiment, so he recommended that I should contact him. I did contact him and was invited to give a seminar at Bell Labs in 1970, where I met Shulman and Dinshaw Patel, his NMR right-hand man. After my seminar, in which I explained how I planned to go about obtaining an equilibrium concentration of the 13C-labelled enzyme-substrate complex using a high concentration of the substrate leaving group to increase the level of the desired structure by mass action, Shulman said it was a very good idea and they would do it. Since he had much better NMR facilities at Bell Labs than at Yale, I agreed to leave it to them and indeed George Robillard carried out and published the experiment, which provided some interesting insights.  I discussed my second proposed project with Wang. This was to purify and crystallise another enzyme. For this, I had selected NADP reductase from spinach, and purified it with one of Wang’s Ph.D. students, Jim Keirns. We succeeded in producing small pale-yellow crystals of spinach NADP-reductase before discovering that Martha Ludwig, by then at Ann Arbor, Michigan was already making progress on it. After some discussion with Wang, he explained that there were thousands of enzymes and, since I was still a young postdoc, it would be much better to pick a new longer-term problem that would come to fruition in 20 years, rather than aiming to take a small incremental step in a topical field. After a day or two, I realised that this was very good advice, and abandoned my initial plans to work on enzyme mechanisms and enzyme structure.  At that time, there was a lot of enthusiasm to understand the structure of membrane and membrane proteins, so I asked myself what was the most interesting membrane protein and chose voltage-gated sodium channels. Voltage-gated sodium and potassium channels had been at the heart of the 1963 Nobel Prize winning work of [Alan Hodgkin](https://www.nobelprize.org/prizes/medicine/1963/hodgkin/facts/) and [Andrew Huxley](https://www.nobelprize.org/prizes/medicine/1963/huxley/facts/), and for someone with a physics background these were very attractive research targets. In addition, Wang had published some theoretical speculations about the mechanism of ion channels, and was keen for someone to look for microwave emissions from ion channels in nerve membranes as they opened and closed during the action potential. We therefore ordered some microwave equipment, and I began synthesizing some small molecules which I hypothesized might bind to and block sodium channel currents in nerves. After synthesizing 3 or 4 compounds, I then spent a week or two looking around at Yale to find someone who could measure nerve action potentials, ending up by making contact and collaborating with Murdoch Ritchie, who was chairman of the Pharmacology Department on the Medical School campus on the other side of New Haven. Although all my compounds had absolutely zero effect on nerve impulse propagation, this initial contact nevertheless led to a fruitful 3-year collaboration with Murdoch Ritchie and two others based in Ritchie’s laboratory, namely David Colquhoun, who was a sabbatical visitor from London, and Gary Strichartz, another postdoctoral fellow.  Our experiments on ion channels that eventually produced some useful insights began with the idea of producing radiolabelled tetrodotoxin using a tritium gas electrical discharge. Prof. Martin Saunders, also in the Yale Chemistry Department, had a moribund basement laboratory that was full of spider webs, but also housed a fume cupboard, vacuum equipment and 10 Curies of pure tritiated water, T2O. After arranging to have the basement lab reactivated, I managed to produce some tritium-labelled tetrodotoxin, purify it using flat-bed electrophoresis, and in collaboration with Ritchie demonstrate specific tetrodotoxin binding to nerves and nerve membranes from a variety of sources. We published a number of interesting papers, but my early steps to extract and purify these volt-age-gated sodium channels (VGSCs) were disappointing, because the channels extracted using either Triton X-100 or deoxycholate detergent, were quite unstable with a lifetime of a few minutes at room temperature or a day at 4ºC. I guessed that it might take another 30 years to solve the stability problem so decided to abandon working on VGSCs and choose instead a simpler membrane protein, with the criterion that it should be stable after detergent solubilisation and available in reasonable quantity. The microwave experiments also failed.  In June 1971, I had attended a meeting in San Francisco of the American Society for Biochemistry and Molecular Biology (ASBMB) and heard a wonderful talk by Walther Stoeckenius describing his discovery of the purple membrane from *Halobacterium halobium* (subsequently renamed as *Halobacterium salinarum*) and his finding with Dieter Oesterhelt and Allen Blaurock that it was composed of a two-dimensional crystalline array of a single membrane protein to which the chromophore retinal was bound via a Schiff base in a 1:1 stoichiometry, responsible for its characteristic purple colour. After following the work that Stoeckenius and his colleagues Allen Blaurock and Glen King were doing during the next year or two to try to elucidate the structure of the purple membrane, I felt they were heading completely in the wrong direction. Therefore, in early 1973, I decided it would be an opportune time to try one or two new ideas to solve the structure of bacteriorhodopsin, the single protein in purple membrane. Bacteriorhodopsin fitted perfectly the criteria of being stable and available in large amounts. By chance, Don Engelman, then Assistant Professor at Yale, had worked with Stoeckenius as a postdoc a couple of years earlier and knew him well, so Don and I phoned up Stoeckenius and asked whether he could send us a culture of *H. halobium*, which he kindly did. Neither of my initial ideas, either to use heavy atom derivatives to determine the phases of the powder pattern rings by multiple isomorphous replacement, or to solubilise bacteriorhodopsin and crystallise it in three dimensions for X-ray crystallography, worked out but these were the two approaches I was pursuing when my 3-year postdoctoral fellowship at Yale came to an end.  Penny and I made many friends at Yale and have kept in touch with them over the subsequent decades. During our years in New Haven, Penny gave birth to our second child Elizabeth, born in January 1971, but she had hydroencephalus at birth and died just over seven months later. Our third child, Alastair, was born on 22 March 1973, a few months before our planned return to the U.K. **Back to Cambridge – 1973 until now****Phase I – bacteriorhodopsin at low resolution** We returned to Cambridge on 20th June 1973 to the MRC-LMB on a 5-year appointment, exactly three years after our departure in 1970 (on an American J-1 visa which had a 3-year limit). Jennifer was now four years old and Alastair three months. During my ultimately fruitless efforts to make any progress in analysing the structure of the purple membrane and bacteriorhodopsin using X-ray powder pattern phasing or three-dimensional crystallisation, I was impressed by a talk that Nigel Unwin gave in October 1973 in the annual MRC-LMB symposium. He spoke about electron microscopy (EM) using a phase plate made from a single thread of spider web silk coated with gold. He was clearly thinking that his images of tobacco mosaic virus contained features that represented the protein structure as well as the negative stain he was using to embed the structure. After his talk, we discussed using EM to study the structure of bacteriorhodopsin in its natural two-dimensional crystalline form without using any heavy metal stain. We worked together very productively for about 18 months, ending up with a low-resolution, three-dimensional structure of the first membrane protein, determined by a novel method. The structure showed seven well-resolved trans-membrane *a*-helices oriented almost perpendicular to the membrane plane, with the implication that this *a*-helical architecture might be found in other membrane proteins, as indeed it has. After that early success, I switched my efforts from X-ray diffraction to electron diffraction, and eventually to electron microscopy. Nigel switched from working on viruses using negative stain to working on membrane proteins and two-dimensional or helical crystals without using heavy metals, so our 1973–1975 collaboration had a profound impact on the direction of both of our future scientific careers. We were jointly awarded the 1999 Gregori Aminoff Prize of the Royal Swedish Academy of Sciences. A photograph of us taken around that time is shown in Figure 4. **Phase II – bacteriorhodopsin at high resolution** After spending about 7 or 8 years unsuccessfully trying to extend the resolution of our bacteriorhodopsin map from low resolution (7 Å) to high resolution (3 Å), where we expected to resolve the chemistry of the structure (i.e. to see the amino acid side chains and understand the mechanism), I eventually concluded that the methods that our group had been trying (model building, molecular replacement and heavy atom derivatives) were simply not powerful enough, and that we would have to embrace the necessity of recording high resolution electron cryomicroscopy (cryoEM) images. We did this from 1984 until 1990, by visiting and collaborating with a number of other laboratories (EMBL Heidelberg with Jacques Dubochet and Jean Lepault; Fritz Haber Institute Berlin with Fritz Zemlin and Elmar Zeitler; and Berkeley with Ken Downing and Bob Glaeser) as well as trying to improve our in-house EM capabilities in Cambridge. Eventually, the problems of high-resolution cryomicroscopy imaging and computer-based image processing were largely solved and we obtained a high-resolution map in 1990, into which we were able to build a nearly complete atomic model of bacteriorhodopsin. In the end, it was only the second membrane protein structure to be determined at high resolution. The first was [Hartmut Michel](https://www.nobelprize.org/prizes/chemistry/1988/michel/facts/)’s bacterial reaction centre membrane protein complex from *R. viridis* solved by crystallisation and X-ray crystallography, for which he shared the 1988 Chemistry Nobel Prize with [Johann Deisenhofer](https://www.nobelprize.org/prizes/chemistry/1988/deisenhofer/facts/) and [Robert Huber](https://www.nobelprize.org/prizes/chemistry/1988/huber/facts/). After 1990, Sriram Subramaniam and I did some trapping of intermediates to help work out the mechanism of the bacteriorhodopsin light-driven protein pump. Our bacteriorhodopsin work was essentially completed by 1999.  On a more personal note during this period, Penny and I arranged an amicable divorce in 1988, Jennifer married Richard Morris in 1993, I married Jade Li in 1995, and Alastair married Laura Williams in 1999. The resulting clan including 6 grandchildren all came to Stockholm on 10th December 2017 (Figure 5). **Phase III – single particle cryoEM** From 1995, following publication of a review I wrote on “The potential and limitations of neutrons, electrons and X-rays for atomic resolution microscopy of unstained biological molecules”, I was convinced that the future of cryoEM would involve imaging of single particles embedded in vitreous ice, a specimen preparation method that had been developed by Jacques Dubochet’s group in the 1980s. This “single particle cryoEM” method was potentially very powerful because it did not require the protein of interest to be crystallised nor did it require the use of crystallographic methods, which was what I had worked on exclusively until that point using X-ray and electron diffraction. Single particle electron microscopy had started with the image processing methods of Joachim Frank and Marin van Heel, as well as Owen Saxton and Wolfgang Baumeister, prior to the development of Dubochet’s plunge-freeze method of producing thin films of amorphous ice, but it was the combination of the two that promised to be particularly powerful.  We worked from 1995 until 2013 to analyse the problems and barriers to making progress, and gradually understood and solved them. The most important were the need for brighter sources, better vacuums, more stable cold stages and better detectors. The electron microscope companies, under pressure from users, addressed the first three. Our group in Cambridge, collaborating with another group at Rutherford-Appleton-Laboratory (RAL) near Oxford, worked out how to improve the detectors, and other people developed better computer programs to take advantage of some of the features of the new detectors (Steve Ludtke, Niko Grigorieff, and Sjors Scheres). As a result, almost overnight in early 2013, everyone started to obtain maps with much higher resolution. This was termed the “Resolution Revolution” by Werner Kühlbrandt (*Science* (2014) 343, 1443). From that point on, there was great enthusiasm from the entire structural biology community and a wider adoption of single particle cryoEM methods, so that now in 2018 cryoEM has become the prime method for many structural biology problems. **Other contributions** I was Joint Head of the Structural Studies Division at MRC-LMB (1986– 1999), Director of MRC-LMB (1996–2006) and a member of the Medical Research Council, which is the governing Board of MRC (2008–2014). Previous Directors were Max Perutz (1962–1979), Sydney Brenner (1979–1986) and Aaron Klug (1986–1996). The current Director is Hugh Pelham (2006–2018). All previous directors at MRC-LMB were also Nobel Prize winners. Probably the most significant achievement that we made during my Directorship was to advocate in 1999 the construction of a new building to house the MRC Laboratory of Molecular Biology in the 21st century, to carefully time the initiative to request funds for the construction to coincide with an upswing in the economic cycle around 2003, and to negotiate the subsequent hurdles for land acquisition and planning permission. This resulted in a superb new 30,000 square metre building, which opened in 2013, is attuned to the needs of modern molecular biology, and has the flexibility to have space reconfigured to parallel the changing needs of research. During my time as Director, Hugh Pelham as Deputy Director took a deep interest in the design and layout of the new building and carried the early planning through to completion during the first half of his Directorship. At the same time, Dr Megan Davies, the Assistant Director from 1996 and Head of the MRC Centre in Cambridge, ensured that our relationships with MRC in London and the local biomedical community in Cambridge were strengthened. An initial invitation soon after I started my Directorship to have dinner with Dr Keith Peters, the Regius Professor of Physik (an old term for Medicine) and Head of the Clinical School, developed into an annual strategic tête-à-tête that helped to keep the interests of MRC-LMB aligned with those of the Clinical School and the NHS Addenbrooke’s Hospital Trust. **Nobel ceremony** My wife, Jade Li, and I spent a wonderful 10 days in Stockholm for the awards of the 2017 Nobel Prizes, with the good fortune to be able to hear the Physics lectures about how gravitational waves were observed for the first time, to meet the [Physiology or Medicine laureates](https://www.nobelprize.org/prizes/medicine/2017/summary/) who had worked out the molecular basis of circadian rhythms, and also the literature and economics laureates, [Kazuo Ishiguro](https://www.nobelprize.org/prizes/literature/2017/ishiguro/facts/) and [Richard Thaler](https://www.nobelprize.org/prizes/economic-sciences/2017/thaler/facts/). A photograph of our family taken on the stage of Stockholm Concert Hall immediately after the awards is shown in Figure 5. |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** | [RH]  Richard Henderson: Hello, Richard Henderson here.  Adam Smith: Oh hello. My name is Adam Smith calling from Nobelprize.org, the website of the Nobel Prize in Stockholm. Congratulations on the award of the Nobel Prize.  RH: Thank you very much.  AS: How did you hear the news?  RH: I’m at a meeting about cryo-EM in Leicester University so I’m just in the session listening to people speaking. So my phone rang in the meeting, and I had to go out of the room, the lecture room, to hear it. And by then the reception had been cut off a couple of times. But eventually after about five minutes I managed to get through and then I chatted to Gunnar von Heijne who I knew first, and then three other people from the Nobel Prize Committee. And then they told me that the Chemistry Prize was going to be awarded with Jacques Dubochet and Joachim Frank who of course I know very well, so I think that’s quite delightful really. Of course there were a few other people who also contributed. But I think all of us know the Nobel Prize awards are always, usually only to three people. So there are often one to two others who’ve made strong contributions who didn’t quite cross the threshold.  AS: The meeting is a wonderful environment to hear in because I imagine that everybody will be celebrating today.  RH: It’s quite a small meeting. There’s only sixty people or something.  AS: Nice for a celebration. You were the first to achieve atomic resolution of biomolecules with cryo-EM. What does it allow you to see? What detail can we now see that we couldn’t see before?  RH: I think the first structures of biological molecules were by x-ray crystallography back in 1959, 1960, with [John Kendrew](https://www.nobelprize.org/prizes/chemistry/1962/kendrew/facts/) who had a Chemistry Nobel Prize for work on myoglobin and developing the x-ray methods. And since we’ve had over the last 50 years hundreds of… at least a hundred thousand structures done by x-ray crystallography, so in a way cryo-EM is just another method of finding out what the atomic structure, high-resolution structure, of your molecules are. But the difference is there are quite a lot of structures in biology that were resistant, were recalcitrant to the other methods, like x-ray crystallography or nuclear magnetic resonance spectroscopy. So it has opened up essentially a kind of new, previously unapproachable area of structural biology. And I think my original work was working on membrane proteins which we found difficult to crystallise. The real power has come from the images where you don’t need crystals, so you just take a picture, you look at it, you process it, you average structures, you get the… so it is a much more direct method than making crystals, getting diffraction plots and then figuring out what the diffraction plots mean. So I think it’s a direct method, easy to understand and much more general in its power and what you can use it for.  AS: Thank you. This is another Nobel Prize for the MRC-LMB for structure determination.  RH: [Laughs] Yes.  AS: It seems that its specialness continues. What is it that makes it such an extraordinary place?  RH: I think it’s got long-term support from the Medical Research Council. And actually this is the 105th year that the UK Medical Research Council has been supporting either medical, or biomedical, or biology-related-to-medicine structural work, and they’ve got a lot of experience in managing groups, units or institutes, and actually they’ve been quite bold in terms of supporting new ideas, and actually closing down other areas that have fulfilled their purpose. The MRC Molecular Biology Lab in Cambridge of course benefitted greatly from the people who founded it back in the 50s. So [Max Perutz](https://www.nobelprize.org/prizes/chemistry/1962/perutz/facts/) was the original first head, he called himself a chairman, and he was very good at recruiting people, allowing them to follow their own ideas in depth. And so that culture has permeated throughout the lab since it started, and that’s, I mean, there’ve been little gaps, but periodically there have been Nobel Prizes for all sorts of different things actually.  AS: Yes indeed.  RH: So it’s been a very successful lab. Obviously I went there as a student. I’ve been there for 51 years or something like that. So, you know, I’ve certainly absorbed the culture and helped to try and propagate it for the future.  AS: Well how nice to find such a good home. They say there’s a Nobel Laureate on every floor of the LMB and now they have another.  RH: [Laughs] Yes, quite a lot of them have retired now, so actually it’s good to have one or two new ones. And I actually partly retired.  AS: We very much look forward to welcoming you to Stockholm in December. Will you be coming?  RH: Oh yes, I’m sure I’ll be able to come, even if I’ve got another booking I’m sure I can change it.  AS: Once again, congratulations, and it was lovely to speak to you. Thank you.  RH: Many thanks then.  AS: Thank you, bye bye. |
| **Interview** |  |
| Q2 | What was the moment when you decided to pursue science? |
|  |  |
| Q6 | How was it to grow up in rural Scotland? |
|  |  |
| Q2 | Has hill walking and exploring fed into your science? |
|  |  |
| Q9 | How did you learn you had received the Nobel Prize? |
|  |  |
| Q9 | What has receiving the Nobel Prize meant to you? |
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| Q15 | What impact has cryo-EM had in the world? |
|  |  |
| Q15 | What has been your invention’s greatest benefit to humankind? |
|  |  |
| Q10 | What is the power of the tea break in a scientific setting? |
|  |  |
| Q1 | What advice would you give to a young researcher? |
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| **Chemistry\_2024-2000** | |
| **ID** | 0322 |
| **Biographical** | I was born on October 21, 1944 in Paris, just before the end of the second world war and a few months after Paris had been liberated by the allies and the French army led by General Charles de Gaulle (August 19–25, 1944). My mother’s name was Lydie Angèle Arcelin and her family came mostly from Normandy. She was born in 1920. My father was Camille André Sauvage and came from the northern part of France. Camille Sauvage was known as a successful jazz musician, both conductor and clarinettist on top of being a composer. Just after the war, he was a popular jazz player and, later on, he composed for French radio, television and movies. When I was a baby, my parents broke up. I stayed with my mother while my father departed to pursue an artist’s life. While I was still a young child, my mother met an officer in the air force, Marcel Louis Grosse, and they founded a family. I was thus fortunate to have a stepfather who took care of me until I became an adult and whose role was truly that of my father. Thus, I always considered him as my real father and I still do. Since my stepfather was in the military and because my parents loved to travel from one place to another, I had a very mobile childhood. When I was three years old, we moved to North Africa, as Algeria and Tunisia were still French colonies at that time. I still have vivid memories of our time in Zarzouna, a small village close to Bizerte in Tunisia. I also spent some time near Oran, in Algeria. I went to school in Tunisia between the ages of 5 and 7. At that time, the French kids and the local Tunisian kids were together in the same classes and I do not believe there were any difficulties related to the fact that the French kids and the Tunisian ones were mingling.  My mother and my grandmother, Suzanne Arcelin, were very close to one another and my grandmother, who used to live in Paris, visited our family a few times. On one particular occasion, we went to southern Tunisia for sightseeing and the photo which is shown below is particularly representative. It was taken when I was about 4 years old.  From 1951 to 1952, my family spent some time in the USA since my stepfather had to become a military engineer in the field of radar applications, a relatively new technology at the beginning of the 50s. We thus spent 6 months in Saint Louis, Missouri, followed by an additional period of 6 months in Denver, Colorado. I had no difficulty in adapting and, in Denver in particular, I used to play with the other children of our neighbourhood. In Saint Louis, we used to go to the movie theatre from time to time and it was of course a very enjoyable event for me. The picture shown below is interesting in the sense that one can see who were the most popular actors of the time.  When we returned to France, we started a long period of itinerancy, spending a few months in a given place before moving to a new city. I thus went to 4 or 5 different schools in the western part of France and in the Paris area when I was 8 to 10 years old. My mother became ill when I was about 10, and it was a difficult moment for my family. She had contracted tuberculosis, which was a very serious disease in the 50s. I was thus mostly with my grandmother for about a year, in the family village of Pacy-sur-Eure in Normandy. After this period, I was again with my parents, who moved to the eastern part of France in the Lorraine region. When I was 15 years old we moved to a small village in the north of Alsace, Drachenbronn, because my stepfather had been transferred to the radar station located on the Maginot Line named “Base Aérienne 901 Drachenbronn.” This move coincided with the beginning of my high school studies and I thus went to the high school in Haguenau, a middle-size city not far from air base 901.  I started to be very interested in chemistry when I was 15 or 16 years old and, in particular, I liked to play with natural molecules such as chlorophylls which I extracted from plants. I had a small and very primitive chemistry lab in the cellar where I was separating chlorophylls on paper or distilling various mixtures. At school, I was probably better in mathematics than in physics or chemistry but the interest of pupils for various topics is obviously very dependent on the personality of the teacher.  After my ‘baccalauréat’ (the French examination obtained at the age of 18 which enables one to begin university), I decided to enter a special and highly competitive structure named ‘classes préparatoires’ which was aimed at preparing the young people to compete for admission to engineering schools. Thus, after two years of a rigorous regime where leisure was limited to a strict minimum, I succeeded and I was admitted to the Chemical Engineering School of Strasbourg. This was exactly what I wanted since I could stay in my new but already beloved city.  I obtained my engineering diploma in 1967 and started my PhD thesis in 1967 under the guidance of Professor [Jean-Marie Lehn](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1987/lehn-facts.html). Jean-Marie had founded his own research team a few years before I started to work with him. He was only 5 years older than I and his research team was developing rapidly in terms of size and breadth of his research interests. Being more a physical chemist up until 1967, he had become interested in making new molecules with novel properties when I started with him. At the time Bernard Dietrich, formally a technician, decided to start his studies so as to become a graduate student, hoping also to do a PhD thesis. Bernard rapidly became my best friend and we worked together in the friendliest atmosphere imaginable between 1968 and 1971. Under the guidance of Jean-Marie we were highly successful, since we made the first macrobicyclic compounds able to encapsulate various ions, including alkali and alkaline earth metal cations (cryptands and cryptates for the metal-free compounds and their complexes respectively). In Jean-Marie Lehn’s research group, I was able to acquire a solid background in organic and physical chemistry, thanks to my own work and to various seminars and group meetings as well as to the many hours I used to spend in the library. Discussions with Professor Lehn and with other members of the group were also very fruitful. Equally important was the influence that Jean-Marie had on me in terms of the relationship between researchers within a group. In particular, I enjoyed his way of managing a research team. He was very direct, placing basically no barrier between him and the PhD students or postdocs he was working with. In other words, hierarchy was reduced at its minimum and this is something which I tried to preserve later on in my own group. Inspired by Jean-Marie’s passion for science, I also became enthusiastic and determined to devote my life to research.  I met my wife Carmen in 1967 and we got married in February 1971. Carmen was a student in History of Art and Archaeology. She was particularly interested in ancient ceramics and had participated in several excavation campaigns on the Anatolian plateau, in Turkey. Although we were not especially religious, we had a religious wedding mostly to respect family traditions (Figure 3). The wedding took place in Thierenbach, a village in the south of Alsace which used to be a place of pilgrimage and which is nowadays famous for its basilica.  We were very happy to become parents of a baby boy, Julien Clément Sauvage, on July 13, 1975. It was a great joy for us. Since Julien’s early childhood we have been very close to him. In 2011 Julien married Diana, originally from Colombia, and since 2012 they settled down in San Francisco. They had a baby on April 9, 2016 so that Carmen and I became the happiest grandparents in the world.  At the end of my PhD thesis work, I obtained a CNRS position as ‘chargé de recherche’ (research assistant) in Jean-Marie Lehn’s group, which corresponded exactly to what I was so eager to get.  After my PhD thesis, I obtained a postdoctoral fellowship in Oxford (UK) where I spent a year in the research group of a very visible organometallic chemist, Dr Malcolm L. H. Green. Malcolm was considered as one of the most brilliant former students of Professor [Geoffrey Wilkinson](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1973/wilkinson-facts.html) (1973 Nobel Laureate in Chemistry with Professor [Ernst Otto Fischer](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1973/fischer-facts.html)). He was a very influential person in expanding my interests to transition metal chemistry and organometallic chemistry. He was also a friendly person who used to do experimental work by himself from time to time. Life in Oxford was particularly pleasant and we used to enjoy the city, its colleges and its parks. We easily adopted the way of life of the other members of the Oxford community.  After my postdoctoral stay in Oxford, I came back to Strasbourg and more precisely to the Lehn laboratory as a permanent researcher. After some work in the field of chiral crown-ethers, Jean-Marie and I initiated a research project in a new field, at least in Strasbourg. It was related to photochemistry and solar energy. The first oil crisis took place in 1973 and it was a clear signal that alternative energies had to be found and that sustainable energies were crucially needed. Solar energy was an obvious and especially attractive option. A particularly appealing project was that of splitting the water molecule to H2 and ½ O2 in order to generate a non-polluting fuel, H2, using photonic energy. Such a big project had already been explored for many years by several groups and there were already discussions and research works published on this general topic in the 50s and later on. More or less at the same time, the ruthenium complex Ru(bipy) 32+ (bipy : 2,2′-bipyridine) was shown to display promising electronic properties in its ground or excited states, in particular in relation to electron transfer and potentially photochemical water splitting. In 1977 we published one of the very first systems leading to photochemical water reduction to H2 based on a combination of species such as in particular Ru(bipy)32+ as a photoactive species and Rh(bipy)33+ as an electron relay leading to H2 formation. After two years of studies on this original system (with Jean-Marie Lehn and Michele Kirch) and related ones as well as on the development of a light-driven oxygen generating system from water (with Jean-Marie Lehn and Raymond Ziessel), I was lucky enough to be promoted to the position of CNRS Research Director, the equivalent of University Professor. I thus founded my own research group in 1980, at first with two highly motivated PhD students, Pascal Marnot and Romain Ruppert. After one or two years, Jean-Paul Collin, a CNRS fellow, and Marc Beley, an Associate Professor, joined our small team. Simultaneously a good friend of mine, Christiane Dietrich-Buchecker, also joined.  As it is often the case for young research teams, we tackled several research projects in parallel in relatively remote areas. Electrochemical reduction of CO2 using [Ni cyclam]2+ as an electrocatalyst led to remarkable data since CO2 could be reduced very selectively to CO in water. This was somewhat surprising since H22 was expected to be obtained as a major reduction product. We also did work in homogeneous catalysis and inorganic photochemistry. In this latter field, our projects were mostly triggered by a collaboration with David R. M. McMillin, who was on sabbatical leave in Strasbourg. David was an already well established photochemist and photophysicist. He was a professor at Purdue University (West Lafayette, Indiana, USA) and his main field of research was photochemistry of copper(I) complexes. This collaboration between our group, with its skill in organic synthesis, and David led to a series of particularly interesting photoactive copper complexes. Perhaps even more importantly, it led to a copper(I) complex containing two intertwined organic ligands which appeared to be the ideal precursors to a compound comprising two interlocking rings. It was thus very tempting to jump from inorganic photochemistry to interlocking ring compounds which, at the beginning of the 80s, seemed to be practically inaccessible molecules. This jump was made possible due to the expertise of Christiane Dietrich-Buchecker, who was a great organic chemist. After a few discussions within our team, we decided to take the risk and to embark on a totally new project concerned with the synthesis of catenanes (i.e. interlocking ring compounds). Within a few months, Christiane was able to develop an efficient preparative procedure for making our first [2]catenane (containing 2 interlocking rings). Respectable quantities could be obtained: batches of 0.5g could be prepared, in particular by Jean Weiss, a PhD student also supervised by Christiane, and the first compound was fully characterised using a variety of techniques. 1NMR provided the first convincing evidence that a [2]catenane was indeed produced. These experiments were carried out by Jean-Pierre Kintzinger, a friend of mine and the brother-in-law of Christiane, who was at the same time an NMR expert. We published our first paper in this field in 1983 in an acceptable but not high-impact journal (*Tetrahedron Letter*). For us it was the beginning of a new era, mostly but not exclusively devoted to interlocking rings compounds and knotted molecules. The field has often been referred to as “Chemical Topology” due to the fact that the compounds have non-planar molecular graphs. In other words, contrary to almost all the molecules known, it is impossible to draw them in a plane (i.e. a sheet of paper) without crossings, regardless of the deformation the molecule can be subjected to.  Besides chemical topology and molecular machines, our group has been active in various relatively remote fields. The principal alternative research area has been that of artificial photosynthesis, with a particular emphasis on photoinduced charge separation, one of the key processes of natural or artificial photosynthesis. In order to elaborate efficient models of the natural photosynthetic systems, and in view of realising the complete water splitting cycle in the future, our group synthesised numerous multicomponent complexes, either incorporating metal-complexed porphyrins or second or third row transition metal complexes (Ru, Os, Rh and Ir) able to undergo light-induced charge separation. Following the synthetic work, the photochemical and photophysical properties of most of the compounds were investigated in various places by more physical chemistryoriented research teams than ours. In particular a long-term collaboration with renowned photochemists located in Bologna turned out to be especially pleasant and fruitful (Balzani and his co-workers, University of Bologna, or Flamigni and Barigelletti, Consiglio Nazionale delle Ricerche, Bologna). Some of the charge separated states were shown to be remarkably long-lived, thus paving the way to real artificial photosynthetic devices reminiscent of the photosynthetic apparatus of green plants or photosynthetic bacteria.  I would like to stress that encounters with various people played a very important role in my professional life. Two teachers were particularly influential when I was a student: Raymond Weiss, who was a very rigorous physical and inorganic chemist, and Guy Ourisson, an exceptional organic chemist who was able to convince all the students he was teaching to that organic chemistry is exciting and can even be fun. Jean-Marie Lehn also had a great impact on my enthusiasm for science and to me he was the perfect model, although this model was totally out of reach. One of the most important encounters was that with Christiane Dietrich-Buchecker, a wonderful person and a great organic chemist whose contribution to the scientific production of our group turned out to be determinant. Finally, it may appear as surprising that Fraser Stoddart and I never looked at each other as competitors. Even more, we both tried to avoid any overlapping with the activities of the other research team. This is mostly because we became friends at the end of the 70s and this was the beginning of a faithful friendship which allowed us to work in a more serene atmosphere than if we had tried to overtake each other. Between 2010 and 2013, I was appointed as visiting professor at Northwestern University, where I collaborated primarily with Fraser and his team. I also enjoyed interacting with other colleagues at this great university. I am particularly grateful to Fraser for arranging for me to get such a position.  I would like to conclude with two pictures separated by approximately 29 years. The first one, Figure 4, was taken at the ceremony to honour Jean-Marie Lehn’s Nobel Prize in 1987. This ceremony took place in the Great Lecture Hall of the Chemistry Department of our university. The second picture, Figure 5, is much more recent since it was taken in Stockholm just after the December 10, 2016 ceremony. |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** |  |
| **Interview** |  |
| Q9 | All Nobel Laureates are asked to bring an artefact to donate to the Nobel Museum here in Stockholm, what did you bring? |
|  | Jean-Pierre Sauvage: There was a tradition in my group, which was, at the beginning of the year, of the academic year in October, to have a long, long discussion about the research projects we were going to tackle in the coming year. And also, about the research projects which were started before and continued, to know how everything was working. I was in charge of this type of seminar and so it says here ‘research project’, I mean it’s a document in French; *Présentation de projets de recherche*. I’m pretty sure you can understand, and it was written on October 7, 1982. So, this is the authentic document, even written on scratch paper, you see the back of the sheet. Jean-Pierre Sauvage: The content is simply the various projects we were going to start at that time. And in 1982, interlocking molecules, like that, were basically unknown. And I think one of the main points is that … so they appear in this document. And there’s already a strategy for making them, a strategy for making an even slightly more complex ‘catenane’. I believe this is my first written document on catenanes. October 1982, so nothing was published ‘til one year later. And this is the paper which kind of represents what happens between the project and what was achieved. It’s a publication which appeared in 1983 in *Tetrahedron Letters*. If I may add just one thing, it has something very special; I have published hundreds and hundreds of papers, but there are very, very few papers published in French; written in French. And this one is written in French. It says, if I translate, “a new family of molecules, metal containing catenanes”. |
| Q4 | So, if I understand right, it took over one year for you to actually succeed with your experiments? |
|  | Jean-Pierre Sauvage: Not for me. For the lady who was doing the work, Mrs Dietrich-Buchecker, it’s a German name because she was from Strasbourg, and she was an incredibly skilful organic chemist. She could materialize the project, convert it to a publication, to some real resource. So, I would take this opportunity to thank her, to pay homage to her qualities. |
| Q5 | How long had you been into research in 1982? |
|  | Jean-Pierre Sauvage: I started my PhD thesis in 1968. A good year in France; the students’ revolution, and I was among them. And in ’68, although the surrounding was very special, I mean there were lots of things happening. I was working pretty hard, with another friend who was a PhD student with [Lehn](https://www.nobelprize.org/prizes/chemistry/1987/lehn/facts/), and together we made the first ‘cage like’ molecules, cryptands, cryptates, and that was published in 1969. It was my PhD thesis work. And Jean-Marie Lehn won the Nobel Prize in 1987. To a large extent in relation to this first piece of work, but of course he expanded the field spectacularly. |
| Q3 | What brought you to science in the first place? |
|  | Jean-Pierre Sauvage: In the first place, you know when you are a kid, you try to do what you like. I was good in math, mathematics was kind of my favourite topic, and that was it. And then I was interested in physics and chemistry, but I preferred math. |
| Q5 | And how come you started, you got interested in just chemistry, and maybe even photochemistry? |
|  | Jean-Pierre Sauvage: Yes, chemistry, I always preferred chemistry versus physics  Jean-Pierre Sauvage: I don’t know, I used to do experiments. You know when I was sixteen, seventeen years old, distillation, separating chlorophylls from plants, things like that. |
| Q2 | Do you remember the moment, or the environment where you actually got the idea that led to this discovery? |
|  | Jean-Pierre Sauvage: Yes, sure. I think you know in some of the recommendations of the Nobel Foundation for the Nobel Lecture, they suggest you to explain frankly, honestly, how you came up with the idea. And that’s what I’ll try to do. I remember very precisely. It was coming from photochemistry; you know we were photochemists. |
| Q4 | And the catenane that you mentioned, if you hold it like that and show me. What is this? |
|  | Jean-Pierre Sauvage: It’s moving. This is the very first catenane we made, which is reported in this publication. The drawings are certainly very naïve in here; they were hand-made. And this is the first catenane we made in 1983. |
| Q4 | And it’s a totally new type of chemical bond, if I understand it right? |
|  | Jean-Pierre Sauvage: It’s a new type of chemical bond, yes, Fraser Stoddart calls it the mechanical bond. And we have been more, let’s say, topology oriented, so we say that it is a topologically non-trivial molecule, or topologically non-planar molecule. This is how topologists in mathematics would refer to this molecule; non-planar. Non-planar meaning that you cannot hold any sheet of paper in a two-dimensional space without crossings; you have to have crossings. And it’s clear here you have two crossings. |
| Q4 | And how does this discovery take us to the chemical machines? |
|  | Jean-Pierre Sauvage: That’s a very good point. It’s very close, in a way, because if you have things like that, you know two interlocking rings, or a ring threaded by an axis, you can relatively easyly figure out that a ring can glide; rotate within the other ring, or the ring threaded by an axis can move along the axis on which it has been threaded, from a position to another position. And this is the beginning of molecular machines. |
| Q15 | Did you have any idea of what the molecule could be used for? |
|  | Jean-Pierre Sauvage: Yes, sure. We and others, again Fraser Stoddart, Ben Feringa and nowadays, many other people. I think the work of Fraser Stoddart in particular, and his group, is really spectacular. Very much in relation to molecular computing, you know storage of information, processing of information, and using molecules. |
| Q14 | In what timespan do you think we will have the molecular computing? |
|  | Jean-Pierre Sauvage: It is too risky to say, I am not going to bet on that. |
| Q2 | How many failures were there before you got the right chemical reaction to achieve this? |
|  | Jean-Pierre Sauvage: The first molecule was relatively easy to make, again thanks to Christiane Dietrich-Buchecker, she was a fantastic organic chemist. |
| Q13 | Was it very, has it been very hard work for you in a laboratory? |
|  | Jean-Pierre Sauvage: No, not at all. The idea was good in a way, and the synthetic strategy was good, also thanks to her, I insist on that. The work, in chemistry, the work done by the people, it’s a *team* work. Each time you have a team of people, working together, and everybody has a function, as a contribution, and *her* contribution was very important. |
| Q10 | What’s important, what different kinds of persons do you need in a team in chemistry to make these big achievements? |
|  | Jean-Pierre Sauvage: I think the first characteristic is to work with people you get along well with. Preferably with friends. She was a very good friend of mine. And I think the same holds true for the students and the postdocs, you have to have very good relations. And the second point is to have people with various backgrounds also. If everybody has the same expertise in the same field, in a way, it’s not going to be very rich in terms of discussions in group meetings, at coffee, or whenever. But if the people have various backgrounds, I mean, it’s very enriching. |
| Q10 | And how would you describe yourself, your type, who are you in this team? |
|  | Jean-Pierre Sauvage: I think I’m an easy to interact with person. And I like friendly relations, to me it is absolutely essential. |
| Q3 | What is needed to get this far? I mean to be rewarded the Nobel Prize? |
|  | Jean-Pierre Sauvage: I think you have to be motivated. The first thing is not to think of the Nobel Prize. Not to think of any prize. |
| Q17 | What’s needed more than not thinking of the prize? |
|  | Jean-Pierre Sauvage: I think you have to be motivated. There are several things: you have to love science, you have to love the idea of making discoveries. And the second thing is you have to pay attention, to be very, very careful to potential research projects you may think of. Every day, every hour. And you have to take any opportunity. When you discuss with your group, when you start a new project, you may have another idea leading you to a different topic. You shouldn’t be scared. You should jump, you know. You shouldn’t ask yourself the question: “Will I be able, will I be good enough to do that?” You have to test yourself. You do it, if it fails, it fails. |
| Q2 | But you never gave up? |
|  | Jean-Pierre Sauvage: No. Well, some projects, we gave up. But if you have ten projects at the same time, then if one or two projects fail, it’s not the end of the world. |
| Q3 | But you never thought of leaving science? |
|  | Jean-Pierre Sauvage: No, never. No, never, this is my life. |
| Q6 | We’ve talked a lot about your research and your career, but what else in life is important for you? |
|  | Jean-Pierre Sauvage: My family. I get along very well with my wife. |
| Q6 | Do you have a big garden yourself? |
|  | Jean-Pierre Sauvage: No, we have a very small garden in Strasbourg, but we have a second house on the Mediterranean, in the south of France, with a nice garden. So, I do a bit of gardening. |
| Q6 | And do you still hope that you will construct artificial photosynthesis, so your flowers can grow even better? |
|  | Jean-Pierre Sauvage: Yes, artificial photosynthesis is a bit ambitious, because you know the … What I hope is that we can convert light energy into chemical energy; make a fuel from light and water and CO2. Artificial photosynthesis in this way could be realistic. But photosynthesis, it’s much more than that. |
| Q6 | Do you have time to spend with your friends and family, or is almost all your time devoted to science? |
|  | Jean-Pierre Sauvage: No, I think I have never been completely focused, and only focused on science. I had vacation with my family every year. |
| Q2 | Do you think that is important, to get a lot of other influences? |
|  | Jean-Pierre Sauvage: Sure. If you want to have a balanced life, you know, sure you have to. |
| Q2 | Are you creative also on your time off from science? |
|  | Jean-Pierre Sauvage: Creative I don’t know, but I think of science, sure. |

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| **Chemistry\_2024-2000** | |
| **ID** | 0323 |
| **Biographical** | I was born in the capital of Scotland on Victoria Day in the middle of World War II. The nursing home in Edinburgh where this cliff-hanger of an event took place, during the early evening of 24th May 1942, was located at 57 Manor Place. It was not anticipated that a little boy weighing in at just under two kilograms would live until the next morning. I have the doctor’s bill, dated 7th October 1942, confirming that I defied the odds he gave against my survival. The bill reads, *“Dr. Douglas Miller presents his compliments to Mrs. Stoddart and begs to intimate that his fees for professional attendance amount to ₤4:4/-.”* It is not the realization that my parents were obliged to pay the princely sum of Four Guineas – equivalent to my father’s monthly salary at the time – to have me brought into this world that resonates with me most of all; rather it is the four and a half months the doctor was prepared to wait before sending out his bill to my mother. How times have changed.  My mother, christened Jane Spalding Hislop Fortune, but known as Jean to the family, had made her own way into the world on 23rd May 1911 at Seggarsdean Farm, in the vicinity of Haddington, a small town about 20 miles east of Edinburgh, in East Lothian. One claim to fame for this town is that it is the birthplace of John Knox, the Scottish minister who was the leader of the Reformation in Scotland and the founder of the Presbyterian Church of Scotland. While still a toddler, Jean Fortune made the move with her parents and two elder brothers, Jim and Tom, to Colstoun Mains which is located three miles south of Haddington. This farm on prime agricultural land was to become the seat of the Fortunes for most of the 20th century. From all reports, my mother was quite a sickly child and did not achieve as much as she might have done at school, leaving the Knox Academy in Haddington when she was 14. Her health improved during her teenage years on the farm and eventually she attended the Edinburgh College of Domestic Science on Atholl Crescent, graduating in February 1935 with a First Class Institutional Management Diploma. Following brief experiences as the manageress of private boarding schools in Yorkshire and Devonshire she became, with financial support from her father, the proud owner and proprietor of the Edenholm Private Hotel in Dunbar, a seaside resort on the North Sea, some eight miles east of Haddington. Old photographs indicate that it was around this time in 1937 that my mother and father met, became engaged and were married in St Cuthbert’s Church in Edinburgh on 16th October 1938, just before the onset of World War II in September of 1939. My maternal grandmother rented a holiday home in Dunbar every summer in the late 1940s so that she could bring all her grandchildren under one roof for a few weeks. I have vivid memories, while in the company of my cousins, of watching pigs swim in a paddock on the outskirts of the town during the Great Floods of 1947 that hit the United Kingdom. These holidays by the seaside bring back happy memories, aside from when my grandmother found the urge to have us all visit the unheated swimming pool, open to the chill waters of the North Sea. How we all dreaded the experience that she informed us was good for our constitutions, yet apparently not hers!  My father, Thomas Fraser Stoddart, always referred to as Tom by the rest of the family, was born on 20th January 1910 in Irvine, Ayrshire on the West Coast of Scotland. His father was a golf professional who, together with his wife, ran the Bogside Golf Course until he retired in 1945. As summer is the high season for golf, Tom Stoddart, together with his two younger sisters Anna and Clem (short for Clementine), were packed off each summer to the farms of cousins in East Lothian. It was at Howden that my father struck up a close, life-long relationship with his cousin, Tom Scott, while also being bitten by the farming bug. After attending Irvine Academy, my father continued his education at the West of Scotland Agricultural College in Glasgow where, after three years’ training, he gained First Class Certificates in most of his classes and won the McAlpine Memorial Prize as the best student of his year in agricultural botany. I can vouch for the fact that my father knew all that there was to know about grasses to be found in the Lowlands of Scotland. When he graduated from the college in December 1932, the then Principal and Professor of Agriculture was to comment in a testimonial that *“He is a young man of energetic and painstaking habits, is methodical in his work, and is possessed of more than the average endowment in grit and determination. These attributes, combined with his sound theoretical and practical knowledge, mark him out as one well fitted for a responsible position in agriculture and dairying.”* That position turned out to be the manager of the University of Edinburgh’s farms, one of them being Shothead, in the neighborhood of Balerno on the west side of the city, within sight of the Pentland Hills. **Edgelaw** When I was only six months old, my father decided to forsake the comparative comfort and relative security of being a farm manager to take on the tenancy of Edgelaw Farm about a dozen miles south of Edinburgh. Part of the Rosebury Estate, it was the middle of three farms on a dead-end road, which defined its remoteness and lack of electricity until I was almost 18. These circumstances, coupled with the fact that I was an only child, were to define much of my early life’s experiences in what I was later to refer to as the ‘University of Life’.  I grew up during the 1940s and 1950s in a post-World War II society coping with the rationing of food, clothes, and petrol (gas), and without access to modern-day conveniences in the home and workplace that we take for granted these days. The consequences for me were that I had to live out a very simple lifestyle, and I also had to find ways of amusing myself in a home where only a few rooms through the winter months were habitable. The need for warmth meant that we often lived as a small and close-knit family huddled together in the kitchen, which was fired by a Rayburn cooker that not only provided localized heat, but also hot water for the scullery, wash-house and single bathroom, in addition to some limited cooking space. It was augmented by another gas cooker that was fueled from a large cylinder of rural (liquid) gas. Other rooms in the farmhouse had to be heated by open coal- and wood-burning fires that were often influenced in an unpredictable manner by the wind and rain outside. Up would go the cry that the fire in the drawing room was ‘smoking’, which meant that the room was filling up rapidly with smoke and would soon have to be evacuated. The one and only telephone was located in the hall, which was rarely, if ever, warm, and so conversations tended to be short during the winter months. Light through the long, dark winter months was provided by a vast array of Tilley and oil lamps.  I remember, as if it was only yesterday, the day ‘the electricity,’ as it was called, came to the farmhouse for the first time. It was Christmas Eve 1959 when we received word that the meter man would not be coming to install the meter until the New Year. The disappointment in the household was palpable. We had been so looking forward to celebrating Christmas and the New Year and the long-awaited (17 years!) arrival of ‘the electricity’ with family and friends. I had helped the electrician – a character if ever there was one by the name of Phil MacKay – during the preceding months wire the farmhouse, steading and cottages, and so was pretty knowledgeable when it came to wiring. Unbeknown to my parents, but egged on by Phil, I waited until the cows had been milked and the assembled company were all getting ready to sit down and have a Christmas Eve supper. At that point, I fetched a pair of stepladders, climbed up to a point near the ceiling where the meter would eventually be installed, and joined up the first pair of wires between the house and the grid with a pair of pliers. As I expected, nothing of significance happened. On bringing the second pair of wires together, however, there was blinding flash and much of the house was ablaze with light for the first time. There was a lot of noise. My mother was beside herself. She was convinced that someone would report us to the police and we would all end up in jail! Reason prevailed. My mother was soon convinced that by closing the curtains (drapes) in all the rooms we could harbor our secret and have ‘the electricity’ after all. And so, it was that for more than a week we had ‘the electricity’ for free and we used it to full advantage. In later years, we became much more conscious of switching off lights, for that practice had some bearing on the size on ‘the electricity’ bill. I reckon we all read more and I had no excuse not to do my homework. A television set arrived not so long afterwards and life was never quite the same ever again.  The whole episode brought out the daredevil side of my character. I discovered on the farm that defying regulations and breaking rules was a way to achieve distant goals on a shorter time-scale and, while there might be a price to pay, there would always be supporters, even secret admirers, and after the deed had been done there was no going back.  From a young age, I was addicted to solving jigsaw puzzles and would stack them up when completed between sheets of newspaper. I ascribe my early fascination in stereochemistry and topology to this addiction, which was to give way gradually to one of the more sophisticated of toys in Britain in the 1950s, namely ‘Meccano’. The opportunity to construct a gadget I had designed myself and then put it to work after a fashion was to find expression later on when my passion for the chemical synthesis of unnatural products began to develop. There is also little doubt that my ‘Meccano’ set whetted my appetite many years later for constructing artificial molecular machinery from the bottom up. My interest in tinkering with machines and motors was increased considerably during those times on the farm, when I would take car and tractor engines apart, decoke them, replace the spark plugs and put them back together again, with the prospect that I would be going through exactly the same routine a few months later. The early internal combustion engines were not all that effi cient or reliable: they demanded a lot of care and attention.  The late 1940s through the 1950s into the mid 1960s were times of rapid development in agriculture. My parents had no choice but to embrace change like there was no tomorrow. The horse and cart gave way rapidly to the tractor and trailer. The binder and all the labor-intensive and time-consuming paraphernalia that followed in its wake yielded more gradually to the combine harvester and the baler. Our 32 cows, distributed between three byres, were some of the first in the district to be milked by machine. Not all change was seen to be desirable: right up to the last days of the farm in 1968, my mother remained a strong advocate of producing eggs from free-range hens. With the onset of mechanization, collaboration between farmers was commonplace. For all the 26 years that my father ran a flock of 160 lambing ewes, the sheep-shearing was completed in one day (weather permitting) by the shepherds from Colstoun Mains, who would arrive in the early morning with all their motorized clippers. It was an occasion when my mother captured their hearts and souls with a wholesome dinner in the middle of the day that was surely second to none.  The farm had two cottages – one for the byreman and the other for the ploughman as well as a bothy (a single-room cottage) that was home to an Irish laborer for part of the year. The cottages experienced a fairly regular turnover of families usually with quite a number of children who were my playmates. We were left free to run wild around the farm and also to roam the countryside at will on our homemade buggies and old bicycles. Creativity and risk-taking came into our play on the grandest of scales in a playground we fashioned to changing circumstances. We invented our own games and learned the hard way about the dangers of climbing on roofs, burrowing through passages between bales of hay in the hay shed, and speeding down hillsides on carts adorned with a variety of wheels in the summer and on homemade sledges in the winter. The concept of playdates had still to be invented.  My formal education began when I was four years old with mornings only attendance at the local village school in Carrington, around three miles from the farm. My mother recalled that when she collected me from the school at noon on the first day and inquired as to how I had got on, my answer was to ask if I could go the next day for the whole day. At first there were only four other children, all girls, including one, Muriel Logan, a very bright girl from Aikendean Farm. As a consequence of the gender imbalance, I learned to knit, particularly stockings, rather well. By the time I Ieft the village school in 1950, the number of pupils had risen sharply to 28. In this rapidly changing educational environment, where the older pupils helped to look after the younger ones, I discovered very quickly that Miss Morrison did not hesitate to use the tawse – a leather strap having one end cut into thongs that was used by schoolteachers in Scotland in the 1950s as an instrument of punishment – for poor performance, let alone bad behavior.  At the age of eight, my mother decided that I should go to one of the many fee-paying boys’ day schools in Edinburgh. She chose Melville College – formerly the Edinburgh Institution and now, as a result of a merger, Stewart’s Melville College – because she was attracted to its predominantly red and black uniform. I was obliged to take an entrance examination which, apparently, I passed with flying colors as a consequence of all that I had learned in the village school from Miss Morrison. I was blessed with some really outstanding primary school teachers – Miss Christie and Miss Pratt come to mind, both of them now in their nineties and still going strong today. They recall a very shy little boy, shyness being a trait that was to take me more than three decades to overcome.  Before I reached the age of 16, when I could negotiate the journey to school on a Lambretta scooter, my mother would drive me in the family’s 1938 Hillman Minx – purchased from James Ross and Sons for ₤155 – the three miles to the nearest bus terminal in Rosewell, at that time a small coal-mining village, to catch the 7:40 a.m. bus to Edinburgh. The popularity of cigarette smoking amongst the office workers and shop assistants meant that you could cut the atmosphere with a knife on the top deck of the bus towards the end of the 45-minute journey to St Andrew’s Square. The bus journey was followed by a mile-long walk down George Street to the school on Melville Street. I was to realize many years later that the education I received at Melville was second to none, maybe because the 1950s were less than two centuries removed from the period of the Scottish Enlightenment that was graced by eminent scholars, such as philosopher David Hume, economist Adam Smith, poet Robert Burns and chemist Joseph Black. I was taught by teachers, most of whom could have been university professors, in Latin, English Language, English Literature, French, History, Geography, Mathematics, Physics and Chemistry. The school’s music master, W. O. (Bill) Minay, was the organist at St. Cuthbert’s Church – where my parents were married on 19th October 1938 – at the west end of Princess Street. It was from Bill Minay that I took piano lessons for many years. With a huge amount of practice and no little encouragement from him, I was able to play the first two movements of Beethoven’s First Piano Concerto. Although enjoyable, that experience told me I was not cut out to be a concert pianist.  Sport was also a major part of the school curriculum. Rugby, cricket and field hockey were compulsory, along with swimming all the year round. During our last three years in school we found ourselves in army-style uniforms as part of a Cadet Force, in which I rose to become the Signals Sergeant. In my final year, the Headmaster appointed me to be the Second Prefect of the School, a position that gave me adequate opportunities to develop leadership skills. This experience was to prove invaluable when I became Head of the School of Chemistry at Birmingham – and later, the Director of the California NanoSystems Institute.  My mother was a terrific cook and an awesome baker, knowing instinctively when to add and mix ingredients, and rarely, if ever, measuring or weighing anything out. She knew just the right moment to stop whisking, heating and beating mixtures. She went about all these activities and more, including dress-making and patching up clothes, while feeding hens, mucking out henhouses, rearing chickens, gathering eggs and selling them in the neighboring villages and townships. My early successes at practical work in chemical laboratories owed much to watching this remarkable time and motion machine in action. My father, by far the best educated and most well-read farmer in the district, set very high standards for himself, expressed most intensely when a heifer was being groomed to perfection, prior to being sold at the Lanark Stock Market, or a flock of lambs, suitably washed in the dipper and individually manicured to perfection, were on their way to the auctioneer at the St. Boswells Sheep Sales.  I was to witness, from a very young age, the essential mating activities that were an integral part of maintaining a herd of dairy cows and orchestrating in October and November the running of around 150 ewes with tups (rams), at an approximate ratio of 50:1 to ensure the arrival of around 250 lambs during a frantic three-week window in March. While tending to cows calving throughout the year on a fortnightly basis, often in the middle of the night, was more or less routine, the lambing season never failed to reduce myself and my parents to states of utter physical and mental exhaustion, from a combination of lack of sleep and very long working days, for spring was also the time to be in the fields from morning to night sowing wheat, barley and oats, to be followed immediately thereafter by potato planting and the sowing of kale and turnips (swedes). In the summer months, I enjoyed nothing more than walking round the 365-acre (one for every day of the year) farm with my father in the evenings of long light. He knew all there was to know about the flora and fauna of the countryside. He was also a walking dictionary – a kind of Google before its time – that was useful for me in building up a vocabulary, and when we were engaged in the evenings in solving crossword puzzles in *The Scotsman*. My vocabulary was also broadened through my friendship with the farmhands, who taught me to swear from a young age. Later in life, my mother reflected that, much to her chagrin, I could swear like a trooper well before I could talk. **Edinburgh** During my four years as an undergraduate student at Edinburgh (1960–1964), I managed to hold my own in Mathematics, Physics, Chemistry and Biochemistry classes, in the face of stiff competition from many very bright students drawn, in large part, from the east coast of Scotland, many coming from the elite Edinburgh schools. A cohort of English students – who entered the Scottish higher educational system having covered much of the first-year science curriculum at A-level in England – got off to a flying start in their first year, but in subsequent years we Scots started to pull ahead of most of them. The chemistry teaching at Edinburgh in the early 1960s was not particularly taxing or stimulating, apart from some excellent lectures given by Tom Cottrell, John Knox, Peter Schwartz and Dai Rees. Organic chemistry, under the leadership of Professor Sir Edmund Hirst, was heavily skewed towards carbohydrate chemistry. A transformation occurred in my third year during a laboratory course in quantitative analytical chemistry. During his introduction, the somewhat abrasive Dougie Anderson announced to more than 100 of us that we would be pipetting by mouth enough cyanide to kill the whole of Edinburgh! After having made this spine-chilling remark, he went on to state that he had been running the 10-week course for more than a decade and in that time no student had ever completed it. Here was my opportunity, I thought, to apply the multitasking skills I had acquired from working on a mixed-arable farm for a couple of decades. I used this experience and finished the course inside seven weeks, gaining a mark close to 100%. This achievement earned me my first visit to the office of Sir Edmund who told me that Dr. Anderson would like to offer me a paid position in his research group during the following summer. I jumped at the opportunity. I felt much more at home in this new research environment, where I was given the opportunity to unravel the structural complexities of plant gums of the *Acacia* genus. There was little doubt from what was already published in the literature that these acidic polysaccharides – accompanied mysteriously by a small amount of protein – were high molecular weight polyelectrolytes constituted around a branched carbohydrate backbone. I was to continue researching these biomacromolecules well beyond a fourth-year research project into the pursuit of a PhD degree as a postgraduate student. My main contribution to the field was to challenge the “main-chain” hypothesis, implying a brush-polymer constitution, and replacing it with a much more highly branched constitution without having the foresight to describe it as a dendrimer before its time. My postgraduate research was to leave me with one lasting impression – namely, that the many gum trees in the Sudan, from whence the nodules I studied came, had never managed to produce between all of them through all of time, two gum molecules which were identical in size and constitution. After this period of handling highly heterogeneous mixtures, I longed to grow acquainted with a molecular world where homogeneity ruled the roost, at least for a time.  Between continuing to work on the farm, and becoming bitten by the research bug, I had to settle for graduating with a BSc Honours Degree in Chemistry and being the top Upper Second, in fifth place overall, in the 1964 Class of 45 students. By contrast, my postgraduate research was a resounding success and I was able to graduate with a PhD degree in just over two years in November 1966, having met the love of my life, Norma Scholan, who had joined the Anderson group as a fourth-year undergraduate research student. Norma made up for my lackluster performance in my Finals by coming top of her class of over 80 Final Year Chemistry students in 1966. In the years to come our two daughters, Fiona and Alison, were to graduate in Chemistry – from Imperial College London and the University of Cambridge, respectively – with First Class Honours degrees just like their mother before them, leaving me the dunce of the family! **Kingston** During the first 25 years of my life I had travelled very little and I yearned to go to North America, with enthusiastic support from my parents and somewhat less so from Norma, who had transferred her allegiance to the Biochemistry Department in the Medical School to begin her postgraduate work in steroid biosynthesis, under the tutelage of George Boyd. For my part, Sir Edmund sprung into action and did not take long to arrange for me to go to Queen’s University in Kingston, Ontario as a National Research Council of Canada Research Fellow. Here I would join the Chemistry group, headed up by Ken Jones, one of his own postgraduate students from his Bristol days. The 1960s witnessed the end of an era in UK chemistry departments, arranging for the department’s best students to go overseas to pursue postdoctoral fellowships in research. How times have changed for the better.  I left Prestwick for Montreal aboard a British Overseas Airways Corporation (BOAC) plane, taking to the air for the first time in my life, on 1st March 1967, with Sir Edmund’s words ringing in my ears, *“Whatever you do in research, Stoddart, make sure you work on a big problem.”* I was not at all sure what he meant by a ‘big problem’ but I was determined to heed his advice to the best of my limited ability. I suspect he anticipated that I would remain a carbohydrate chemist for the remainder of my professional life but that did not turn out to be the case. In the event, as soon as I set foot in the Jones laboratory, Ken confided in me that come 1st April he would be leaving for Curitiba in Brazil to spend one whole year there on sabbatical leave. This totally unexpected piece of breaking news, although quite a shock for me at the time, was to work to my advantage in the long run. I found myself assisting Walter Szarek, a former graduate student in Ken’s group, who had returned to Queen’s from Rutgers University to take over its supervision. It was good early experience for me in helping Walter run and mentor a medium-sized research group.  Communications between Canada and Brazil were dependent on the back and forth delivery of airmail letters, with a complete turnaround of information taking about three weeks, by which time the news was often obsolete. We were quickly relieved of this frustration when the Canadian postal service was brought to a halt by strikes for months on end. These circumstances left me with enough time on my hands to go in search of Sir Edmund’s ‘big problem’. I stumbled upon it in the chemistry department library under the guise of a short communication by [Charles Pedersen](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1987/pedersen-facts.html) in the *Journal of the American Society* (*JACS*) in the Spring of 1967, describing the efficient template-directed synthesis of dibenzo[18]crown-6 in 48% yield. This breaking news, coming out of the Dupont Laboratories in Delaware, flew in the face of all the teaching I had experienced as an undergraduate student at Edinburgh, where I had been led to believe that, while making five-, six-, and seven-membered rings was commonplace, large-sized rings were a totally different kettle of fish. I also realized that these macrocyclic polyethers – or crown ethers as Pedersen had called them – shared some of the constitutional features (OCCO repeating units) with the sugars. So, I set off on a mission to pursue what I referred to as ‘lock-and-key chemistry’ by simply marrying conceptually Pedersen’s crown ethers with [Emil Fisher](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1902/fischer-facts.html)‘s carbohydrates. Of course, it was easier said than done, for I was only one pair of hands with many other things on my mind. One of them was to return to Edinburgh in the Fall of 1968 to say goodbye to the farm – for my parents had decided that after my leaving for Canada it was simply too much for them to handle on their own – and the other was to get married in Glasgow in the presence of close family members to Norma on 8th October 1968. We returned to Canada the next day via Montreal, my newlywed wife occupying her time during the flight by completing mountains of immigration paperwork. At the airport, we were greeted by a customs officer who took one look at us, summed up the situation, crumpled the papers into a ball, threw them into a waste-paper bin (trash can) with the words *“we grow trees in Canada and far too many of them get turned into paper”* and waved us through to begin our married life in a foreign country with a welcome we were never to forget. Perish the thought that such a welcome would occur at an international border in today’s world.  Our remaining 15 months at Queen’s were blissful ones. We lived at 432 Alfred Street after I had negotiated to rent the house from the owners, Thelma and Dave Buchan, who had more or less become my Canadian ‘aunt and uncle’ during my first 18 months as a boarder in their home. Norma had completed research for her PhD degree, like myself in just over two years, but not without a never-to-be-forgotten incident following the decision that I would type the manuscript on my portable Olivetti typewriter. It was approaching midnight and I was typing the last few pages of her thesis. Norma decided I needed a cup of coffee and duly set the cup down on the table next me. The next time I triggered the carriage return it hit the cup fair and square on its side and propelled most of the contents right over the stack of 150 typed pages. Norma retired to a corner of the room sobbing her heart out. After a kiss and a cuddle, I sent her off to bed and then stayed up all night, retyping much of the thesis by the following morning. When disaster strikes, it is best to waste no time in putting the experience to rest.  During my stay at Queen’s I found it easy to interact with the faculty. Saul Wolfe, in particular, took me under his wing and transmitted to me the importance of being on top of the current literature. He brought to my attention the teachings of Kurt Mislow at Princeton on the importance of applying molecular symmetry to stereochemistry. Mislow had just introduced the concept of topism for analyzing the topic relationships between atoms and ligands in molecules. Amongst other attributes, it rendered the interpretation of NMR spectra a much easier task and helped to save me the embarrassment of coming to a wrong conclusion more than once. I had the opportunity to travel down to Princeton with Saul to meet this sage of stereochemistry. There were other opportunities to listen to lectures by the intellectual leaders of their time in organic chemistry, among them the famous Harvard professor and synthetic chemist par excellence, R.B. Woodward, whom I recall holding an audience in the palm of his hand in Ottawa for more than three hours. Then the Queen’s chemistry department invited Saul Winstein from the University of California at Los Angeles (UCLA) to give the MacCrae lectures in the Spring of 1969. Winstein was considered by many to be the intellectual leader in physical organic chemistry at that time and would almost certainly have been the recipient of a Nobel Prize in Chemistry had he not died very suddenly of a heart attack, at age 57, in November of that same year. What I recall most vividly about the MacCrae lectures was the manner in which Winstein launched into a 20-minute diatribe against H. C. Brown, reflecting the bitter controversy that raged between them for years over classical (HCB) versus non-classical (SW) carbocations. I could not have known in 1969 that almost 30 years later I would be making my way to UCLA to become the second holder of the Winstein Chair, following [Donald Cram](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1987/cram-facts.html) who shared the 1987 Nobel Prize in Chemistry with Charles Pedersen and [Jean-Marie Lehn](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1987/lehn-facts.html) from the University of Strasbourg.  Saul Wolfe was a pupil of the highly influential and renowned carbohydrate chemist, Ray Lemieux, for whom I had acquired an enormous respect after hearing him give a series of remarkable named lectures (Purves, if I recall correctly) at McGill University, which ultimately led me to write a monograph on the *Stereochemistry of Carbohydrates*. I set out on this mission with the support of Ken Jones, who had returned from Brazil, without realizing the responsibility one assumes when writing a book! My attendance at a symposium hosted by the US Army Laboratories at Natick led to my meeting Ernest Eliel, the author of *The Stereochemistry of Carbon Compounds*, a classic published by McGraw-Hill in 1965. It had been my bible from my Edinburgh days and so I decided that I would approach Dr. Eliel at the end of his inspirational talk and ask him if he would be kind enough to look over and comment on my manuscript. I sent him the manuscript and within a very short space of time it came back plastered in red ink. This experience taught me that having my manuscripts scrutinized by experts wherever possible would save me no end of embarrassment in the fullness of time. On this occasion, no doubt, Ernest saved my bacon: he and his wife Eva were to become close friends of myself and Norma for the rest of their lives. **Sheffield in the seventies** As the 1960s came to a close, Norma convinced me that it was time to return to Old Blighty, where we would give some thought to raising a family. Sometime in the summer of 1969 Ken Jones came back from a conference in the Caribbean with the news that David Ollis from Sheffield had given a lecture (with demonstrations) on the conformational behavior of a 12-membered ring compound known as tri-*o*-thymotide, or TOT for short, that had captured everyone’s imagination. I decided to apply for an ICI Fellowship to go to Sheffield but initially failed to make the cut. Three months later I heard the good news that I had, after all, landed this prestigious fellowship, as one of the successful candidates had decided not to accept the offer. We decided it would be practical to ship our goods and chattels across The Pond and enjoy an ocean liner experience onboard the West German flagship *Bremen* during the week before Christmas. Five days after leaving New York we arrived in Southampton to be greeted by thick fog, which made the drive north to Edinburgh, stopping off in Sheffield on the way, all the more challenging.  There were several reasons for going to Sheffield. One was to attend the Annual Sheffield Stereochemistry Meeting, where I had the opportunity to hear [Jean-Marie Lehn](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1987/lehn-facts.html) speak for the first time. It was such a pleasure to listen to this young French chemist with a research agenda in the making that was destined to chart new territory for the subject beyond the molecule or, as Lehn named it subsequently, supramolecular chemistry. Another reason for being in Sheffield was to introduce myself to David Ollis. When the subject of my start date came up he insisted I should be present in the department for the 1st of January 1970. This edict infuriated Norma, and I was not best pleased either, given the fact that we were heading to Scotland where New Year’s Day is a national holiday. The crossing of swords with Ollis would go on for the best part of two decades.  On my return to the chemistry department on 1st January it became apparent that I was not going to be allowed the independence to carry out the kind of research that was the fellowship’s official remit. In addition, when Ollis learned that I would be spending some of my time writing the final chapter of the book, he immediately expressed his displeasure, stating quite emphatically that *“people at my stage should not be writing books”*. Norma, who was illustrating the manuscript with India ink and stencils, convinced me to ignore his decree and the monograph was published in 1971 by Wiley. If the welcome to Sheffield was muted from on high, Norma and I were made to feel very welcome by the postgraduate community, particularly by David (Dave) Brickwood (whom I was delegated to supervise), Stephen (Steve) Potter and Richard (Dick) Taylor. Little do they really know how much they helped us through those difficult times.  I was working in my laboratory (E19) on Good Friday in 1970 when Ollis walked in to tell me that at a meeting of the Organic Staff the day before, it had been decided that I should be offered a Lectureship in Chemistry – a position that had unexpectedly fallen vacant with the resignation of the youngest member of the staff – from 1st October. I was, of course, happy to have some long-term job security, although it in no way earned me my independence. It was 1973 before Andrew Coxon became my first independently supervised postgraduate student. For my first lecturing assignment, I was handed a poisoned chalice in the shape of teaching the first-year medical students (all 180 of them) organic chemistry, in the knowledge that the course would soon be discontinued. The refrain from the students was very much along the lines of *“Why are we having to take this course when it’s about to be withdrawn?”* It was a tall order to hold their attention in lectures and laboratory classes, but I did my very best to engender their enthusiasm by introducing all sorts of innovations into my teaching. Nonetheless, when brought before a group of medical staff in the presence of their dean, I was informed by him that *“we might as well be teaching our students biblical studies”*. It was a crushing put-down but I reasoned that I should not have been the person from the chemistry department finding himself in this particular lion’s den!  Despite the fact that my progress in research was being forestalled at every turn by the antics of the professors in the department, Andrew Coxon, and later Dale Laidler, made some notable advances in their research with carbohydrate precursors to crown ethers, to the extent that when I was invited to speak at international conferences and symposia I had some interesting results to talk about under the banner of ‘lock-and-key chemistry’. A major turning point in my fortunes came in 1976, when I was invited to give no less than 17 lectures and seminars, nine in the UK, including Oxford, Imperial College London, Edinburgh and Glasgow, four in the US, including Columbia, Princeton and Dupont, and four in Canada, including McGill and Queen’s. I was also fortunate in being invited to give a talk at the Centennial American Chemical Society Meeting in New York in early April. This invitation afforded me the opportunity to listen to [Donald Cram](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1987/cram-facts.html) speak and to meet with him one-on-one – along with his shopping bag full of CPK space-filling models – for the first time. Once again, I found myself in the company of an eminent American chemist, who not only enthused about his own research, but also about mine, an experience for me that was uplifting beyond my wildest dreams. Don was also the RSC Centenary Lecturer in May 1976. He insisted that I would be one of the supporting speakers in Manchester and, two days later, in London, at University College. When the powers that be at the RSC questioned my double act, Don swept aside their protestations with the comment that *“apart from Fraser and myself, those in the audiences in the two places will be different”* and, of course, no one could argue with him, for he was right! David Ollis was livid, but Don was drawing considerable satisfaction from the situation because he knew how I was being treated on home turf. Don also presented his Centenary Lecture in Sheffield and went out of his way to say he had come because of my presence in the department. He went on to lavish praise on my research group, leaving Ollis red with rage!  During these meetings, Don encouraged me to apply to the Science Research Council (SRC) for a Senior Research Fellowship to spend the first three months of 1978 on sabbatical leave at UCLA. This short stay in the UCLA Department of Chemistry and Biochemistry was a real breath of fresh air and served to increase my yearning to move to the US one day in the future. Interest in hiring me had been mooted in a number of different US universities, but then something else happened in the UK that I could live with very comfortably, and that left Norma happy that our two girls, who had arrived on the scene in 1973 (Fiona) and 1976 (Alison), could continue their education in the UK. That development involved the SRC, who were ready, willing and able to support my secondment to the ICI Corporate Laboratory in Runcorn, under the auspices of a brand new Cooperative Research Scheme for three years, from 1978 to 1981. It also received the backing of a number of ICI’s senior management, including Tom McKillop and Bernard Langley. I was over the moon. I was free at last to carry out my own research in a highly supportive and amazingly well-equipped environment, staffed with research scientists who were second to none. We sold our home on Derriman Avenue in Sheffield and moved across the Pennines to a brand-new house in Curzon Park in Chester, with a six-month layover in a small rented property in Little Sutton, on the Wirral. The next three years were amongst the happiest that we spent as a family in England. **Runcorn** I joined Warren Hewertson’s Catalysis Group at ICI’s Corporate Laboratory and supervised a couple of postgraduate students in Runcorn, plus half a dozen who remained in Sheffield, where I spent minimally one day a week. The Corporate Laboratory, situated on The Heath at Runcorn, was probably the closest one could get to a Bell Laboratories experience in the UK. It was in this setting that I quickly struck up a highly productive collaboration with a brilliant young chemist, Howard Colquhoun, who had only recently joined the laboratory. Following some discussions about what different kinds of complexes could be formed with crown ethers, we came to the conclusion that, as far as we knew, transition metal ammines had not been put to the test. We were fortunate insofar as there was a treasure trove of these ammines down in the basement of the laboratory that had been prepared by Joseph Chatt when he was an employee of ICI during the 1950s. I could not believe our luck. Before long we had lots of crystals of adducts of transition metal ammines with crown ethers, whose solid-state superstructures were solved at the drop of a hat by David Williams, X-ray crystallographer extraordinaire, down in London at Imperial College.  Amidst all these many superstructures, one caught our attention. It was the 1:1 adduct in which dibenzo[30]crown-10 (DB30C10) wraps itself round a dicationic platinum complex, carrying a 2,2′-bipyridyl ligand in addition to a couple of *cis*-diammine ligands, in such a manner that the ammine ligands form hydrogen bonds with the polyether loops of the crown ether, while the two π-electron rich catechol units sandwich the π-electron deficient bipyridyl ligand in a stacking manner. The structural similarities between this bipyridyl ligand and the bipyridinium herbicide Diquat (DQT) was pointed out to us by former ICI research scientist Eric Goodings. Sure enough, when the transition metal complex was replaced by DQT we obtained deep orange crystals of a 1:1 complex with DB30C10, as revealed yet again by its solid-state superstructure. Both the adduct and the complex, when associated with soft counterions, are reasonably stable in acetonitrile solution, as indicated by the presence of diagnostic charge-transfer bands that render the solutions light yellow and bright orange, respectively.  We had injected new life into Alfred Werner’s concept of second-sphere coordination in the process of establishing donor-acceptor interactions as a force to be reckoned with in molecular recognition processes. They would ultimately serve as the sources of templation in the making of molecules with mechanical bonds. Although we had still to address the need to form complexes between crown ethers and Paraquat (PQT) – the other component of the wipe-out weed-killer that ICI marketed worldwide for many years – we had given the search for the ‘big problem’ an enormous fillip from an unlikely starting point. If I had not spent those years at ICI’s Corporate Laboratory, my role in the development of mechanically interlocked molecules, that has led to designing and synthesizing molecular machines, would either not have happened or would have taken a very different course. All of what I was subsequently to achieve in research can be traced back to these three years.  I left Runcorn in the late summer of 1981 with a heavy heart, but there was no option. My three-year secondment was coming to a close and, more disturbingly, the writing was on the wall for the Corporate Laboratory. Norma and the girls had come to enjoy life in Chester and it was going to be challenging for all of us to return to Sheffield. Once again, the transfer was staged by my acquiring a small semi-detached home in Bradway, from which we were able to purchase the ideal family home in the shape of an Edwardian house on Dore Road. **Sheffield in the eighties** My situation at Sheffield had been strengthened by my industrial experience and I was promoted to a Readership in Chemistry in 1982. Although many of the same issues still existed in the chemistry department at Sheffield, I was much more able to handle the slings and arrows of outrageous fortune. With growing confidence, I became quite vocal at the national level about the weaknesses, as I saw them, in the British academic system. My pronouncements and my writings – often to the British national newspapers – did not win me many friends, but at the same time they served to define where I stood on a wide range of issues. Eventually those in influential positions started to notice and take note.  At this time, I struck up another important relationship that not only turned out to be of immense value in the promotion of my research as it developed during the 1980s, but also helped me launch some university-wide initiatives, such as the Sheffield Industrial Forum in 1986. That relationship was with Roger Allum, the Press Officer for the University. He was extremely supportive and would always seek to make our research intelligible to the wider public. If I ever felt a little depressed from working in a department that was brim full of politics, I could take a walk up to the Edgar Allen Building and have a reassuring chat with Roger. He always had time for me, no matter how busy he was tending to other university business. I would leave his office with my spirits lifted and ready to take on the world.  As I moved from one university to another, the importance of maintaining good and close relationships with the talented individuals in media relations remained with me. Martin Hicks at Birmingham continued in the footsteps of Roger and once I reached the University of California, Los Angeles (UCLA), I was to learn a lot from Stuart Wolpert on how to handle live and recorded interviews for radio and television. At Northwestern University (NU) I have been blessed many times over to have Megan Fellman working closely with myself and members of my research group in getting story after story out into the public domain. More recently, I have discovered a soulmate in Stephanie Russell, Editor of the *Northwestern* magazine, who has gone to considerable lengths, and well beyond the call of duty, in presenting me and my research to the alumni and friends of NU, following my award of the Nobel Prize in Chemistry.  On the scientific front, after some wasted effort and unproductive years, we were able to demonstrate quite simply that a constitutional isomer of DB30C10, namely bis-*para*-phenylene[34]crown-10 (BPP34C10), forms a strong 1:1 complex with PQT. The fact that the solid-state superstructure of this complex was ‘rotaxane-like’ in its appearance led me to suggest that it be called a [2]pseudorotaxane, a name which eventually transmogrified into meaning a template that could subsequently be converted into a catenane as well as a rotaxane. We had established that we could thread a *p*-acceptor through a ring containing two laterally disposed π-donor units. Our next challenge was to reverse this recognition motif by making a cyclophane in the form of cyclobis(paraquat-*p*-phenylene) and containing a couple of parallely disposed bipyridinium units held rigidly apart at a plane-to-plane separation of approximately 7 Å by two *para*-xylylene units, through which π-donors of many different persuasions could thread. In the first instance, Mark Reddington was able to prepare this cyclophane starting from 4,4′-bipyridine and xylylene dibromide in a 12% yield.  During our efforts to publish the synthesis and full characterization of this cyclophane in *Angewandte Chemie*, I received a curt letter from Siegfried Hünig at the University of Würzburg, explaining that one of his students had synthesized a whole range of very similar cyclophanes and studied their ability to complex aromatic hydrocarbons, a piece of information that was available, but overlooked by me, in *Dissertation Abstracts*. I wrote back to Professor Hünig, who had clearly been one of the reviewers of our communications, and suggested that he write up a communication on his work while we delayed the publication of our communications so that all three could appear in the journal in a row. Thereafter, Siegfried and I became close friends, to the extent that he and his wife invited Norma and myself to Würzburg to help celebrate his 80th birthday in 2001. The publication of our two communications coincided with the beginnings of my use of color – red for π-donors and blue for π-acceptors – so that the cyclophane soon became known in the literature as the ‘little blue box’ and was to gain considerable notoriety as a promiscuous host for a wide range of π-donors, including benzidine and tetrathiafulvalene. Subsequently, employing both templates and catalysts – and some other tricks – we have been able to prepare the little blue box in all but quantitative yield.  The stage was now set to carry out the template-directed synthesis of the first donor-acceptor [2]catenane in a remarkable 70% yield, by very simply employing the ingredients used in the preparation of the little blue box in acetonitrile at room temperature in the presence of three molar equivalent of BPP34C10. This experiment, which was carried out by Cristina Vicent and Neil Spencer, was one of the most memorable as we all gathered to watch the reaction mixture turn orange and crystals start growing on the side of the reaction flask within 10 minutes. I realized there and then that we were sitting at the entrance of a gold mine as we prepared the manuscript for publication in *AngewandteChemie* in October of 1989. While the manuscript was out for review, I received a phone call from Jean-Pierre Sauvage in Strasbourg saying how impressed he was by the contents and offering me his congratulations. He was obviously one of the reviewers. The 1980s represented a sea change for my group, as I began to realize that our level of research performance could be raised out of all recognition by welcoming postgraduate students and postdoctoral fellows from overseas. The arrival of Franz Kohnke from the University of Messina, not to mention the short visit of Cristina Vicent from Madrid, had a profound effect on the group culture as we became increasingly international in our composition. The cultural change also encouraged home-grown PhD students to raise their sights. Following graduation with their PhD degrees, David Leigh went to Ottawa in search of postdoctoral experience with David Bundle, while John Mathias, equipped with a postdoctoral fellowship, was invited by George Whitesides to go to Harvard.  Pier Lucio Anelli, who came to Sheffield as a postdoctoral researcher from the University of Milan, was another of a growing number of makers and shakers. Employing a pre-prepared dumbbell-shaped molecule as a template, he synthesized by templation a degenerate [2]rotaxane with two π-donating, hydroquinone-based, recognition sites for encirclement by one little blue box, which could be shown by dynamic NMR spectroscopy to be darting back and forth between the recognition sites at around 2000 times per second. I called it a molecular shuttle and concluded in a 1991 *JACS* communication that it was *“the prototype for the construction of more intricate molecular assemblies where the components will be designed to record, store, transfer and transmit information in a highly controllable manner following their spontaneous self-assembly at the supramolecular level*.” The development of this next step in the research program had to wait until a move to the University of Birmingham had been planned and executed. **Birmingham** I had been approached in 1991 by the then Vice-Chancellor of the University of Birmingham, Sir Michael Thompson, to consider moving to Birmingham as the Professor of Organic Chemistry. He had been attracted by my refusal to join the large group of whingers in British academia at that time. The Department of Chemistry was in a badly run-down state and morale was low to say the least. After much discussion and an undertaking by the Vice-Chancellor to implement a staged refurbishment of the Haworth Building and invest in some key state-of-the-art equipment, including NMR and mass spectrometers, I accepted the chair and started a phased move of my research group, now growing in size, from Sheffield to Birmingham. Norma remained in Sheffield to look after the everyday needs of the group members there, while I oversaw the revamping of the top (seventh) floor of the building and prepared for the new spectrometers to arrive on the scene. While Neil Spencer accepted the challenge of establishing the new NMR facility, I managed to persuade the highly gifted senior technician, Peter Ashton, to also make the move from Sheffield to Birmingham and establish a mass spectrometry facility that was second to none in the country. I commuted between Birmingham and Sheffield for more than a year, given the added responsibility of being one of the organizers, along with Norma and David Fenton, of the 1991 International Symposium on Macrocyclic Chemistry, at which both Donald Cram and Jean-Marie Lehn received Honorary Degrees in Science from Sheffield University. It was also the occasion when the first International Izatt-Christensen Award was presented to Jean-Pierre Sauvage.  A life-changing event was to occur in February 1992 when I took an early morning phone call in my Birmingham office from Alison, her first words being, *“Something terrible has happened, Daddy.”* She went on to explain that her mother was in hospital, having suffered a brain hemorrhage overnight. I wasted no time in jumping into my car and driving up to Sheffield, only to be told by the surgeon in charge of her case that he was going to have to operate and that there was no better than a 50% chance that Norma would survive the surgery. It was a long day that was to take a turn for the better when the surgeon informed me in the early evening that the artery in Norma’s brain had self-healed and he would not need to operate. Relief all round! We moved from our Edwardian home in Sheffield to a 1930s home in Edgbaston, close to the campus of the University of Birmingham, on 1st April. With Norma still very much in a convalescent state, I was approached by Ken Houk at UCLA, who asked me if I would consider moving to UCLA to assume occupancy of the Winstein Chair on the impending retirement of Don Cram. My reply – with mixed emotions – was an easy one. Norma was too ill for me even to share this news with her and I was in the throes of a complicated relocation. I assumed that my message to Ken declining his offer would be the last I would hear of the Winstein Chair at UCLA and that this tantalizing prospect had slipped out of my grasp. This assumption proved to be incorrect.  As far as research was concerned, my seven years at Birmingham were to exceed my wildest dreams. Our first bistable [2]rotaxane, that could be switched both chemically and electrochemically, reached the literature in 1994, following a sojourn by Richard Bissell at the University of Miami with Angel Kaifer. Olympiadane was self-assembed by David Amabilino, while Gunter Mattersteig synthesized the first bistable [2]catenane, in which the two π-donating hydroquinone recognition sites in the degenerate [2]catenane were replaced with tetrathiafulvalene and dioxynaphthalene recognition sites. A highly fruitful collaboration, in which this catenane and many other bistable MIMs were switched chemically, electrochemically and photochemically, was struck with Vincenzo Balzani and Alberto Credi at the University of Bologna. Jon Preece spent time in the laboratory of Helmut Ringsdorf at the University of Mainz learning how to produce Langmuir monolayers and films of both degenerate and bistable [2]catenanes and preparing the way for device fabrication when we reached UCLA in 1997.  Douglas Philp was a major intellectual driving force in the group during its early days in Birmingham. Aside from his high level of productivity that matched his creativity every inch of the way, he left a considerable legacy by writing a much-cited review on “Self-Assembly in Natural and Unnatural Systems” that was published in *Angewandte Chemie* in 1996. While Peter Glink established hydrogen bond templation (known within the group as ‘ammonium binding’) as a means of templating the synthesis of MIMs, Narayanaswamy Jayaraman and Sergey Nepogodiev launched ambitious programs of research into glycodendrimers and the synthesis of cyclic oligosaccharides related to the cyclodextrins. Steven Langford and Matthew Fyfe took over where Douglas Philp left off by bringing their keen intellects and dedicated commitment to the development of MIMs to a highly sophisticated level in relation to their physical organic chemistry.  Unwelcome news kept breaking in 1992. In August, Norma was diagnosed with breast cancer and underwent surgery in the form of a lumpectomy, followed by radiation and chemotherapy. The cancer recurred two years later in 1994, resulting in a mastectomy and yet more of the inevitable back-up treatment. This did not halt the progress of the disease, which was diagnosed as having become metastatic in 1996. During a visit to UCLA in 1994 to participate in a symposium to mark Don Cram’s 75th birthday, Ken Houk raised once again the availability of the Winstein Chair, reiterating the interest of the Department of Chemistry and Biochemistry in my coming to occupy it at UCLA. My feeling that Norma was not receiving the best of medical care in Birmingham was accepted by her in early 1997 and so we decided to go on a trip to the US, visiting the M. D. Anderson Clinic in Houston and the Jonsson Comprehensive Cancer Center at UCLA, where Norma was told by the oncologists we met that, while she had a chronic disease, they had 50 different ways of treating it. At this point it was decided that I would step down from being the Head of the School of Chemistry at the end of June and formally move to Los Angeles to take up the Winstein Chair on 1st July 1997. Some 15 members – including first-year graduate students Stuart Cantrill, David Fulton, Sarah Hickingbottom, James Lowe and Anthony (Ant) Pease – of my research group made the transition from the middle of England to the West Coast of America, with postdoctoral fellow Françisco Raymo acting out the role of the scout. Coming to grips with the very different way American academia operates compared with that in the UK, together with getting my mind round the funding system from the federal agencies and beyond, constituted a baptism of fire for a 55-year-old. We simply rolled up our sleeves and got on with it. Norma, for the first time gainfully employed as a research assistant to my group by UCLA, helped in all this. **University of California Los Angeles (UCLA)** In just over a decade at UCLA, from 1997 to 2008, we broadened the scope of our template-directed approaches to mechanically interlocked molecules (MIMs) by appealing to both hydrogen-bond and metal templation, as well as developing donor-acceptor templation to cover the production of a wide range of molecular switches. Stuart Rowan joined my research group in 1998, with the intention of establishing his own independent academic career in the United States, after having played a major role in the furtherance of dynamic covalent chemistry (DCC) at the University of Cambridge with Jeremy Sanders. This thermodynamically controlled approach to the template-directed synthesis of MIMs can be extraordinarily powerful. It eventually led to high-yielding syntheses of molecular Borromean rings and Solomon knots. Template-directed approaches under kinetic control to MIMs began to rely more and more on the use of ‘click chemistry’, as popularized by [Barry Sharpless](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/2001/sharpless-facts.html). Amongst the ring leaders during this period – in addition to Stuart Rowan (University of Chicago) – were Ivan Aprahamian (Dartmouth College), Adam Braunschweig (Hunter College), Sheng-Hsien Chin (National Taiwan University), William Dichtel (Northwestern University), Amar Flood (Indiana University), David Fulton (University of Newcastle), Jan Jeppesen (University of Southern Denmark), Steve Joiner (Moorpark College), Ken Leung (Hong Kong Baptist University), Cari Meyer (Pierce College), Ognjen Miljanić (University of Houston), Al Nelson (University of Washington), Brian Northrop (Wesleyan University), Hsian-Rong Tseng (University of California, Los Angeles), Bruce Turnbull (University of Leeds), Sebastian Vidal (University of Lyon), Scott Vignon (Washington DC) and Jishan Wu (National University of Singapore).  The UCLA era was characterized by numerous efforts to uncover applications for molecular switches, both the non-degenerate catenated and rotaxanated varieties. One of the most rewarding and fulfilling collaborations was with Jim Heath in the field of molecular electronics. The marriage between molecular switches and electrodes is far from being an easy one, and I have to say that Jim picked his way through what turned out to be a bit of a minefield with the greatest of ease. By employing crossbar devices, he and his highly skilled team of graduate students and postdoctoral fellows were able, using the LB technique established during the Birmingham days, to lay down monolayers of switchable catenanes and rotaxanes between parallel wires of polysilicon (bottom electrodes) and orthogonally disposed parallel wires of titanium capped with aluminum. By 2007, using an amphiphilic bistable [2]rotaxane, a 160,000-bit molecular electronic memory circuit had been fabricated at a density of 100,000,000,000 bits per square centimeter. The entire 160-kbit crossbar device was smaller than the cross-section of a white blood cell. It transpired that there is one fatal weakness with the crossbar devices, and that is their lack of robustness. When Omar Yaghi arrived at UCLA in 2006 we started a joint program of research, whereby bistable MIMs are being incorporated inside metal-organic frameworks – and it continues today at Northwestern University (NU) in collaboration with Joe Hupp and Omar Farha.  For a time Norma’s oncologists kept her cancer at bay, chiefly by moving in the face of resistance to treatment from one anticancer drug to another, and subsequently to a cocktail of two or three or more of them. She and I were able to travel the world together for a while, visiting many cities, including Paris, Stockholm and Vienna in Europe and Kyoto and Nara in Japan. Slowly and perceptibly, Norma’s state of health started to wane as the side effects of the drugs began to sap her energy, causing her to seek refuge in our small Santa Monica townhouse, assisted by a kind and marvelous caregiver, Sylvia Mena, and no end of material and psychological support from Alice Jung, wife of my colleague Mike Jung, who was a dab hand at making Norma laugh and in so doing lifting my spirits. She referred to Mike’s other half as ‘Alice the Angel’. By late November 2003, the 25th to be precise, Norma’s head oncologist, John Glaspy, told me what I had already guessed: it was that the disease had reached her brain and that it was only a matter of time, a few weeks at most, before a battle that had occupied a fifth of her life and demanded our attention for a third of our married lives was about to end. Norma always insisted that her brain was her last refuge: if and when it was invaded by the “little buggers,” she would throw in the towel. Her final foray into the outside world was a sight to behold. It was an excursion to Gap in Santa Monica to purchase a large selection of garments for her grandson, only a few weeks away from being born to Fiona and Quentin McCubbin, yet she was not going to set eyes upon James Fraser (the Second!). Norma’s shopping sprees were legendary, but this one stole the show. For the first time since 1966, she was oblivious to the spirit and trappings of Christmas as she prepared to make a dignified exit, simply commenting that she had drawn the short straw. During the final days of her life she communicated with me using a pencil and writing pad, being too weak to speak. Her last comment, written the night before she passed away on 12th January 2004, was, “Am I dead yet?” She sank into oblivion as I was struggling to decipher her question and so I was not able to provide her with an answer. In the last few weeks of her life she was insistent that her main legacy were ‘her girls’ and there is no arguing with that statement to this day. She had every right to feel proud of Fiona and Alison.  The departure in 2003 of Jim Heath to the California Institute of Technology (CALTECH) signaled two changes in my professional life. One was the taking over of the Directorship of the California NanoSystems Institute (CNSI) from Jim, the founding director, first of all in an acting capacity and then subsequently for real. Despite these developments, Jim and I maintained our collaboration in the realm of molecular electronics, aided and abetted by Bill Goddard’s entry into the program. Through his impressive computational investigations, he did much to vindicate our proposed switching mechanism exhibited by monolayers of bistable rotaxanes in crossbar devices. I became a great admirer of Bill’s command of his science and the fearless manner in which he tackles large and complicated problems, a trait that continues to this day. No one knows and understands our donor-acceptor catenanes and rotaxanes all the way from bistable molecules through to devices better than Bill: this belief is supported by arguments presented in more than 30 joint publications. Another positive change that occurred around 2003 was the forging of a close and equally fruitful collaboration at UCLA with Jeff Zink, whose knowledge and practical expertise in relation to the preparation of mesoporous silica nanoparticles led to the covering of the surfaces of these 100–200 nanometer diameter particles with both bistable/switchable rotaxanes (nanovalves) and their supramolecular counterparts, which we called snap-tops, as a sophisticated means of controlling the release of small molecules, such as anticancer drugs. My foray into drug delivery systems was undoubtedly influenced by my day-to-day experiences of living for 12 years with a cancer patient. I have to admit, however, that I am coming to the opinion, after having co-authored more than 30 articles with Jeff, that, while more and more sophisticated ways of delivering drugs to patients suffering from degenerative diseases can prolong their lives, they are probably never going to provide the cures that many people would like to think are just around the corner.  After graduating with his PhD from UCLA in 2001, Stuart Cantrill spent a couple of years at CALTECH as a postdoctoral scholar with [Bob Grubbs](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/2005/grubbs-facts.html), one of the 2005 Nobel Laureates in Chemistry. The outcome of this association was yet another collaboration, in which Grubbs-catalyzed olefin metathesis in many of its different manifestations was introduced into the thermodynamically controlled syntheses of MIMs using hydrogen bonding as the source of templation.  Stuart returned to UCLA in 2003 to take on my undergraduate teaching responsibilities and to assist me in the running of my research group while I was CNSI Director. During what turned out to be a three-year sojourn, he also became the *de facto* Associate Editor of *Organic Letters*. It was during this time that he not only made sure that the research he had initiated in relation to the dynamic synthesis of the molecular Borromean rings reached the light of day in the literature, but he was also to discover that his own future lay in scientific publishing. On his return to the UK in 2005 he found employment with the Nature Publishing Group, first of all as an Associate/Senior Editor with *Nature Nanotechnology*, before being given the responsibility in 2008 to launch *Nature Chemistry* as its Founding Chief Editor. It is this kind of career progression by my students that I look back upon with immense pride.  Two bolts appeared out of the blue in late 2006 and early 2007 that could be considered as serious game-changers. The first one arrived in the context of a phone call on 13th November 2006 from Bob Pierce, the British Consul General in Los Angeles. To my consternation, Bob asked me if I would be prepared to accept an appointment to Her Majesty the Queen as a Knight Bachelor. My acceptance, under a cloak of secrecy, became public knowledge in the 2007 New Year Honours List. It led to my attending an investiture in June 2007, accompanied by David Leigh, a 1987 PhD graduate from my Sheffield days, along with Fiona and Alison. The second great surprise came in the form of a call to my cell phone from my assistant, Christina Oliver, while I was attending the Third Annual FENA Review Meeting at the LUXE Hotel in Los Angeles. On this occasion, the message, which encroached upon a conversation I was having with Youssry Botros (Intel), who was appointed as a consultant from industry to the Center for Functional Engineered Architectonics (FENA) directed by Kang Wang at UCLA, was from the King Faisal Foundation in Riyadh to say that I had been selected to receive the 2007 King Faisal International Prize (KFIP) in Science. Youssry, who was born and brought up in Egypt, was immediately raised to a highly excited state on learning the news from me. In the event, I invited Youssry, a fluent Arabic speaker, to accompany Alison, her then fiancé Mikey Ho, and myself on our first trip to Saudi Arabia to receive the Prize from the King in the middle of April. During a week-long visit, Youssry and I had our first meeting with Prince Turki Al-Saud who was then Vice-President of the King Abdulaziz City for Science and Technology (KACST), and he is now the President of KACST. Following this meeting, KACST has generously funded six projects at Northwestern University related to energy storage, energy harvesting, molecular electronics, porous materials, membrane technology and drug delivery, under the auspices of a Joint Center of Integrated Nanosystems (JCIN). Managing JCIN along with my highly supportive co-Director Majed Nassar, has been aided and abetted in a big way by Alyssa Avestro, Ashish Basuray, Tracy Chen and Mark Lipke.  It became clear towards the end of 2006 that the fortunes of the CNSI were set to suffer as a result of a change in the State of California Administration in Sacramento. Although buildings were nearing completion at both UCLA and the University of California, Santa Barbara (UCSB), it was apparent that there would be next to no funds made available from the State to equip the two buildings. I had little desire to find myself in charge of two white elephants.  I had tried to interest Chad Mirkin at Northwestern University in moving to UCLA to take over the Directorship of the CNSI from me. He was not interested but then turned the tables on me by inviting me to move to NU. Negotiations with the then President Henry Bienen at NU began in February 2007 and proceeded at such a pace that an announcement of my move could be made in August of that same year, allowing a few members of my group to start relocating a month later into newly refurbished laboratories in the Technological Institute. Although it was to take until August 2014 for a brand-new building, sanctioned and supported on my advice by the President, to house some of the major items of departmental equipment (spectrometers and diffractometers) to materialize, it was well worth the wait. I moved up to Evanston on 1st January 2008 amidst a spate of gong-collecting. It seems that awards and prizes feed off one another to a considerable extent. In January 2010 my research group, under the guidance of Doug Friedman, moved with military-like precision from the Tech building into the newly opened Silverman Hall to occupy research space second to none in our previous 40-year history. It did not take long for it to be called the Research Palace – or RP for short. **Nortwestern University** At Northwestern, a decade of broadly based activity in research relating to supramolecular chemistry, as well as mechanostereochemistry, has relied heavily on simply allowing a team of extremely creative graduate students and postdoctoral scholars free rein within the remit of the grants that support their research. This approach to invention and innovation in research has been highly successful, leading to a host of serendipitous events. One of these accidental discoveries, by Ron Smaldone – who was joined on its realization by Jeremiah Gassensmith and Ross Forgan – relates to the unexpected ability of γ-cyclodextrin to form highly porous extended structures with Group IA metal cations, particularly potassium, rubidium and cesium ions. This discovery in turn has led to the establishment of a start-up company, PanaceaNano, in 2010 with Youssry Botros as its Chairman and Chief Executive Officer (CEO). The company has developed several Organic Nano-Cube (ONC) based materials that are completely safe for use in many industries, such as cosmetics, home and personal care, health and medicine, chemical, environment, food and beverage, and agriculture. In less than one and a half years, the company has developed and shipped many prototypes for testing by collaborators and distributors in the cosmetics, fragrances and drugs areas. The other chance discovery, by Zhichang Liu, relates to a remarkable lock-and-key fit between α-cyclodextrin and potassium tetrabromoaurate in a 2:1 ratio within a linear and rigid supramolecular polymer, which aggregates in its thousands – like drinking straws in a box – to form needle-like crystals within minutes in aqueous solutions. A start-up company, Cycladex, was launched in 2014 with Roger Pettman, one of my early postgraduate students from my Sheffield days, as its CEO. The company is offering the opportunity to the goldmining industry to abandon the use of cyanide and mercury in the isolation of gold from ore and to adopt a much less expensive environmentally friendly way of achieving a better outcome.  In the realm of supramolecular chemistry, the trio of Michal Juríček, Jonathan Barnes and Edward Dale devised much more user-friendly and efficient approaches to the synthesis of the little blue box, before going on to expand the dimensions of this tetracationic cyclophane to yield much larger receptors they called ExBox and ExCage, which turned out to be ideal for complexing polycyclic aromatic hydrocarbons. An intellectually satisfying piece of research carried out in collaboration with Jay Siegel at Tianjin University was the induced-fit catalysis of corannulene bowl-to-bowl inversion, which illustrates very nicely the principles of enzyme catalysis. In what is a simple textbook example, catalysis of the inversion process in corannulene, induced by its stereoelectronic binding inside ExBox, can be followed along a single ‘reaction’ coordinate, where the reactant and product are the same. A full paper published in the *Journal of the American Chemical Society*, “ExCage” – one of the shortest titles ever for an article on chemistry – amounts to a tour de force in contemporary physical organic chemistry enacted by the ExBox/ExCage trio.  The reason that the laissez-faire approach to supervising graduate students and postdoctoral scholars in the Northwestern chemistry department thrives so well is because it is an approach that is endorsed to the full by the vast majority of the faculty. The experimentally and computationally active members in different research groups interact with each other so well − more often than not from the bottom up − that it has led to the comment that we hunt in packs in the Department of Chemistry at Northwestern. Allowing these interactions to take their own course without meddling or interference is an extremely effective dynamic when it comes to the attainment of high-quality research. It is a dynamic that, is by and large, lost on university administrators and the regulatory authorities, who are much attracted and enamored by the concept of research being performed in silos. The fact that the laissez-faire approach is the dominant practice in the Northwestern Chemistry Department despite the presence of rules and regulations that would dictate otherwise, has rendered it possible for my research group personnel – Gokhan Barin, Ali Coskun, Marco Frasconi, Sergio Grunder, Chenfeng Ke, Severin Schneebeli, Cory Valente and many others, to collaborate with their counterparts in the groups led by Mike Wasielewski, Joe Hupp, Omar Farha, Bartosz Grzybowski, Emily Weiss, Chad Mirkin, Mark Ratner, George Schatz and Lin Chen, while maintaining active collaborations with Bill Goddard’s group at CALTECH and Omar Yaghi’s group at UC Berkeley. Add to this list the name of my fellow Nobel Laureate Jean-Pierre Sauvage, who spent a couple of years (2010–2012) coming from Strasbourg to Evanston from time to time as a visiting professor, and you have yet another source of intellectual stimulation *par excellence*. His overarching presence encouraged us all to spend a considerable amount of time thinking deeply, practicing painstakingly and writing wisely about chemical topology, a subject area that will surely come into its own right in years to come.  Two additional developments at Northwestern deserve special recognition. One was the demonstration in 2010 by Ali Trabolsi, and followed through by Albert Fahrenbach, of the strong 1:1 complex formed between viologen radical cations and the bisradical dicationic cyclophane, obtained on reduction of the little blue box in the presence of methyl viologen or its derivatives. It was somewhat counterintuitive that three ‘free’ electrons would hold a complex together in the face of substantial Coulombic repulsion, but it is a fact! This discovery led to the template-directed synthesis of catenanes and rotaxanes. While Jonathan Barnes set about making the homo[2]catenane of the little blue box – an achievement which Diego Benítez described as being intellectually disruptive – Hao Li employed radical templation to make rotaxanes that have been introduced subsequently into the design and synthesis of a rapidly growing range of artificial molecular pumps by Chuyang Cheng, Paul McGonigal and Cristian Pezzato. This story is featured in my [Nobel Lecture](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/2016/stoddart-lecture.html) – produced, as in the case of hundreds of other presentations, with the help and expertise of graphic artist Alex Bosoy.  The other development worthy of special mention was the writing, along with Carson Bruns, of a major treatise on MIMs. In every respect – both words and pictures – the heavy lifting was done by Carson during a 30-month period that spilled over into some of his time as a Miller Research Fellow at Berkeley. It was quite fortuitous that Wiley ended up introducing the work to the world at large in the early part of November last year, halfway between the announcement of the 2016 Nobel Prize in Chemistry on 5th October and the prize-giving in Stockholm on 10th December. The manuscript was reviewed critically by many colleagues and the production of its six chapters, along with all the necessary components that go into the making of any book, were orchestrated by two people in particular. One was Xirui Gong, who read the proofs sentence-by-sentence, word-by-word, letter-by-letter, and number-by-number. The other was Margaret (Peggy) Schott, who assisted me in the demanding task of quality control as well as assuming responsibility for the production of the index in a highly effi cient manner. Over the past 10 years at Northwestern University, Peggy has helped me, day-in and day-out, to guide a team of highly talented, yet often quite demanding, young researchers, from the day of their arrival to that of their departure and beyond into their own independent careers. These activities reflect only the tip of the iceberg when it comes to hailing the support Peggy – a PhD chemist and Northwestern alumna – provides to so many in the chemical community – locally, nationally and internationally. **Epilogue** In reflecting upon my peripatetic journey, which started with my valuable early experiences at the ‘University of Life’ on the farm, I can look back with feelings of pleasure interspersed with times of personal and professional hardships. There have been occasions marked by joy and others by sorrow. There have been periods that were characterized by success and others by failure, which I did my best to mitigate. Through all my life’s experiences, the aim has always been the same: to emerge from life’s roller coaster better informed and more knowledgeable about the ways of the world.  Putting all the ups and downs aside, I have been immensely privileged to be able to practice my hobby almost every day of my life in the presence of highly intelligent and outstandingly gifted young people, roughly aged between 18 and 32 drawn from nearly all quarters of the globe – and to do the things I love doing with them as a result of the generosity of those institutions and people, often without my being able to put a label or face to them, who have lent their support to my vision and mission from the Athens of the North (Edinburgh University) to the Windy City beside Lake Michigan (Northwestern University) with interludes on the edge of the Canadian Shield beside Lake Ontario (Queen’s University), in the Socialist Republic of Yorkshire (University of Sheffield), on the Plains of Cheshire beside the Wirral (ICI Corporate Laboratory), in the Heartland of Albion (University of Birmingham and in the City of Angels alongside the Peaceful Sea (University of California, Los Angeles). My journey is far from over: it will continue as long as family and friends fail to raise a red card telling me that I have reached my sell-by date.  Science is global and there’s no going back: scientists the world over live in a global village. There are no better words to catch this sentiment than those of the Scottish poet Robert Burns. In an epic poem, he emphasizes that “we’re all the same under the skin.” It is a statement of egalitarian sentiments. The poem reads –Oh, that people who exercise power and influence in the world over we ordinary mortals might be guided by these sentiments. What a wonderful world it would be for all humankind if there were no borders – and rejoice at the thought, no countries. |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** | [JFS]  J. Fraser Stoddart: Hello.  Adam Smith: Oh Hello, my name is Adam Smith. I’m calling from Nobelprize.org, the official website of the Nobel Prize in Stockholm. Well, first of all congratulations on the award of the Nobel Prize.  JFS: Oh thank you very much. I’m overawed, and in a state of shock [Laughs].  AS: [Laughs] What did you do first after hearing the news?  JFS: Well I have got in contact with my two daughters. They’re thrilled to bits, and I wished to share the news with them because I sadly lost my wife 12 years ago from breast cancer. It would have been nice to be able to share this experience with her since she played such a big part.  AS: I’m so sorry to hear that, and what a sadness not to be able to tell her. But how very thrilled your daughters must be.  JFS: Oh they’re totally overwhelmed. The people who spoke to me told me that it would be shared with Jean-Pierre Sauvage, in Strasbourg, and Ben Feringa, in Groningen in the Netherlands, and I just feel thrilled about that. These are two scientists that I have held in extremely high regard all through my academic career and we have actually worked very closely together.  AS: How nice that the Prize celebrates that fellowship.  JFS: There’s so much to be had from bringing people together from different cultural backgrounds, and the amazing thing is that when you put them in a research laboratory they work like sisters and brothers. I find that, you know, I have this father, and now probably grandfatherly, relationship with them so you do just learn over the years that diversity really does enrich the process of discovery and invention and so on and so forth.  AS: People often think of chemistry in terms of bangs and smells but your work really emphasises the creative, sort of artistic aspect of the subject.  JFS: Yes, absolutely. I was not in any way drawn to chemistry by bangs and smells. In fact when lectures of this ilk appeared I subsequently would just go away and stay in the background because this was never my real empathy with chemistry. It was much more about its corresponding interaction with art and culture and so on, and so that’s what’s driven me through chemistry, its wonderful ability to express yourself in an artistic form.  AS: Thank you.  JFS: Thanks very much.  AS: Bye bye.  JFS: Bye bye. |
| **Interview** |  |
| Q9 | How did you first get the news that you had been awarded the Nobel Prize? |
|  | “I was in bed. It was 4.05 a.m. when I got a call. So, of course, I thought something bad had happened, either in Japan or in the UK, where my daughters live. When I answered the phone and got told about the Prize, I also thought it could be a hoax. Fortunately, I am good at detecting English being spoken by people of different nationalities. I soon understood that: ‘Yes, this person is speaking Swedish-English’. Then I knew it was for real.” |
| Q4 | It has been a while since you conducted the research on molecular machines for which you received the Nobel Prize. What are you working on now? |
|  | “I am 75 going on 76 years old. One of the projects that I am most excited about is giving the 30 to 35 very bright young people in my lab, from all over the world, pretty much free rein to do what they like. If only one or two of them come up with something out of this world, it would be a rewarding experience. The Prize has done a lot to open up these opportunities as well as funding for the project.” |
| Q9 | What was your experience like in Stockholm, both receiving the Prize and meeting the other Laureates? |
|  | “Unforgettable. I think this is a week that has been choreographed down to the last detail. Everybody was of the mind that the diversity of the experience was amazing. One of the great joys of Stockholm was spending time with my co-Laureates. There have been Laureates in the past who have been at each other’s throats and not being at all friendly. It seemed to me that we were very much one family.” |
| Q1 | What advice would you give this year’s Laureates? |
|  | “I would hesitate to give any advice because I think it is such a personal experience. I find it difficult when people ask: ‘How do you win a Nobel Prize?’ First of all, statistically it is absolutely reigned against you. And secondly, you should not pursue your profession as a scientist with this mission as your goal. You should do your research and enjoy doing it. Maybe a Nobel Prize will happen for you, but the likelihood is very small.” |
| Q18 | You are a tweeting Nobel Laureate. What made you decide to start using Twitter? |
|  | “Yes, I am totally taken over by Twitter. I feel that I must reach out to the young people who are coming into science at the moment. Twitter breaks down a lot of barriers and I become one of them. I was persuaded by my ex-graduate student Stuart Cantrill to start tweeting when I went to Stockholm. I took his advice and I am now labelled as a twitter monster! My mission is to try and get my co-Laureates and people from my generation involved. But my success rate has been very low. I have put the screw particularly on Ben Feringa to see if I can get him to start to tweet. He just looks at me and implies: ‘I am not getting into that, Fraser.'” |

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| **Biographical** | It is a great privilege to be able to stand on the shoulders of the giants of chemistry and in doing so experience the marvels of the molecular world and provide “challenges for our youth, dreams for the people, and opportunities for industry.” For me being a scientist engaged in designing new molecules and chemical systems is a life-long “adventure into the unknown,” entering an uncharted territory of astonishing beauty, surprises and amazing perspectives. Over the past decades on many occasions we have lost track on our intended journeys, reaching places in chemical space we could never have imagined. On these occasions, one of my heroes, Abel Tasman, comes to mind. Several hundred years ago, Tasman, an adventurer, departed from a small village close to where we live, sailed in a primitive wooden ship to the edge of the known world, lost his bearings and as a consequence made the serendipitous discovery of what we now call Tasmania and New Zealand. From the outset of my academic studies as a young adult I ventured on an unexpected odyssey into chiral space, however my fascination for the unknown, for “exploring beyond the border,” began in my childhood. **The early days** In 1866, my grandfather, then 3 years old, moved with his family, poor Roman Catholic buckwheat farmers from Emsland, a few miles across the German-Dutch border, to settle in the great Bourtanger moor; a vast, largely uninhabited and remote area in the northeastern part of the Netherlands. The two main reasons for these “Siedler” to build a living in this desolate area were a lack of fertile soil and the threat of conscription into the Prussian army. It was in that same year that the Kingdom of Hanover was dissolved. They were among the founding families of the village of Barger-Compascuum. Starting in primitive turf houses, they slowly established themselves by farming and digging peat. The rather harsh living conditions imbued the family with a strong work ethic, being independent and self-supportive and with a strong desire for knowledge, which we also experienced in our childhood. My father Geert Feringa, who was the youngest of the family of ten, ran the farm while being involved in village community organizations including the local bank, school and church councils. The family of my mother Elizabeth Hake has a similar background, also originating from the border region. Facing poverty, the whole family of her ancestors decided to emigrate to the USA in the 1800s except for the youngest son, who became the first headmaster of the elementary school in Hebelemeer, a German village close to where we lived. Her parents also moved across the border, reclaiming land, and my mother grew up at their farm as the eldest of a family of ten.  My parents married in 1949 and I was born in 1951 as the second of ten children. I cannot remember that I ever left the village during my early youth; most of the first 10 years I spent within 800 meters of the border (except while attending school). The farm and the vast wilderness just behind our fields being my world and that of my brothers and sisters as well as the dozens of nephews and nieces that formed our community. This playground definitively stimulated my imagination, sense of teamwork and desire to explore. Crossing the border behind our farm was always a hard-to-resist adventure and the wilderness on the other side provided many unexpected engagements and findings. Our family was largely self-supporting with animals for milk, eggs and meat, peat for heating, a water well, and a large garden for vegetables and fruit, the latter being my mother’s pride and joy. There were no luxuries but we were comfortable and to this day, I am amazed at how she managed to feed all ten of us with an abundance of healthy food even throughout the winter. From an early age, each of us had our own tasks, and as I grew, I tended the chickens, helped in the garden and later would cut peat for the stove. Observing the behavior of animals, growing three-meter-tall sunflowers and questioning the origin of peat without doubt stimulated greatly my inexorable desire for knowledge. **Basic and high school education** I am extremely grateful to my elementary school teachers, who provided us with a solid primary education. My life long appreciation of history and geography started with their accounts while covering these topics, which was further stimulated by the fascinating stories told by my father and uncles during long-winter evening gatherings at the farm. Being asked frequently why “playing with molecules is so much fun,” the proper answer is perhaps that I am striving to fill the gap in my early education left by fact that I did not attend a kindergarten. Both of my parents had little more than elementary school education but they were nevertheless top of their classes and on the occasions that I failed to deliver the proper answer to the headmaster, he would remind me that my mother would have known the answer. Our parents were certainly role models for learning and encouraged us to seize opportunities absent to them in a remote farmer’s community in the pre-war period. It may be hard to imagine today but we should remember that there were no TVs, PCs or smartphones; but there were certainly books at home or in the local church library that we could reach for in our search for knowledge.  The next step in my education was to attend the Katholiek Drents College, a secondary education called the HBS, which was held in high esteem in the Netherlands. I had the good fortune to attend a rather small school with a team of excellent academically trained young teachers covering a wide range of topics. Confronted with biology, mathematics, physics, and chemistry, a new world opened for me fueling my thirst to know how and why. I remember vividly that most of our teachers could address topics beyond the textbook and put the material we had to learn in a broader context.  Our chemistry teacher, Op de Weegh, was an exceptional inspiration, always eager to challenge us. In the later part of my high school education, when the next step in academic education was approaching, he was particularly influential in my decision to do chemistry. Although mathematics was my most successful subject, the fact that in chemistry you could experience color, odor or beautiful crystals and see practicality ranging from fertilizer to drugs were decisive factors. At a recent reunion of my high school, talking to my chemistry teacher reminded me of one of his sayings: “I wish every child in his or her life at least one excellent teacher.” I had the good fortune to have several! Cycling 15 km every day to school with my friends – there was no public transport – also gave room for intense debates, sharpening our minds. This was also the time that I started to play for the local soccer team, and although I was a player of modest talent, and digressed for a few years playing handball, I have enjoyed playing soccer for a long period extending well into my academic career. Perhaps the best gift of my high school education was that I learned to appreciate many disciplines.  A perhaps unexpected influence during my late high school and early university studies, that wild period of the student revolts and social upheaval, were the endless discussions at home among my brothers and sisters. Our Sunday debates on topics ranging from world politics to inventions, religion, and human behavior are still vividly remembered by all of us. Let me not conclude describing this period without mentioning perhaps the single most influential person. I always bore the desire to become a farmer but had the good sense to follow my father’s wise advice to study first and only later, perhaps, reconsider my options.  As a consequence, I spent most of the long summer holidays during high school and university working alongside my father on the farm. He shared with me the fascination and admiration for the natural world, the wonder of ears of wheat growing from a tiny seed, the beautiful colors of the flowers in the fields, and cows giving birth to their offspring. Such wonder alleviated the muscle ache that followed the solid day’s work and while we were puzzled by the shape of clouds or the flow of water, and as we struggled with the nature of gravity, it invariably guided us back to our work with the soil. **University education** I entered the University of Groningen as a major in chemistry in 1969 and I quickly learned to appreciate the academic environment, the various aspects of student life and the many hours of demanding courses and lab work. Two factors I consider of major importance for this period of my undergraduate education. First, we were the first cohort of students to work in our then brand-new laboratories; we take pride in being a part of that community. Second, several of our professors were either US citizens or trained in the USA and they challenged us – we felt their sense of expectation. They had modelled the chemistry department after top US institutes and their rather unique spirit did not go unnoticed. My real love for synthetic chemistry started in my third year when I had my first opportunity to work on a short research topic. I hold fondly the memory of the exhilaration that I felt making my first new compound – a compound never prepared anywhere in the world. My next experience of research was a period in the inorganic department, where I learned to handle the most air and moisture sensitive early transition organometallic reagents, in particular organotitanium compounds. Every time I see a nice painted wall the vivid memory of a leaking seal of the Schlenk flask, with oxygen slowly creeping in, springs to mind.  My decision to carry out my Masters research, I think, says a lot about my character then. I had declined a project proposal from a chemistry professor who had indicated that prior to working on that topic I should do a lot of routine measurements, as “the problem was too difficult for me.” I was eager to be challenged and was fortunate that another professor, Hans Wijnberg, struck the right cord by providing a topic that had no prior art whatsoever. Asymmetric coupling of phenols; how to couple two radicals generating axial chirality, as in BINOL? I started exploring Fe-analogs of chiral camphor-based -diketonate ligands, reported in 1974 by George Whitesides for his chiral europium NMR shift reagents. Although during my Masters research I failed to accomplish the asymmetric coupling of 2-naphthol, it was rewarding that ultimately during my PhD studies I was able to realize BINOL formation with 16% optical purity using a chiral copper amine complex as oxidant. These were the years that I became fascinated by stereochemistry, not least by the excitement that arose in the field as a result of many amazing discoveries in asymmetric catalysis. The general interest in the group on fundamental aspects of stereochemistry ranging from ORD and CD spectroscopy, absolute configuration and absolute asymmetric synthesis to enantiomers lacking optical activity and the pioneering work on asymmetric organocatalysis using cinchona alkaloids was a fertile learning environment. It was also important that numerous prominent (stereo-) chemists – among them Sharpless, Eliel, Barton, Turro and Kagan – visited Groningen during that period and we were strongly encouraged to discuss with these great scientists. I continued my PhD studies in the Wijnberg group and discovered among others small differences in selectivity between a racemic mixture and pure enantiomers in stoichiometric reactions. We named this phenomenon the antipodal effect and, although our initial submission met with disbelief from the referees, ultimately our work was published. Much to our delight, 10 years later, Henri Kagan demonstrated that related phenomena occur in catalytic reactions and formed the basis for the now widely accepted non-linear effects.  Perhaps the most decisive moment in regard to my later career was the design of chiral overcrowded alkenes that did not bear a stereogenic center but for which both the cis and trans stereoisomers consisted of enantiomeric pairs. The idea was rather simple; if a biaryl can be chiral due to hindered rotation around a single bond, the question arose “can an olefin form a stable homochiral compound exclusively due to torsion around the double bond”? Taking advantage of then newly discovered McMurry coupling of ketones, the chiral overcrowded alkenes were indeed prepared and reported in JACS 1976. How could I have realized at that moment that this discovery would later form the basis for our chiroptical molecular switches and our unidirectional rotary motors. In retrospect, the PhD period provided me with the essential atmosphere for discovery in which we were encouraged to question conventions and break paradigms. My fellow students, in particular Bert (EW) Meijer, Kees Hummelen and Henk Hiemstra, who have each made prominent academic careers over the past decades, greatly added to the stimulating and challenging atmosphere in the group. The summer of 1977 was another highly important period in my career, when I was dispatched to the US to attend the Organic Symposium in Morgantown, WA. Hans Wijnberg introduced me to many distinguished chemists but I was most impressed by the superb 2 h 20 min (a rather short lecture I was informed) evening lecture by the great Prof. [R. B. Woodward](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1965/woodward-facts.html). As my mentor had also arranged for me to make a short lecture tour, I had the privilege to give presentations about my PhD work at Penn State and Cornell among others and Princeton where I also had the opportunity to discuss stereochemistry with my hero Kurt Mislow. After my American journey, I was convinced that my next step was postdoctoral research in the US. But as is so often the case in life our journeys can take unexpected detours. **The Shell period** In the months writing up my thesis work I realized that national service, then compulsory in the Netherlands, would inevitably quench any dreams of a postdoctoral adventure. By good fortune, I was offered a position at the Royal Dutch Shell Research Laboratories (KSLA) in Amsterdam that, because of my expertise in stereochemistry, exempted me from active military service and provided the next best thing to a Postdoc period in the US; as a young academic, I was entering a highly prestigious corporate research institute, comparable to Bell Labs or DuPont central research, with a worldwide reputation in catalysis. Indeed, I experienced an amazing exposure to both fundamental and applied catalysis research during my 6.5 years at Shell. Most of my own research focused then on catalytic oxidations and novel ligand and catalyst design. In my first months, I shared an office with David Reinhoudt, who introduced me to the then rapidly emerging field of supramolecular chemistry. Although I was working on fundamental problems in catalysis, for instance photo-redox catalysis, I strongly benefitted from the interaction with process chemists also. The exposure to numerous industrially relevant projects provided me with important insights that have helped to shape my future collaborative research projects, as well as in teaching our students, the majority of whom would enter industrial careers. Definitively, my later projects on asymmetric catalysis and phosphoramidites with DSM, catalytic oxidations with Unilever and liquid crystals with Philips over the past decades, were partly rooted in my industrial research period at Shell.  Apart from the KSLA period, I spent nearly 1.5 years at Shell Biosciences center in Sittingbourne, Kent, UK, working on herbicides. This period was equally fascinating, discussing with biochemists and plant physiologists among others. Immersion in total synthesis and chemical biology further stimulated my admiration for the power of synthetic chemistry to create and the unlimited opportunities presented by molecular design. Equally stimulating were regular meetings with Sir John Cornforth and members the British chemical community. Following my return to Shell Amsterdam and the catalysis group of Piet van Leeuwen, I realized that reading the latest discoveries in the prime chemistry journals still inspired me more than delving into industrial problems. When I was approached in 1984 by my Alma Mater to consider a junior faculty position in the chemistry department, theere was no hesitation. The fact that in that year I had married my wife Betty, who then lived in Groningen and was employed by the University Medical Center there, made the decision even easier. **University of Groningen** My research program over subsequent years was based firmly in synthetic organic and physical organic chemistry. Although it developed along two main lines, catalysis and molecular switches, stereochemistry remained the overarching theme. Exploring chiral space regularly provided fascinating surprises, be it a novel method to determine enantiomer excess without an external source of chirality, chiral amplification through sublimation, or DNA-based asymmetric catalysis (together with Gerard Roelfes).  Catalytic oxidation is key to many of the world’s most important industrial processes, and confronted with the challenge to design selective oxidation processes we focused on anti-Markovnikov Wacker oxidation and non-heme iron and manganese based catalytic systems. As part of these programs I enjoyed superb cooperation with Larry Que (Univ. Minnesota), Ronald Hage (Unilever/Catexel) and Wesley Browne (Univ. Groningen) over many years. Building my research team in the late 80s, I became intrigued by the lack of a highly enantioselective method for conjugate addition of organometallic (alkyl-zinc and copper) reagents. The introduction of chiral phosphoramidites as a novel privileged class of chiral ligands in asymmetric catalysis resulted ultimately (in 1996) in the 1,4-addition of organozinc reagents with synthetically useful enantioselectivities. From this period on, I had the privilege to work together on highly successful projects with my close colleagues Adri Minnaard and Suzy Harutyunyan, focusing on challenging total syntheses and equally challenging problems in asymmetric catalysis. It took another 8 years before we succeeded in taming Grignard reagents for similar conjugate additions and allylic substitutions; the key was to go deep and understand at a mechanistic level both the catalyst and the reaction as a whole. Spurred on by this success, finally, after 20 years of effort, we were able to achieve catalytic asymmetric C-C bond formation with the notoriously reactive organolithum reagents. Controlling aggregation behavior and applying well defined copper complexes provided the long-awaited solution. This was the stepping stone for our current program on ultrafast organolithium cross coupling.  I was appointed as full professor in 1987, succeeding my scientific father Hans Wijnberg in 1988, and gave my inaugural public lecture at the University of Groningen (the academic oratie is a fine Dutch tradition) in 1989 entitled “Order and Dynamics in Synthesis.” The discussion on that occasion among others centered on “intelligent molecules”; I pondered on how far we could go in building functional molecules that were designed to perform specific tasks, ultimately creating tiny molecular robots.  This event was the starting point for over 25 years of work on molecular switches and motors. The basic idea was to design molecular information storage materials taking advantage of the dormant overcrowded alkene switches from my PhD period. The excellent switching properties (photo-bistability) and inherent chirality (for non-destructive read-out) were decisive factors that enabled the birth of an entire class of chiroptical molecular switches. The merging of synthesis with mechanistic studies, photochemistry, materials chemistry and spectroscopy, in close cooperation with Wesley Browne, attracted students with distinct training and expertise who beyond doubt were highly influential in our discussions and approaches taken during the next two decades. An important collaboration on the absolute configuration of chiral overcrowded alkenes was started with Noboyuki Harada in Sendai. We extended our program on photoswitches to control biosystems such as MsCl protein channels and SecY protein transporters (with biochemist Armagan Kocer and molecular microbiologist Arnold Driessen, respectively). As our research slowly evolved from molecules into dynamic molecular systems we worked on control of organization along different length scales, i.e. gels, polymers and liquid crystals. The studies on chiroptical switches culminated in the discovery of our light-driven unidirectional rotary motor, reported in 1999. This was also the starting point for the design of several generations of motors, surface anchored rotary motors and motorbased liquid crystals (in cooperation with Dick Broer, then at Philips Research). Being a member of both the Stratingh Institute for Chemistry and the [Zernike](https://www.nobelprize.org/nobel_prizes/physics/laureates/1953/zernike-facts.html) Institute for Advanced Materials at the University of Groningen was a major advantage, providing access to a wide range of facilities (in particular for surface characterization) and highly beneficial to my students working on these multifaceted problems. The Spinoza grant was the immediate reason for the design of a four-wheel drive molecular car tackling the fundamental challenge of how to convert rotary molecular motion into translational motion across a surface. After 7 years we succeeded, in close cooperation with Kalle Ernst at EMPA, Zurich. These were fascinating years for my “motor team” as we designed single motors that could move in both directions, motors powered by visible light, multitasking chiral catalyst and self-assembled nanostructures based on rotary motors among others. In hindsight, probably the most memorable event in all these years was the direct observation by the naked eye of a micro-object rotating, while floating on a soft liquid crystal surface, by a light-driven motor.  I had the pleasure to spend a major part of my life at the University of Groningen’s Chemistry Department with fine colleagues and an open border-free atmosphere encouraging students to cooperate and staff to discuss and work together. I enjoyed working with my group on diverse chemical problems stimulating creativity and cooperation with ample opportunities to learn and explore beyond our comfort zone. It was indeed a privilege to join my highly talented students on a fascinating journey into the largely uncharted territory of molecular motors and machines.  The long tradition of spending a week each year with my whole group abroad, visiting industry and another university or research institute, is highly valued. This “workweek” with student-organized lectures ranging from industrial innovation, ethics, chemical warfare to molecular cooking, joint symposia and sports and pub events greatly stimulated a fine team spirit.  Shortly after my appointment in Groningen, Betty and I decided to move to the village of Paterswolde just south of Groningen, giving us both the chance to enjoy a decent daily cycle to and from our respective workplaces. “Moving in Flatland” in the northern Netherlands of course gives plenty of time each day to think about the three-dimensional puzzles that we were facing in the lab. Just as memorable have been the annual BBQ’s in our garden when the whole group gathers together (often during European and World Cup Soccer events) and the many PhD graduations, for which we have the tradition of making a movie about the candidates’ time to ensure that their many unexpected talents in and out of the lab are remembered.  I enjoy long-distance skating, and as a farmer’s son it is a delight to have our own piece of land with a meadow, horse and vegetable garden which allows me not only to exercise in the weekends but never lose contact with nature. Our three daughters shared the enthusiasm for learning and sports. Femke, a cell biologist, is in the final year of her PhD studies at the Netherlands Cancer Institute (NKI), Hannah just started a PhD in the area of food allergies at the Utrecht University Medical Center and Emma is a Masters student in movement sciences at the Free University of Amsterdam. The week of skiing in the Swiss Alps every winter and the sailing events on the Frisian lakes each summer provide ample opportunity for challenges beyond chemistry and are very precious moments with Betty and the children. I am extremely happy to have experienced great support during my entire career from my family and that they tolerate me being distracted by “crazy molecules” at unexpected moments. Betty always reminds us of my passion: “Being a scientist is a way of life.” I could not agree more, and I am grateful that she was and is always alongside me on our journey. |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** | [BF]  Speaker: Hello.  Adam Smith: Oh hello, may I speak to Professor Feringa please?  Speaker: Who is this?  AS: This is Adam Smith calling from Nobelprize.org, the official website of the Nobel Prize.  Speaker: OK, can you hang on for a few seconds?  AS: Most certainly, yes.  Bernard Feringa: Hello, Ben Feringa.  AS: This is Adam Smith, many congratulations on the award.  BF: Thank you very much. Thank you. I’m emotional and I’m deeply honoured.  AS: And I can hear many happy people behind you.  BF: Ja, ja, ja. That is a huge number of people, the whole institute and all the students, and I think they deserve a lot of credit for all the work they did to make it possible.  AS: I just spoke to Fraser Stoddart and he emphasised how much of a scientific family you all are.  BF: Yes, you are absolutely right. We know the community, we are the scientific family, we have meetings, we cooperate, we encourage each other, we exchange students. You are absolutely right.  AS: How wonderful. So you describe your work as being inspired by nature?  BF: Ja, of course. If you look at the cells in our body or the functioning of the organism, it is flabbergasting. It is fantastic to see how this intricate machinery works. And when I’m taking about motors, as we focus on motors, if you look at the essential functions in the cell, like cell division, like transport, like making your muscles move, bacteria that go to food or [unclear …] it’s all controlled by molecular motors, and so the biological motors, and the biological machinery, is so crucial to all these functions. And of course we get great inspiration from that, while we as chemists are extremely good in building all kinds of materials, and that is what intrigued me. And there is where we look at mother nature, but of course we have to build it more or less from scratch because many of the systems that mother nature uses we cannot use in our nanomachinery, because they are soft materials that are not very stable that only function properly in the complex cell environment etc. So that is the reason that we build these machines. And compare it to a flying machine. We don’t build a Boeing after a pigeon. A pigeon flies perfectly, the bird flies, ja, but the Boeing is not the same materials, it has not the same flying principle, but it works perfectly to transport 3-400 people across the ocean.  AS: That’s perfect. And people often make the comparison with Lego. They say you’re building with the tiniest Lego.  BF: Absolutely. So we use molecules as a kind of Lego kit, ja. And so we have access to this unlimited number of molecules and we use them to build the new materials, the drugs of the future, and in this case also the nanomachinery and the smart materials of the future. And yes, I feel often, and me and my students and the team, and I’m sure that it’s the same for the other teams of Stoddart and Sauvage, we feel sometimes like kids playing with these molecules and seeing what are the possibilities to build, like with Lego. As a kid you had fun to build new kinds of castles, and that is actually what we are doing. And then hopefully, and this is our main goal of course, to build in all kinds of new functions. And in this case the function of transport, motion, machinery.  AS: That’s a fantastic, inspirational message for the next generation of scientists. Just go out there and express yourself and have fun.  BF: Thank you. Thank you so much.  AS: And you’ll come to Stockholm in December?  BF: Absolutely.  AS: Fantastic, we look forward to welcoming you very much.  BF: Thank you so much.  AS: Thank you. |
| **Interview** |  |
| Q12 | How has your upbringing affected you? |
|  | “It was absolutely wonderful being such a big family. Growing up on a farm was a continuous adventure, because we were a self-sustaining farm; we had cattle, pigs and chickens. My father was also growing crops and everyone in the family helped at the farm. We all had our own duty and there was always action, such as small baby calves being born. All these things that you were intensely involved in, made you ask yourself questions. How can I understand how nature operates? How is it possible to grow these beautiful sunflowers from small seeds?  My father and mother never got the opportunity to study further than elementary school. Even so, I think they easily could have gone to higher education. They were very interested in stimulating us, answering questions and debating with us. We had many books at home even in this remote area. In a farm with so many kids, uncles and aunts living in the neighborhood; we were a big family making our own adventures. That gives you a feeling for creativity and discovery. I think that is where it all started. Asking questions, being creative and imagining.” |
| Q10 | You often say that universities should be playgrounds. How can we make sure that this is the case? |
|  | “I’m a strong believer in challenging students at all levels – to think, to discover and to go beyond the current knowledge. I think this is true for students at all levels, it starts already in kindergarten. The universities have a special role here, because academic training and science should go beyond the current horizon. I think that we shouldn’t forget that we shouldn’t train our students for today or tomorrow; we should train them for 10 to 20 years from now. Because then they will be the innovators in our society, then they will be the persons that make a difference. If we want to create an inclusive society, it’s really important that we train our students for tomorrow. That means that they have to be able to surpass the border of our current knowledge. This is what I mean with playground, that you have sufficient space to think, to discover and to be free to make mistakes. But in particular to make the next steps, be creative and not limited by what should be done. Because a lot of things happen by accident and suddenly you get a major breakthrough or new insight. Schools should encourage students to ask questions and be creative.” |
| Q5 | What is it that you like so much about teaching? |
|  | “I really enjoy the transfer of this beauty of knowledge; insights, questions, things that we don’t know, or the limitations of what we know. Also, this pleasant feeling of understanding something, even if it’s very difficult. I think that you share with your students the opportunity to transfer some knowledge, but also get a lot of things back by asking questions and discussing. Across all fields, from natural sciences to humanities, you have knowledge and insights built upon generations and decades. I think it is wonderful to be able to share that with young people that have an open mind and want to learn and are eager to know what we already know and what we don’t know.  At the universities we have to transfer a lot of knowledge and teach students the basic skills and techniques. But it’s also our duty to go beyond that – to ask them questions about what we don’t know and what improvements can we make for the future. The way we do surgery in the hospital now, it might be taken over by robots in the future, how are we going to deal with that? Or will we be able to make fuel for airplanes? These are challenging and tough questions but to share those with the students is really nice. Most of all, I think the beauty of knowledge and the excitement of insights and discoveries is fantastic.” |
| Q5 | How important do you think it is to have great teachers in school? |
|  | “I often ask an audience if they remember a teacher from their school period. Everyone always remembers a bad teacher, and particularly an excellent teacher. You always have one or two excellent teachers that made a difference and inspired you.  When I came to high school I didn’t know anything about chemistry and physics, as you don’t study those topics that much in elementary school. But I had a teacher that was really great. He challenged us and did a lot of experiments with us. He was such a great stimulating person that made me decide to go into chemistry because I loved the colours and smells and to the ability to do reactions and make something. You need inspirational persons that both tell you basic information but also give you this flavour of excitement. To me it made a big difference. I value great teachers a lot and I think we should invest more in our teachers; to encourage, stimulate and help them. I value this because I think that it makes a difference in our society if you have good teachers at elementary school and onwards, even if the students come from a household where education isn’t the norm.  I think every kid has a talent. Some kids become a carpenter or car mechanic. Others become teachers or painters. For teachers to stimulate that talent and encourage each kid is so crucial. You cannot expect this from all parents, because some parents never had that capability. But the teachers can recognise that, despite the fact that this kid comes from a family that has no opportunities, they have a talent.  I think the role of good teachers shouldn’t be underestimated. If you train and educate your teachers well, they will educate and stimulate your kids to reach their highest potential. Because without any doubt, every kid has a talent that we should encourage. Teachers play a crucial role there, in my opinion.” |
| Q5 | What challenges have you found when it comes to teaching right now during COVID-19, how are you coping with that? |
|  | “After my Nobel Prize, I held lectures at high schools to talk about the importance of teaching and about my work. But now I can’t do that anymore. I’m now in the lab where we work in shifts. That’s a bit difficult, especially when you work in chemistry, or physics or natural sciences. I think practical training is crucial. But it is tougher to do experiments because some people might have limited access, and with the large number of people in research labs it’s difficult to give all the experimental training that we want to give. That’s an issue I’m a bit worried about, because we want to train them at the right level before they finish.  The second issue is that most of the lectures are online. As a teacher, I must say that there are good courses on the internet, and it’s good that you have filmed lectures that can be reviewed. But I think the interaction in class with the students is really important. I like to discuss with my students, to be in the midst of them and to ask questions. When teaching online you sit in front of the screen, don’t see the faces of the students and receive questions in the chatbox. There is no direct contact. Last week, I was allowed to have a physical lesson with a group less than 20 people. I was really happy during those two hours. The students seemed happy too to attend a live lecture again.  For me, it was a delight, because I could talk with the students, I could ask them questions, I saw their eyes glittering and that is a great feeling. You can also improvise because you feel if they understand you or not. You can see a raised hand and a student asking something, and that is the kind of interaction that is really important for teaching. There are a lot of advantages with computers. But I’m strongly advocating that we don’t forget to also have physical contact with students, because asking questions and discussing is so important for teaching.” |
| Q11 | Do you think that education is inclusive nowadays or do you think that this is something we should improve? If so, how can we improve that? |
|  | “That is difficult to say but we still could improve in some sense – to make it inclusive for everybody so we stimulate and challenge every kid and get the best out of each kid. I think we shouldn’t forget that a lot of children learn not only from a book or screen but also by doing practical things, especially in the natural sciences.  There is a tendency that practical research and conducting experiments in lab settings is becoming less important. I think practical learning is crucial, because a lot of kids learn by practical exercises and solving problems. That is also part of the inclusiveness for some kids. There are several aspects to this but I think schools should be a place where the talent of each student should be stimulated. Each student irrespective of background, gender and social situation should get the possibility to let their talent grow. I don’t like that schools offer better and worse education depending on where the school is located – we should have a certain minimum standard and it should be inclusive.  I grew up in a tiny village, where nobody ever went to university, certainly not from my family. My brother and I were the first to attend higher education. Without the stimulation from my teachers and parents, I would have never been there. It is so important that we give kids this opportunity. I was so lucky that my parents stimulated us a lot but it’s not the same in every family. Getting stimulation from different sides is crucial. I know, from personal experience, how difficult it can be, and how important it is that kids get that. It is the basis of their future.” |

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| **Chemistry\_2024-2000** | |
| **ID** | 0325 |
| **Biographical** | Asked to reflect on my background, I realise that the conditions under which I grew up were very different from those that young scholars encounter today. I was raised and educated in post-war Stockholm, Sweden, where I was born on 28 January 1938. My parents lived on one of the large islands in central Stockholm called Kungsholmen, but moved to the western suburb of Bromma within a few years, with a rented summer cottage in the adjacent archipelago. I obtained my early training in Stockholm and retain many friends there.  My father Robert was a businessman with a deep interest in literature (Fig. 1). He had spent several years in France as a young man, and there he acquired a life-long enthusiasm for haute cuisine; he was an excellent cook himself. My mother Ethel (Fig. 2) became a university administrator and later moved on to a similar post in the Swedish parliament. She was greatly helped in that venture by fluently speaking six foreign languages, a talent I unfortunately have not inherited. Neither of my parents had any background in natural sciences, but they nevertheless always gave me unconditional support.  An important factor in our family life was the close relationship between my father, his sister and his three successful brothers. They all lived in Sweden and saw each other regularly. My oldest uncle, Erik, was a professor of economics in Uppsala, where he was a main teacher of [Dag Hammarskjöld](https://www.nobelprize.org/nobel_prizes/peace/laureates/1961/hammarskjold-facts.html). Uncle Helge, chairing the association of Stockholm lawyers, had a pleasant house in the Stockholm suburb Bromma, where my parents also moved. My aunt Ingeborg became a high school teacher in French. The two youngest brothers, Gunnar and my father, were particularly close, and uncle Gunnar’s constructive advice to my parents was very influential on the early life of me and my younger brother, also called Gunnar. Uncle Gunnar was an eminent surgeon who became the Director of a large hospital in western Sweden at Torsby. He collected modern French art. On his excellent advice, my brother and I were given Christmas presents when we were young boys in the form of colourful original lithographs by French artists such as Maurice Estève. Seeing these beautiful abstract pictures for most days of my life has been helpful to gain some understanding and love of fine art, although I am a hopelessly incompetent draughtsman.  As a younger teenager, I developed an interest in botany and spent several summers bicycling around the large, limestone-rich island of Gotland in the Baltic, searching for rare wild orchids. **High school (gymnasium)** I was fortunate with my high school education in that our family lived close to an excellent upper secondary school, Bromma Läroverk (now Bromma gymnasium), where I was a student for most of eight years (Fig. 3). At that time, the Bromma school had teachers of outstanding calibre, with Fredrik Ehrnst (mathematics) and Karin Brandt (chemistry) as well as the Headmaster himself (Dr Gustaf Iverus), being especially impressive and helpful.  Many pupils at Bromma were also exceptional. My class of 30–35 co-educated individuals included Björn Svedberg, later chief executive of the large L M Ericsson telecommunications company (now Ericsson), and Olle Orrje, a talented engineer, mathematician, poet, jazz musician and expert on high jump. A close friend at that time was also the late author and essayist Torsten Ekbom, although we met at the Kungsholmen rather than Bromma school.  I was not particularly talented in sports, although I enjoyed long-distance running before it became fashionable, but I spent much more time on music. I played the piano, both classical music and jazz, and became a good sight-reader. But I did not practice enough; I could get through most Beethoven sonatas but not adequately perform the brilliant romantic repertoire by Chopin and Schumann (Fig. 5). Debussy became a long-term favourite. I also played jazz music (Fig. 4), a common talent among students in Bromma, initially in New Orleans and dixieland style on the clarinet or soprano saxophone, but gradually turning to modern jazz on the piano, with Bud Powell and Thelonius Monk as particular sources of inspiration. Since jazz is dependent on collective improvisation, I made many inspiring friends that way, and I have been glad to have heard from several of them, after many years, in connection with the recent publicity about my Nobel Prize. My short career in jazz ended when I entered medical school; in Sweden there was still a general military draft system at that time. In order not to delay medical training, initial military service of three months each summer for three years was done by future doctors. So, I could hardly practice music in the summer, whereas my friends became more advanced, and obviously I was left behind in musical accomplishment. It was no comfort at all that I instead had become trained to use pistols, guns and machine guns, and throwing grenades and bombs.  Our family was typically middle-class, not rich, but because Sweden is a hightax society that provides free education, my parents never had to pay school fees for me or my brother either in good high schools or in medical school (Fig. 6). Admission to sought-after university programmes such as medicine depended on excellent school marks, whereas interviews, fees or private funding did not occur. When I later considered giving up my medical studies to concentrate on scientific research, which of course was a very risky future, it seemed important that I had not already taken out substantial student loans. **Karolinska Institute** With the strong encouragement of my uncle Gunnar, I decided to apply to the medical school in Stockholm, called Karolinska Institute (Fig. 7), after graduating from high school. I had adequate but not outstanding school marks; I prefer to blame this result on a lack of focus because of too many competing interests. But the important outcome was that I scraped into medical school.  After initial studies in anatomy, histology and physiology, I became especially excited about biochemistry and bacteriology. On the other hand, an introductory course in surgery demonstrated clearly that I was impractical and incompetent in this important speciality.  At that time, the Department of Bacteriology started a new initiative to recruit medical students who might consider taking a one-year break from their medical studies to attempt a serious basic research project, guided by an experienced scientist on the faculty. I was intrigued by this prospect and was accepted, with very little competition for the post. This became a new departure, although it took many years before the Swedish Army stopped their annual query if I had completed my training in surgery. **Wine tasting** I never became enthused about academic student life and preferred to interact with my friends in the fields of literature and jazz music, but during my initial medical studies I made an influential new friend, Johan Liljenberg, the son of a Stockholm doctor. Johan had picked up an unusual and esoteric new interest, which was little considered at the time, that is, fine wine. In those days, the Swedish wine and spirits monopoly system allowed this state agency to buy the most superb Bordeaux wines of fine mature vintages for sums that today seem ridiculously low. Still, the public showed little interest. In the Swedish monopoly system, there was a dull-looking catalogue of the 300–400 different wines which could be purchased. Johan and I, and a couple of other friends convinced the biggest food magazine in Sweden, *Allt om Mat*, to buy a bottle each of all these wines, and we then tasted them over a series of evening sessions. We wrote critical, or positive, comments on each wine as capsule reviews which were then printed with similar typography as the official one. This yearly hard-hitting annotated wine catalogue became a commercial success, and I was sorry to have to give it up many years later due to other, more “serious” interests and moves abroad. For my efforts during those years, I obtained a tiny honorarium, but could order as much wine as needed for all tastings and comparisons of the changing assortment. I particularly recall two red Bordeaux wines from 1949, Château Lafleur (Pomerol) and Château Mouton-Rothschild … Of course, the general public was more interested in whether a certain inexpensive wine was good value for money, or awful, and in the latter respect we were not at all polite in our comments, as you might have expected from irreverent young medical students. **Starting research on DNA** At Karolinska Institute there was a small annex to the Bacteriology Department used by the retired chairman and professor of chemistry, Einar Hammarsten (Fig. 8), and a very small group of his co-workers. Einar was a pioneer in DNA research before it became clear how important this large molecule is. I found him fascinating, with his total absorption in scientific research. His attitude of complete devotion to his main interest reminded me of top musicians. In a typical incidence, Einar explained an interesting problem to me, the beginner, and we went into the large cold room to pick up some reagents. There, he became absorbed with his argument and continued a detailed explanation; it did not occur to him that we could just as well have stepped out of the cold room and continued the discussions outside. He had had the most distinguished students and co-workers in his field in Sweden, e.g. Torbjörn Caspersson, Peter Reichard, Torvald Laurent and Ulf Lagerkvist, but when I got to know him he was to some extent an extinguished volcano. Still, I found him inspiring, a real artist of science. He told me a couple of years later that when the Karolinska campus moved from small premises in central Stockholm to its current location just north of the city, he was given money from the Swedish government for the new buildings. But when the bills later arrived, they could not be paid because Einar had already used the funds to purchase new research reagents and consumables, modern instruments and equipment. When he was seriously admonished by the university administration, he just shrugged his shoulders and said that they might consider sending him to prison.  The most interesting research problem I worked on together with Einar was the behaviour of DNA in glycol solution. DNA is best soluble in aqueous solution, and tends to precipitate when an organic solvent such as ethyl alcohol is added. But Einar had observed an interesting exception, DNA solutions could also be made when ethylene glycol replaced water. To pursue this topic further, I was able to learn the technique of bacterial transformation by DNA from an American sabbatical visitor, Professor John Spizizen. Armed with this new method, together with biochemistry, I could show that the biologically active double-stranded structure of DNA survived in a salt-containing 99.8% solution of glycol below 30°C. Such DNA solutions were much less viscous than aqueous solutions. A colleague I later met at Princeton, Dr David Henley, was trained in polymer chemistry and explained to me the concepts of good vs poor polymer solvents. I am surprised that the compact form of native DNA in the “poor solvent” ethylene glycol has not been used more in experimental biochemical work on nucleic acids. **A long visit to the US** Since my work in Stockholm concerned isolation and characterisation of nucleic acids, I was invited to spend a short time at Princeton University in New Jersey, in the group of Professor Jacques Fresco. An important and helpful intermediary was Professor Carl-Göran Hedén at the Karolinska Bacteriology Department. Fresco was interested in preparing large amounts of transfer-RNA to attempt crystallization and structural definition. This visit to Princeton lasted over three years, and I very much enjoyed the friendly and relaxed atmosphere in the Fresco laboratory at the University Chemistry Department. Fresco had been working with the grand old man of nucleic acid chemistry, Professor Paul Doty at Harvard, and he was a dynamic and positive mentor (Fig. 9). He talked a lot, and had not always sifted his new ideas, which made some colleagues underestimate him. However, you quickly learnt not to pay any attention to some of his suggestions, whereas other ideas could be really novel and helpful. One of Fresco’s earlier collaborators apparently had already used the same constructive approach with a positive outcome. He was Bruce Alberts, who later became a very distinguished scientist as well as President of the U.S. National Academy of Sciences.  At Princeton, I collaborated with a young American colleague, Alice Adams, who later became my wife. Together, we produced some interesting work in the Fresco laboratory, in particular the finding that a specific tRNA could be stabilised in two different forms depending on the solvent conditions during the isolation procedure. Only one of these two conformers was biologically active in amino acid acceptance during protein synthesis, which was the first formal proof that the folding pattern of tRNA was biologically relevant. Alice and I later moved to New York and Sweden together, and we have two lovely and successful children, Lena and Nils. But after over ten years, Alice and I drifted apart and separated, which was largely my fault. She ultimately returned to the US with the children and took up a university position in Minnesota.  From Princeton I moved to the Rockefeller University in New York. Since I had been successful in the Fresco group, I obtained a prestigious Helen Hay Whitney postdoctoral fellowship, and I joined the laboratory of Professor [Gerald Edelman](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1972/edelman-facts.html), a highly intelligent but very tense man, whom I found difficult.  Edelman was awarded a Nobel Prize at that time for his pioneering work on the structure of antibodies. In his group, my ambitious and premature project concerned the genetic and biochemical mechanisms for generation of antibody variability, a complex problem to which I could only contribute in a minor way many years later. Since it seemed possible that genetic recombination events were crucial for antibody variability, I took a biochemical approach and searched for enzymes in lymphoid cells that might be involved in such DNA processing. Some such enzymes of DNA metabolism had just been discovered by others in the bacterium *E. coli*, an important model system, but it was not known if mammalian cells contained similar factors. I found and characterised the first mammalian DNA ligase and DNA exonuclease, but we did not have the techniques available to attempt to prove their roles in intracellular recombination events. This only became possible with the introduction of DNA cloning and sequencing, years later.  During my biochemical work at the Rockefeller University I was told by a senior colleague and friend in Sweden, Professor Giuseppe Bertani, that the Swedish Natural Science Research Council had advertised an independent research post on the junior professorial level for investigations of the conformation of biologically important macromolecules in solution. I applied, and somewhat to my surprise I was offered the post in competition with a more established scientist from Uppsala. I had had some controversies with Gerald Edelman, but nevertheless he became angry when I told him I was leaving to go back to Sweden for a different job. **Return to Stockholm** At Karolinska Institute, I obtained a small research laboratory of my own within the famous Medical Chemistry department, where Peter Reichard and [Sune Bergström](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1982/bergstrom-facts.html) were professors. I was successful in obtaining my first research grants from the Swedish Research Council and the Swedish Cancer Society. With this support, I could hire a technical assistant, Barbro Nyberg, who luckily turned out to be a meticulous and talented scientist. I remained in my laboratory at the Karolinska for nine years (1969–1978), and did much of my best work there, which has been described separately in my Nobel lecture. My main research topic was the intrinsic chemical instability of DNA, which suggested that special DNA repair mechanisms must exist to counteract such spontaneous DNA damage.  I had an interesting and serious diversion into tumour virology during this time. The background was that Peter Reichard was promoted to a special research professorship in a separate building at Karolinska after the retirement of the Nobel Prize winner [Hugo Theorell](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1955/theorell-facts.html). But I had just been able to obtain some additional laboratory space, and my work was going well, so I decided to stay in the Medical Chemistry Department, although I continued to take part in Peter Reichard’s departmental seminars. However, the main emphasis of the important Medical Chemistry Department was research on prostaglandins and bile acids, topics far from my own interests, so Reichard knew I was somewhat isolated there. At that time, Peter was contacted by his good friend at Karolinska Institute, the famous tumour virologist and immunologist George Klein, with a query whether Peter could recommend a young molecular biologist to collaborate on work on the Epstein-Barr virus (EBV), a human virus that is the cause of infectious mononucleosis and is also involved in the origin of the human tumour Burkitt’s lymphoma. George Klein had made fundamental contributions to EBV tumour biology, but at that time very little was known about the biochemistry of EBV, although it was known to be a herpes virus, and relevant preliminary studies had been done by Professor Joe Pagano’s group in the US. An important question at the time seemed to be the definition of the integration sites of EBV DNA in the human genome. In my collaboration with George Klein’s group, I first set up DNA hybridisation techniques to demonstrate the presence or absence of EBV DNA in apparent rare EBV negative cases of Burkitt’s lymphoma. But my key work concerned the intracellular forms of EBV DNA in transformed (“immortalised”) B lymphocytes. I had been intrigued by a beautiful recent paper by Jun-Ichi Tomizawa at the NIH, in which he showed that the large *E. coli* bacteriophage P1 did not integrate at all in the bacterial chromosome, but persisted stably as a circular plasmid in the bacteria. I speculated that perhaps the EBV genome also could be carried in such a non-integrated form, and devised procedures to attempt to isolate such hypothetical EBV DNA circles from cells. This technically difficult experiment was successful, and the discovery of full genome length EBV DNA circles in transformed lymphocytes, including, in collaboration with George Klein, human biopsies of Burkitt’s lymphoma from Africa, became my main contribution to the EBV field. I had worked on the EBV project together with an American colleague, Beverly Griffin, who had her own laboratory and research group at the Imperial Cancer Research Fund (ICRF) in London, studying polyoma virus.  Beverly and I soon spent increasing amounts of time together, and at that time I also left Stockholm to move to Sweden’s second city, Gothenburg. The main reason for this was that my comfortable independent research position with the Swedish Medical Research Council had one main obligation; if a professorship became available in my field at one of the five Swedish universities, I was expected to apply. This rule of course made sense from the point of view of the Research Council, who expected their promising young scientists to move with the times. In consequence, when my formal application for a job in Gothenburg was approved I had no clear alternative, although I had lived and worked in Stockholm for most of my life. My department chairman in Gothenburg, Ulf Lagerkvist, was a delightful, helpful and highly cultured colleague. Soon after my move Beverly came to Gothenburg for a six month sabbatical (Fig. 10). She and her postdoc John Arrand had cloned the EBV genome as a set of large defined DNA fragments, and together with our Gothenburg colleague Lars Rymo we did some work on such DNA. Beverly was also in touch with her former mentor, [Fred Sanger](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1980/sanger-facts.html) in Cambridge, and she persuaded him to sequence the entire EBV genome. It was the longest genome from any source that had been sequenced at that time, and became an important research tool.  In Stockholm, I recruited my first graduate students, who greatly contributed to the improving reputation of my research group; they were Stefan Söderhäll, Siv Ljungqvist and Marla Anvret. In Gothenburg I was then fortunate to receive several outstanding postdocs and sabbatical visitors who put the DNA repair aspect of the laboratory in international focus, including my future long-term collaborator Peter Karran. At that time, I was also pleased to be elected to EMBO, a helpful honour. **Move to Britain** While my work in Gothenburg was going well, Beverly and I had not resolved the problem of staying together in one place. But then I got a tentative offer from Sir Walter Bodmer, the Research Director of ICRF, to become head of a newly renovated laboratory building in outer north London, the Clare Hall Laboratories. This generous offer included not only excellent facilities and space for my own research group, but also the possibility to recruit and initially fund several new independent research groups to generate a critical mass. This position clearly surpassed my professorship in Gothenburg. So Beverly and I moved to a 300-year-old Georgian cottage in Highgate Village in north London, and she became a professor of virology at the Royal Postgraduate Medical School of Imperial College, London. I continued to work on both DNA repair and EBV, but because of increasing international competition in both fields and new exciting developments in the DNA repair field, I gradually scaled down my tumour virus work. After 35 years together with Beverly, she sadly became increasingly ill after a stroke, and she could not attend the Nobel festivities in Stockholm.  At the Clare Hall Laboratories, I was lucky to have two superb administrative co-workers: Frank Fitzjohn who managed the actual laboratories and Brenda Marriott who dealt with all staff problems (Fig. 11). They were responsible for the friendly and positive aspects of running the laboratories, which made these labs attractive to co-workers on all levels. The only problem with the Clare Hall Laboratories was that they were geographically somewhat remote from all the excitement in central London. But for a scientist who wanted to focus on his/ her research, it has had many advantages. A similar recent development appears to be the Janelia Farm outside Washington, DC, where hand-picked young scientists are offered generous support and facilities, and only nominal teaching obligations. At the Clare Hall Laboratories, we decided to focus on a limited number of overlapping research areas and attempted to become internationally top-class in these fields, which included DNA repair, DNA recombination, control of DNA replication, mutagenesis, and control of transcription. Among the most successful scientists on site were Steve West, David and Birgit Lane, John Diffley, [Tim Hunt](https://www.nobelprize.org/nobel_prizes/medicine/laureates/2001/hunt-facts.html), Rick Wood and Jesper Svejstrup. In the summer of 2016, the scientists at the Clare Hall Laboratories, together with those at the Lincoln’s Inn Fields Laboratories (formerly ICRF) and those at the National Institute of Medical Research at Mill Hill in North London, are scheduled to move to a newly built large laboratory close to King’s Cross in Central London named the Francis Crick Institute, with [Sir Paul Nurse](https://www.nobelprize.org/nobel_prizes/medicine/laureates/2001/nurse-facts.html) as Director.  At the Clare Hall Laboratories, I continued my work on DNA repair mechanisms. The field had changed remarkably since I made my first studies in an unfashionable and underappreciated field, and it certainly helped the Clare Hall Laboratories that I was able to attract several prestigious sabbatical visitors and remarkable postdocs. These included Bruce Demple, Larry Grossman, Bob Painter, Phil Hanawalt, Errol Friedberg, Grigory Dianov, Claude Prigent, Primo Schär, Keith Caldecott, Arne Klungland and Yun-Gui Yang, and they were complemented by two excellent British senior staff members in my lab, Barbara Sedgwick and Deborah Barnes.  As in Stockholm, I depended greatly on outstanding technical staff, who included the eminent Peter Robins and a frequent visitor from the Gothenburg laboratory, Monica Olsson. Two influential short-term visitors and junior colleagues from Scandinavia were Erling Seeberg and [Svante Pääbo](https://www.nobelprize.org/prizes/medicine/2022/paabo/facts/). Erling was a brilliant Norwegian scientist who sadly died from cancer in his 50s, after having made key contributions in the early days of DNA repair. Whenever I felt a little isolated from mainstream research in Gothenburg, I thought of Erling who was worse off, since he initially had a very small and isolated lab outside Oslo. Svante applied the techniques of molecular genetics, and especially studies of DNA damage and repair, to create an entirely new research field, ancient DNA. And Svante and I shared some bête noires; he could not find any DNA at all in fossils many millions of years old, in spite of enthusiastic publications in the leading scientific journals, and my view was that the intrinsic instability of DNA made it impossible to isolate and sequence DNA from organisms as old as dinosaurs.  In 2005, at the age of 67, I had to step down from the position as Director of the Clare Hall Laboratories. John Diffley and Steve West ensured that topquality research would continue on site. Moreover, I continued as head of my own research group for another 4 years, but in 2009 I closed my “wet lab” at Clare Hall and concentrated on a scientific advisory role, both in Britain and at several places in continental Europe (including Sweden). One particularly interesting assignment was as Director of the Scientific Advisory Board of IFOM, the molecular oncology institute in Milan, Italy, where the Director, Marco Foiani, and I attempted to influence the emergence of IFOM as an internationally important research institution; in my opinion the best in Italy.  Perhaps in the near future I will have more time for gardening and playing the piano, but so far my retirement period has been as busy as before, which on balance is a good thing. I still hope to promote studies on one of the first mammalian DNA enzymes I found, the nuclear exonuclease Trex-1 (initially called DNase III). I remain convinced that this little-studied enzyme which removes unwanted single-stranded DNA fragments is a key to understanding autoimmunity and some serious inherited diseases in man. Time will tell if I am right or wrong.  In recent years I have received several treasured recognitions for my research work, especially in 2009 the French Prix Étranger of INSERM, in 2010 the Royal Medal of the Royal Society (London), and in 2013 the highest award of the Royal Society, which is their Copley Medal. I am particularly indebted to the Royal Swedish Academy of Sciences for awarding the 2015 Nobel Prize in Chemistry to myself, Paul Modrich and Aziz Sancar for our work on the chemistry of DNA repair. For me, it was a special honour to be the first Swede in over 60 years who has been awarded the Chemistry Prize. A field that started as a small speciality 45 years ago has achieved full maturity. |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** | [Adam Smith] Oh hello, my names Adam Smith, calling from Nobelprize.org, the official website of the Nobel Prize in Stockholm  [TL] Hello.  [AS] Hello. Many congratulations on the award of the Nobel Prize.  [TL] Thanks very much.  [AS] Could you tell me, how did you hear the news?  [TL] I had a phone call early this morning, just a couple of hours ago I guess, or an hour ago, from the Swedish Academy telling me this very good news.  [AS] An amazing phone call to get. What was your first reaction?  [TL] Well, surprise to some extent, not 100% surprise because Im getting up in the years and I know that I have been one of the well known scientists in my field of science, which is DNA repair for many years. So the question was will there be a Prize for DNA repair, and I think many people have now realised its a very important topic of research, and if so there would be 10, 15 excellent people you could choose from, and you cant give the Nobel Prize to more than three people. So I feel very lucky and privileged to be included in the top class that was awarded.  [AS] And it must be very special because I think you’re the first Swede to receive the Chemistry Prize for 67 years, since Tiselius …  [TL] That may well be, yes.  [AS] Does that make it more special?  [TL] Yes, I think so because I got my initial training in Sweden, and I also had the difficult decision to do there, in that I was studying medicine, and research started looking very interesting and intriguing, so should I put aside my clinical studies for some time and concentrate on the research instead. And that’s a risky decision to make for a young fellow, but I took the chance and I think it has worked out.  [AS] It has paid off, yes. As you say the Prize is for the field of DNA repair and you’re considered a father figure in the field, and you’ve devoted your life also to cancer research for some decades, and …  [Phone beeps]  [TL] Pardon.  [Phone beeps]  [TL] Im not a politician, Im not used to talking on two phones at the same time, sorry …  [AS] I was just saying you’ve devoted your career to cancer research for some decades also, and these DNA repair mechanisms, they help protect our DNA but they also in some ways help protect cancer cells don’t they?  [TL] Yes, that’s an important topic of modern research. We want to understand repair mechanisms in some detail so that we can prevent the cancer cells from repairing DNA when we, for example, expose them to radiotherapy. But we do need the repairs to protect us against DNA damage that occurs inevitably.  [AS] Lastly, would you say the prospects for cancer research, for treating cancer or at least for turning cancer into a chronic disease, are good at the moment?  [TL] Yes, that is a very good and hot topic, not only for cancer but I think for many diseases. In this case we are getting away a little bit of trying to find a cure for everything and convert diseases into something we can live with. The reason weve had for a long time with diabetes. Its difficult to cure diabetes but we have good ways of treating diabetic patients. And I think with regard to DNA damage that will be increasingly important aspect of it. Im home now because I was going to do some writing at home today, but after this message it was decided that a driver will take me out to the laboratory where the work has been done in North London.  [AS] Yes  [TL] That’s the Clare Hall Laboratories.  [AS] Are you enjoying this? This attention?  [TL] Of course. Its always nice at the end of your career to have recognition that what you have done is actually important.  [AS] Indeed, indeed. Well how lovely to speak to you, thank you. I look forward to seeing you again in Stockholm in December and hopefully sooner in London.  [TL] OK.  [AS] Thank you. Bye bye, congratulations. |
| **Interview** |  |
| Q3 | What’s your story? What brought you to science? |
|  | Tomas Lindahl: What brought me to science? My early education and I started out as a medical student in Stockholm after going to a gymnasium in a suburb of Stockholm. And the reason I went into medicine was our family had an influential uncle, Gunnar Lindahl. He was a director of a big hospital in Sweden and not only because of that he advised my parents that if I as a teenager had to make a decision about the rest of my life, its too early, so the best is to go in to a broad carrier where you later on can find something to do that you really like to do yourself. And they suggested the best I could do was to start studying medicine because if you are compassionate about your human beings, like providing care, that’s fine, but if you like more theoretical questions that may arise in a laboratory, that’s also quite compatible with being medic.  So you put off the big decision for a few years what you are actually going to do with your life and that’s wise, because you are not always capable to decide that in the best possible way when you are sixteen years old. You are a much better bet when you are in your mid-twenties. So that is how I got into medicine and sure enough it turned out that I started liking the theoretical part of medicine, especially biochemistry and microbiology and that is what I specialized in. I had to do some medical studies, but I wasn’t particularly good at it and I realized that I would be happier to try to do something important in the laboratory. So that was the start of it. |
| Q4 | Describe your Nobel Prize-awarded work in one minute. |
|  | Tomas Lindahl: I think many people are now aware of that in ourselves there is the carrier of genetic information and that’s the DNA. And if there are changes in the DNA, that causes mutations which are usually damaging. So the conclusion from those facts was that DNA should be very very stable, a fantastically stable chemical. We were the first ones that really started looking at could this be right? What kind of macromolecule would be so stable that it could carry all the genetic information without any risk for mistakes or errors? That’s just not possible, so we defined the errors that can occur spontaneously in DNA. If that was right, there had to be a repair mechanism to deal with these errors and we looked for such repair mechanisms and found them, these are enzymes that act on DNA by cutting away the damage bits so that the DNA can be repaired. |
| Q14 | What questions remain to be answered in your research? |
|  | Tomas Lindahl: Directly in my own field the repair mechanisms are very diverse and important and we only know part of them. Its not just one type of DNA repair, there are many types of DNA repair and we have gradually defined some of them and so have my colleagues, but there are still additional problems that can happen to DNA, that just haven’t been looked at yet. So it’s a very wide-open field right now and I am sure that in a couple of years or already within five years there will be new progress and new enzymes found that act on the DNA in ways that we don’t know about today. |
| Q2 | What’s the toughest challenge you’ve faced? How did you overcome it? |
|  | Tomas Lindahl: What has been a tough challenge in my life? Well, besides personal controversies that I guess most people go through. In science, the tough choice was when I had successfully entered the Karolinska Institute medical school in Stockholm and was on the way of becoming a doctor and then decided to do something risky. I stopped my medical studies half-way and said that I’ll make my own carrier in an area that doesn’t really officially exist. I will work in the lab and see what happens. And then I think I would probably have come down on my feet, I could have lost a number of years, gone back as a somewhat disappointed doctor at a later stage, but that didn’t happen. |
| Q4 | What motivated you to pursue your research? |
|  | Tomas Lindahl: The main motivation was to find out how our cells work in the body. I think that is a fantastic challenge and very interesting to find out. How does life function? We are all composed of cells, but each cell – what drives it forward? And how can that happen? I don’t have any religious aspects on this at all, I think it is strictly a Darwinian evolution we are looking at, but that is fascinating, because we don’t know all the details yet. And we do need to understand all the details before we can device new medicines against many common diseases now. I am convinced that the solution to many of the major health problems in life are to be found in basic research. We just first have to find out how something works, and I would even have thought that it is fairly obvious. If you want to understand how something works, a watch or the human body, you understand how it operates, you don’t just go in and say I am going to do something applied with this, but you don’t do something applied with a watch that doesn’t show the time. |
| Q10 | Where do you do your best thinking? |
|  | Tomas Lindahl: Where I do my thinking? Anywhere. You don’t come to work and sit down in the morning at the desk and say now I am going to think. Good scientific research is a bit like an absorbing hobby. You think about it all the time. And best ideas can come to you in a totally irrelevant place, over a weekend or a vacation, just as well as when you are in the laboratory. Then you have to go back to the lab and do some experiments to show that you are right or wrong, but the basic idea can come to you anywhere. |
| Q2 | Have you had a eureka moment? |
|  | Tomas Lindahl: Probably. What I am being awarded for here is the understanding that DNA is not at all as stable as people have been thinking, because if our DNA is falling apart, as it does, there has to be some kind of repair mechanism or other strategy to deal with this. I was convinced about that, that we should start looking for repair of endogenous DNA damage, just what happens to our DNA in the cell without any direct provocation, by radiation or dangerous chemicals from the outside or something like that. Something that happens all the time to our DNA, and if that is so, that means we are repairing our DNA all the time, it actually turns over at a slow rate and that is not what the textbooks are telling you at all. We were doing these experiments and found that DNA is very labeled and once you convince yourselves that its not some kind of clumsy artifact but it’s a fact, then the obvious conclusion is that the cells must have figured out how to deal with this problem and they have. |
| Q5 | Who was your most inspiring teacher? |
|  | Tomas Lindahl: An old professor at Karolinska Institute called Einar Hammarsten and his name was Einar, Einar Hammarsten, Swedish name Hammarsten. He was the teacher not only of me, but of some other very well-known Swedish scientists, Peter Reichard, who was a leading scientist at Karolinska Institute until his retirement a few years ago, he is a few years older than me. Hammarsten was inspiring because he was totally dedicated to experimental science and basic research. That was really basic science although, he was a powerful professor in a medical faculty. He realized at an early stage that you got to do basic research to figure out how things work and he would be in the lab many hours and show up over holidays and so because he was so fascinated by it all. And I found that very inspiring and so did other of his pupils, I am sure, because he was like an artist. You don’t ask a violist or a pianist Does it become boring to sit and practice every day? If you think it is boring, you should do something else. |
| Q1 | What advice would you give yourself at 20 years old? |
|  | Tomas Lindahl: Probably, I can’t think of any better advice than the kind of carrier I’ve had, to reiterate, start studying medicine to get a broad education while you are thinking about what you are going to do. And then if you like basic science it is a fascinating area to work in. I am really pleased to have been able to do this and actually do some useful work in this field, I assume since I got an award for it now. Talent, you have to have a talent for what you want to do, I would have loved to be a great concert pianist, but I just don’t have the talent for it. But to become a scientist isn’t all that bad either. |
| Q17 | What does intelligence mean to you? |
|  | Tomas Lindahl: It’s a difficult question because many people mean different things by intelligence. I think it’s ability to think outside the box, not to do what everybody else is doing, but come up with some new ideas. I don’t think intelligence is the same thing as some people have photographic memory and they can immediately memorize a page out of the phonebook. That’s an interesting party trick, but that is not what I mean by intelligence. If you talk to people and discuss with them and you immediately get challenged. It’s exciting to talk to such a person, that’s an intelligent person, because they are somebody who can put you on your toes and make you think about what you are saying.  I always had broad interests and I think that’s an important part to science, you should try to avoid being to specialised, especially when you are young. Take an interest in the arts, literature, anything in addition to the science you are doing. Because it helps you become more creative. If you just try to focus on one special little field and solve all the details in that little field, sometimes you will then come to end or stop, because you don’t have the background to think in a creative way what to do next. Instead of working very hard you should try to be creative and do things that you enjoy doing, reading good books for example. And I think it’s much better to read good books than watching TV. Some of my oldest friends have been literature critics and essayists and not in science. |

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| **Chemistry\_2024-2000** | |
| **ID** | 0326 |
| **Biographical** | **Ancestry** My knowledge of my ancestry is limited. My paternal grandparents emigrated from Croatia in the late 1800s and settled in the coalfields of southern Colorado. My father Laurence Modrich was born in 1912 in Walsenburg, Colorado and spent his early years in Ludlow, which like a number of other coal camps in the area, was owned by the Colorado Fuel and Iron Company. These mining camps have been described as “feudal dominions” [1] where wages and living conditions were poor. This prompted the Colorado coal strike of 1913–1914, largely organized by the United Mine Workers, and a period of violence that culminated in the 1914 Ludlow massacre, an attack by mine guards and the Colorado National Guard on the tent colony occupied by the striking Ludlow miners and their families, a tragedy chronicled by Woody Guthrie in his song of the same name. My paternal grandfather left at some point thereafter, and my grandmother moved her family a few miles south to Trinidad, Colorado where my father and his two sisters received their education and worked to help support their family. My father never talked much about this period in his life, but it was clear that it imbued him with a strong work ethic, which he imposed on my brother and me while we were growing up.  After graduation from the University of Colorado in 1935, my father moved to Raton in northeastern New Mexico, a town of about 8,000 people just south of the Colorado border, as a coach and biology teacher. He was drafted into the Army Air Forces in 1942, and while on leave from basic training with a friend from Muscatine, Iowa, he met my mother Margaret McTurk, a young woman of German and Scotch-Irish descent. They married in Muscatine in June of 1943 just prior to his transfer to Europe. After my father’s discharge in 1945, they returned to Raton where I was born in 1946 and my brother David in 1948. **Growing up in New Mexico** My parents had quite different perspectives on many things, including child rearing. My mother was doting and highly involved in our daily lives, while my father was more hands-off and insistent that we develop independence. I recall my mother walking me the four blocks to and from school during kindergarten and my father’s judgment that I should henceforth be able to make it on my own, which I did.  Although Raton was relatively isolated in the foothills of the Sangre de Cristo mountains, it was for me an ideal place to be a child: a safe community of mostly warm-hearted people and a physical environment that I found (and still find) quite beautiful, and despite the town’s relatively provincial nature, it had an excellent school system. Given my father’s coaching responsibilities, our family life in those days was in many ways dominated by athletics. I enjoyed the excitement of high school football and basketball games, which were major family and community events, and playing pickup games with friends, but despite my father’s encouragement, participation in organized sports did not appeal to me.  I was more interested in photography and learning about nature, especially biology and astronomy. I spent a lot of time wandering the hills enjoying the abundance of plant and animal life, and I read popular scientific magazines, especially *Scientific American*, when I could get my hands on a copy. I am fairly certain that my lack of athletic interests was a disappointment to my father, but he and my mother were both extremely supportive of my developing interests in science. I took his sophomore biology course (he was the only biology teacher in town), which was presented from the classical perspective and which I found quite enjoyable. The following year he was a participating teacher in the experimental Biological Sciences Curriculum Study, which introduced molecular aspects of biology into the high school textbook, and he advised me to “learn about this DNA stuff because it’s really interesting,” which I eventually did.  I found reading about science to be satisfying, but I wanted to be more than a spectator. Paging through an issue of *Scientific American* when I was 15, I came across an ad for a set of radioisotopes, which at the time you could possess in small quantities without a license. I thought I might be able to do some fun things with them and convinced my father to order them for me. About two weeks later he received a call from the freight manager at the train depot informing him that they had a package addressed to him that was labeled radioactive and with the admonishment “Do not stand within 15 feet of this parcel unless absolutely necessary.” He nevertheless picked it up and brought it home to me (I now know that the low level quantities in the samples are relatively harmless unless ingested). There were about six different isotopes, including 32P-phosphate, 35S-sulfate, 131I-iodide, 22Na-chloride, and 65Zn-chloride. I used solutions of these isotopes to germinate tomato, corn, radish, and bean seeds, or allowed geranium and violet leaf cuttings to absorb the isotopes. I also injected them into several frogs. After several days I exposed the seedlings, leaves, and pithed frogs to X-ray film to visualize the isotope distributions. The results were particularly striking in several cases: the 32P and 131I revealed the vascular structure of the leaves and the former isotope concentrated within the skeletal system of the frog, while the 35S was uniformly distributed throughout the seedlings. When we were going through my mother’s things after she passed away in 2002, my wife found the notebook and films documenting my first experiment. I had forgotten about it, but my mother had saved it all those years.  In 1963 after my junior year in high school I participated in a National Science Foundation summer program at the University of Colorado Institute of Arctic and Alpine Research. The high altitude laboratory (9,000 or 10,000 feet as I recall) was located in the Rockies, where we lived in small cabins. The high school students assisted in the counting and dating of trees and plants within defined ecological stands and in the collection water samples from glaciers and snowbanks. Because this was the period of Nevada above-ground nuclear testing and because the snowmelt fed the Boulder city watershed, the latter samples were analyzed for radioactive fallout. I asked the director, whose name I cannot recall, if I might also collect plant and animal samples from the area. He graciously agreed, and I collected a variety of plant samples and trapped field mice and shrews downstream from the glacier/snowbank runoff. After dissection of the animals, I used a gasflow counter in the evenings to determine radioactivity in the residue from incinerated plant and animal samples. The data from these experiments became my first and only science fair project, which did well locally and secured a trip to the National Science Fair in Baltimore. Although my entry received only an honorable mention at the National, the Baltimore trip with a side excursion to the 1964 World’s Fair in New York City was my first urban experience and a memorable adventure.  With strong encouragement from my father and a little grumbling from us, my brother and I acquired paper routes when we were in junior high school, delivering newspapers after school and on Saturdays, with the idea that we should begin saving for college. One of the major contributors to Raton’s economy at the time was a racetrack that hosted some of the best quarter horses in the country, attracting racing fans and gamblers from throughout the Southwest and almost doubling the town’s population on summer weekends. I began working several evenings a week as a clerk at a local motel when I was 16, and at the track on weekends where I sold and cashed parimutuel tickets. The racetrack position was highly exciting and taught me a great deal about human nature. I continued every summer into my early college years. **College** I was admitted to M.I.T. with scholarship and loan support. With supplementation from my savings and some help from my parents, I was able to get by. My arrival in Cambridge in 1964, where I moved into the East Campus dormitory, was an academic culture shock. My education in Raton had been solid, but I quickly learned that the vast majority of M.I.T. freshman had completed more advanced courses, especially in math. When Professor Mattuck began his first calculus lecture with the statement “I assume you all know what a derivative is,” I knew I had my work cut out for me. The first semester was a struggle, but with the support and friendship of several dorm mates, I managed to catch up and things became much easier.  With the exception of those who advanced-placed out, M.I.T. freshmen and sophomores were required to take the same courses in math, chemistry, physics and humanities along with one or two elective courses selected by the student. I enjoyed vector calculus and statistical mechanics, but was captivated by the introductory biology course taught by Cyrus Levinthal, which used the first edition of [Jim Watson](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1962/watson-facts.html)‘s *Molecular Biology of the Gene* as a text, and I declared biology as my major. M.I.T. is justifiably known for its strong commitment to undergraduate education, and this was especially true for the Biology Department, which at the time hosted a relatively small number of undergraduate majors. I recall as particularly memorable a superb course in microbiology taught by Salvador Luria and another in biochemistry, taught primarily by Vernon Ingram.  As a freshman, I worked about 15 hours a week on the evening shift at a campus grill, which I loathed, but I needed the money. During my sophomore year I approached Dr. Luria, who was my undergraduate advisor, about the possibility of a part-time position in the Biology Department. He got me job with Ethan Signer, who was studying genetic recombination in bacteriophage lambda. Ethan’s lab was a popular destination in the Biology Department, and the majority of the graduate students and postdocs in his group at the time, which included Fred Ausubel, Jim Zissler, Steve Heinemann, Marc Shulman, Martha Howe and Ira Herskowitz, would have their own distinguished careers. My initial responsibility in the Signer lab was washing glassware, but Fred Ausubel and Steve Heinemann got me involved in experimental work, and I began spending much of my time in the lab assisting with the recombination studies. I found the work incredibly interesting, read the few papers I could find on the mechanism of recombination [2–5] and took a graduate course in genetics taught by Ethan Signer and a recent arrival at M.I.T., David Botstein. I loved the intellectual and experimental aspects of the laboratory experience, and decided that this was what I wanted to do with my life. Because it was obvious that genetic phenomena could be understood only in terms of molecular events occurring at the DNA level, I applied to graduate school with this in mind and was admitted to the Stanford Biochemistry Department, which was widely known for its seminal contributions to DNA biochemistry. **Graduate school and postdoctoral work** My wife Ann and I bought a used Corvair Corsa from an M.I.T. professor, who oddly commented at the time of the sale that “this car doesn’t leak a drop of oil.” This proved to be untrue, but we made it safely across country and arrived in Palo Alto in August of 1968, where I learned to do science working in Bob Lehman’s lab. Bob was the perfect mentor, a great scientist but a kind and gentle man who gave me the freedom to pursue my ideas with only a nudge now and then when I needed it. Despite the intensity of the environment within the department, perhaps the most intense I’ve experienced in my career, I was extremely comfortable and happy in the Lehman laboratory, and totally consumed by my experimental work, which addressed the mechanism and biology of *E. coli* DNA ligase. Sixty-hour weeks were the norm, but the science and camaraderie made the long hours enjoyable.  The department was quite small, individuals from different research groups worked in common laboratory space, and equipment and reagents were shared. The family-like intimacy fostered close friendships, in my case with Dick Gumport, Bruce Konrad, Jack Griffith, Fred Schachat and Doug Brutlag, and my social life largely centered around the department, with a periodic poker game providing great fun and wonderful company. Ongoing science was the favored topic of conversation over lunch and dinner, and we all knew in some detail what was going on in other laboratories. It was during one of our daily trips to the hospital cafeteria that I met two young faculty members of the Pathology Department, Errol Friedberg and David Clayton, who graciously shared their table with us, and we continued to meet and chat on many occasions. I had some familiarity with ongoing work in DNA repair, but it was with Errol that I had my first serious discussions about the status and future of the field.  This was a particularly exciting time at Stanford Biochemistry: the mechanisms responsible for initiation of DNA replication were being solved in [Arthur Kornberg](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1959/kornberg-facts.html)‘s lab, and gene cloning methods were being developed in the laboratories of Dale Kaiser and Paul Berg. The Stanford faculty took great interest in all of the students in the department. George Stark and Buzz Baldwin had particularly important input into my development as graduate student, as did Arthur Kornberg, who with Bob Lehman had a continued and important influence on my life long after I left Stanford.  My intent after finishing my Ph.D. was to do two postdocs, the first with Charles Richardson at Harvard Medical School studying DNA replication and the second with Jean-Pierre Changeux in Paris where I would work on the acetylcholine receptor. However, while at Stanford I was approached by the University of California, Berkeley Chemistry Department about a possible junior faculty position. I interviewed for the job and was offered the position. This put me in a quandary because I was not looking for a job at the time and had nothing to compare with the UC offer, and Berkeley would permit only a one-year grace period for postdoctoral work. The appeal of the position was that Jim Wang was in Berkeley Chemistry. I greatly admired Jim’s elegant topoisomerase and DNA structural work, and knew him well because we had collaborated a year earlier on some ligase experiments. After a number of discussions with Bob, I decided to accept the Berkeley position. I canceled my postdoc with Changeux and after completing my thesis, left Palo Alto to spend a year in Charles Richardson’s lab. I’ve had many second thoughts about the decision to alter my postdoctoral plans, and given an amateur interest in neurobiology that began during my undergraduate days, I still reflect now and then on “the road not taken” to the Changeux laboratory.  Ann, our son Adam, who was born seven months earlier in Palo Alto, and I arrived in Boston in June of 1973 where we moved into an apartment in Brighton. Given the familiarity with DNA work that I had acquired at Stanford, it was a simple matter to get underway in Charles’ lab, where the primary subject of study was bacteriophage T7 DNA replication, although my first day did not go too well. Upon arrival in the Richardson lab, each new person was given a matched set of expensive quartz cuvettes, and I managed to break both of mine within the first few hours. I confessed to Charles and wondered whether he was having second thoughts about the new guy he had hired. My work addressed the nature of the *E. coli tsnC* gene product, which is required for T7 DNA replication *in vivo* and as I found, *in vitro* as well. I identified the *tsnC* protein as a small 12 kDa polypeptide that forms a 1:1 complex with the 80 kDa T7 gene 5 protein, previously identified as the DNA polymerase, and showed that both subunits are required for polymerase functionality. The small protein was identified as thioredoxin shortly after I left the lab.  Charles made a conscious effort to ensure that has lab was a fun place to work. We took turns cooking lunch on Fridays and at 4:00 each afternoon Judy Campbell, Jack Chase, Roger Fleishman, David Hinkle, Warren Masker and I would retire to Charles’ office for beer and tall tales. Practical jokes were common, and those perpetrated by Jack Chase often involved small explosions. It was highly entertaining, the year passed quickly, and it was soon time to leave. **The University of California and Duke University** We arrived in Berkeley in early July of 1974 and moved into a small apartment within walking distance of campus. My first visit to the Chemistry Department was disappointing in several ways. I learned that the lab space I had been shown during my recruitment was not available and that I had been assigned a much smaller lab on the basement breezeway level of Hildebrand Hall, four floors from the nearest cold room (an essential tool for a biochemist). I also learned that rather than one freshman chemistry lab section a week as I had been promised, I would be responsible for all of the lab sections in the freshman honors Chem 4 course, and the first semester would deal with quantitative analysis, about which I knew very little.  On the plus side, an NIH grant application that I had written while in Charles’ lab had done well, and we had funding to begin work. Genetic regulatory proteins that recognize unique DNA sequences were of great interest, and like many others, I was intrigued by the mechanisms that such proteins might use to locate and identify their relatively rare recognition sites. The recently discovered EcoRI restriction endonuclease and modification methylase [6] seemed ideal for pursuit of such questions because we could compare two different proteins that recognize the same d(GAATTC) sequence and because recognition by either protein culminates in covalent alteration of the sequence in ways that are easily scored. I hired an outstanding technician, Donna Zabel, and we spent the rest of the summer setting up the lab and getting EcoRI endonuclease experiments underway. I devoted my spare time to learning about quantitative analysis.  Life became much more intense once classes began. Juggling my teaching obligations, experiments, and family responsibilities proved difficult for me, and I was spending little time at home. I also learned that my research interests were not very appealing to the chemistry graduate students, although my first student, Bob Rubin, did join the lab in the spring of 1975. I was unhappy and discouraged, and discussed my predicament with Bob Lehman, Charles Richardson and several other friends. I don’t know the details, but this prompted a call in the fall of 1975 from Bob Hill, Chair of the Department of Biochemistry at Duke University, who informed me that he had a junior faculty position available in his department and encouraged me to interview for the position. I enjoyed the Duke visit, was very impressed by the department, and enchanted by the rural beauty of the North Carolina Piedmont. I was offered and accepted the job.  Bob Rubin flew to North Carolina with our enzymes, North American Van Lines moved our lab equipment, and Ann, Adam, our seven month-old daughter Amy, and I drove across country, arriving in Durham midsummer of 1976. With the knowledge that we were coming, Gail Herman Geier, a Duke M.D./Ph.D. student had joined the group and began setting up the lab prior to our arrival, and we were up and running shortly after our equipment arrived. The department was extremely supportive, the lab began to grow, and because my teaching load was fairly light, I had plenty of time for my own experimental work, which has always been a source of enjoyment for me.  Our early work at Duke focused on the EcoRI enzymes. Like many others, I was interested in the nature of the protein-DNA contacts involved in specific recognition, but my primary interest was the mechanism utilized by this class of protein to search a DNA molecule in order to locate a specific recognition site within a huge background on nonspecific sequence. Manfred Eigen had suggested that the high kinetic efficiency of this process might reflect a constrained diffusion mechanism in which initial collision of a protein with the DNA molecule is followed by a diffusion process that is largely restricted to the domain of the polynucleotide [7], but direct evidence for this idea was lacking. Bill Jack, Brian Terry, and David Wright proved that kinetic interaction of EcoRI endonuclease with DNA is dominated by such a mechanism. I regard these experiments as some of the personally most satisfying that we’ve done in the lab.  At the time, recognition of palindromic DNA sequences was believed to be mediated by homodimeric proteins, as is the case for recognition of the d(GAATTC) sequence by EcoRI endonuclease. However, Bob Rubin found that unlike the endonuclease, EcoRI methylase recognizes this sequence as a monomer. This curious finding prompted us to look at a second DNA methylase, the *E. coli* DNA adenine methylase (Dam methylase), which we chose for two reasons. Like EcoRI methylase, the Dam enzyme recognizes a simple palindrome (d(GATC)), but the biology of the Dam methylase was particularly intriguing. Genetic inactivation of the *dam* gene had been shown to result in a large increase in mutation rate, suggesting that Dam methylase plays an important role in genetic stabilization [8]. We were also aware of Matt Meselson’s suggestion that DNA methylation might provide the strand signal for correction of replication errors by mismatch repair [9], which would be consistent with a DNA methylation function in mutation avoidance.  Gail Herman isolated Dam methylase in pure form, showed that like the EcoRI enzyme it functions as a monomer, and contributed in a small way to confirmation of the Meselson proposal that methylation controls the strand direction of *E. coli* mismatch repair, which was the beginning of our work on this pathway. Our biochemical studies on the mechanisms of mismatch repair began with A-Lien Lu’s demonstration that she could detect the reaction in extracts prepared from *E. coli* cells, and we spent the next twenty years working out the molecular nature of the bacterial methyl-directed pathway and its involvement in the fidelity of DNA replication and genetic recombination.  When Jude Holmes entered the lab as an M.D./Ph.D. student in 1987, I suggested that he try to detect strand-directed mismatch repair in extracts of *Drosophila melanogaster* and human cell lines. Jude was successful, and our work on the human reaction quickly expanded as others joined the lab. Our interests in the mechanisms and functions of human mismatch repair have occupied us for twenty-five years and remain ongoing. A particularly memorable occurrence during the early stages of this work was the publication of two papers showing that tumors from patients with the common hereditary cancer Lynch syndrome, as well as a subset of tumors from sporadic cancer patients are characterized by frequent mutations in simple repetitive DNA sequences [10, 11]. Because we knew that mismatch repair plays an important role in stabilizing such sequences in bacteria, I had a suspicion that these tumor cells might be defective in mismatch repair. We quickly confirmed this possibility, a finding that has made our subsequent work on mismatch repair all the more rewarding. **Personal life** My children Adam and Amy displayed little enthusiasm for science as youngsters, although both demonstrated interest and talent in art. Amy now teaches art in Livermore, California, and perhaps oddly is nurturing a late-blooming interest in astronomy. Adam suffered a traumatic brain injury in an automobile accident in 1995, and although mobile and usually in good spirits, he remains effectively disabled. Adjustment to this life-changing event has been difficult for Adam and for us as parents, but your only choice in such a situation is acceptance, and I believe we have achieved that. The funds from my Nobel award will ultimately contribute to Adam’s support when I am no longer alive.  My second wife, Vickers Burdett, and I married in 1980. We met at Duke where Vickers had a non-tenure track faculty appointment and her own laboratory in the Department of Microbiology, where she studied the mechanisms of bacterial tetracycline resistance. The non-tenure track position required that she obtain 100% of her salary from research grants, which she did for 20 years. When she lost her grant, she lost her job and moved to my laboratory in 1998 as a Senior Scientist where she has worked on mismatch repair. During the past seventeen years we’ve spent twenty-four hours a day together, and we still enjoy each other’s company. **In appreciation** The Duke Department of Biochemistry has provided a wonderful environment for our work and has been my secondary home for the past forty years. Bob Hill was a superb Chair, who nurtured my career during the critical early stages and tolerated an occasionally irreverent assistant professor. Bob Webster, Irwin Fridovich, K. V. Rajagopalan, Tao Hsieh, Ken Kreuzer, and Chris Raetz have enriched my life both personally and professionally, as have University of North Carolina colleagues Darrel Stafford, Jack Griffith and Aziz Sancar.  A research laboratory in many ways is like an extended family, and the longterm personal connections have always been a source of pleasure to me. My lecture acknowledges many of those who contributed to our mismatch repair studies, but time constraints precluded description of the contributions of Beverly Yashar, Dwayne Allen, Leroy Worth, John Taylor, Marc Prudhomme, David Miller, Wendy Bedale, Susan Littman, Dawn Chandrasekhar, Yizhong Sha, Greg Runyon, Maynard Bronstein, Rochelle Bazemore, Derek Duckett, Shuntai Wang, Kent Christiansen, Qing Dong, Len Blackwell, Keith Bjornson, Diana Martik, Claudia Spampinato, Rochelle Bazemore, Sihong Chen, Ravi Iyer, Sally York, Lored Asllani, Olga Lukianova, Yanan Fang, Elisabeth Penland, Yiyong Liu, Xingdong Zhang, Hongbing Shao, and Shanen Sherrer. I also want to acknowledge the collaborators who contributed to the work I did not describe: Josef Jiricny, Jeffrey Miller, Bill Thilly, Miro Radman, Henry Friedman, Aziz Sancar, David Lilley, Robert Brown, Dorothy Erie, Karen Vasquez, and my long-term structural collaborator, Lorena Beese. I also thank Barbara McCaskill and Joanne Bisson for their superb assistance in administration of the laboratory. |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** | [PM]  [Paul Modrich] Hello.  [Adam Smith] Hello, this is Adam Smith. So where am I calling you?  [PM] We’re in New Hampshire. We have a little cabin in the woods in New Hampshire and we’re on vacation. Our last day is actually tomorrow. So this was sort of a shock.  [AS] And there was you thinking you’d got away from it all.  [PM] We thought so.  [AS] So how did the news reach you in your cabin?  [PM] I started getting emails about 6.30 this morning and I was stunned. Difficult to believe actually.  [AS] So apart from being stunned what was your first reaction?  [PM] Shock, I guess. Surprise. Excitement. I’m not a very eloquent speaker, very …  [AS] I think you’ve said that very well. But it’s funny that you’ve escaped up there because presumably Duke University is keen to get hold of you and do a press conference, but there you are.  [PM] [Laughs] I’m in the right place at the right time.  [AS] Exactly. Yes, so in fact if you shut off your telephones you’re completely free, for a day.  [PM] Exactly.  [AS] Presumably the last free day you’ll have for many days.  [PM] I hope not. [Laughs] Actually our plans tomorrow were driving back through Boston and we plan to stop and visit the person I post-doced with actually, many, many years ago, Charles Richardson.  [AS] Well that will be a nice surprise for everybody. There’ll be Nobel celebrations as well as your visit.  [PM] Well, we’ll see. The people are the important thing.  [AS] Exactly. It’s a lovely recognition of the field of DNA repair, this Prize.  [PM] It is. And I think the field, for many years, didn’t receive the attention I think that it really deserved and it’s important, I think now, unequivocally established for controlling the production of mutation both in a positive and negative way.  [AS] Of course we’re very much looking forward to welcoming you to Stockholm in December.  [PM] When, in December?  [AS] So the awards ceremony itself is on 10th December in Stockholm in deepest darkest winter, but the Swedes know well how to deal with dark. And then there are a number of days of activities, including a lecture you’ll be asked to give leading up to that.  [PM] OK. [Laughs] Certainly.  [AS] Many, many congratulations, and it’s so nice to talk to you.  [PM] Thank you so much, a pleasure talking to you.  [AS] Thank you, bye bye. |
| **Interview** |  |
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| **Chemistry\_2024-2000** | |
| **ID** | 0327 |
| **Biographical** | **Ancestry** “On 11 March 1890, a five-hour banquet for hundreds of invited guests was held in the festive chamber of the Berlin City Hall. A festival of a magnificence perhaps unparalleled in the history of science … The vast chandeliered room was decorated with palm trees and laurel leaves, and one end was dominated by a five-metre-high oil painting of Bismarck and other European statesmen *carving up the Turkish empire at the Congress of Berlin*.”  I first read this paragraph in 2004, in John Buckingham’s excellent book about the history of chemistry, *Chasing the Molecule* [1]. The banquet was in honor of Kekulé, who is the main formulator of the theory of chemical structure (the theory that all molecules have definitive 3-dimensional structures) and whose discovery of the hexagonal molecular structure of benzene in 1865 was a major breakthrough in both pure and applied chemistry. I was impressed by the central theme of the Benzolfest and the celebration of chemistry, and of science in general, described in the Introduction, but also struck by the cavalier attitude of the Europeans of that period – and apparently of the author – about “carving up the Turkish Empire.” These two subjects, science and the Turkish Nation (Ottoman Empire and Republic of Turkey), not necessarily in that order, have dominated my thinking for as long as I can remember. I grew up as, and still am, a Turkish patriot and from the age of about 10 I was also an aspiring, and later practicing, scientist. **The early years** I was born on September 8, 1946, in a small town named Savur in the Mardin Province of southeastern Turkey, the seventh of eight children of Abdulgani and Meryem Sancar. I also had two half-brothers. Father was a farmer, and Mother took care of the children and the house. By the standards of the day we were a lower middle-class family. We always had enough to eat, but shoes were luxuries, and until the seventh grade we wore them only when we went to school. Much of my early youth was spent in the valley below our house where, alongside my brothers and father, I tended the fruit and nut trees and the vegetable garden that provided our family nourishment and income. We also had a few farm animals that provided milk and meat for our family throughout the year. My most pleasant memories from childhood are the flowering of the almond and plum trees in our orchard in the spring. In those early years, I began to learn about Islam and was convinced that Paradise must look like our orchard when the almond trees were in full bloom.  Overall, I did not like farm work. The terraces in the vegetable garden were held in place by stone walls constructed without mortar and required constant maintenance by me and my brothers. Walnut harvesting was hard work, and as one of the younger children, I had to climb very high into the trees to make sure all the walnuts fell. But the worst was herding baby goats, because they could run faster than any 5–7 year old boy. My younger brother and I were in charge of herding them and spent many terrified hours trying to find the runaways before Father noticed they were gone.  Our large extended family was an important part of my early childhood. Uncles, aunts, and many cousins lived in Savur, and there were often other relatives visiting from towns farther away. Visits with my Uncle Sevket and his family in Mardin City were another high point. Mardin is known for its beautiful architecture which dates primarily from 1100 A.D.–1300 A.D. Sleeping in large beds on the rooftop of Uncle’s house was always a treat. As I fell asleep, I would watch on the horizon the lights of two nearby Syrian towns, and in the morning I would wake to the call to prayer from the historic Sehidiye Mosque about 200 meters from our house. **Early influences** The three most important influences in my early education, in addition to Mustafa Kemal Ataturk, were my mother Meryem, my father Abdulgani, and Kenan, my oldest brother. Beginning in 1911, and until the end of the Turkish War of National Liberation in 1922, the Ottoman Empire was in a constant state of war trying to prevent the “carving-up of the Turkish empire” by the Europeans, leaving the country economically exhausted and decimated due to the loss of much of its most productive lands and populations. During this time of turmoil and economic hardship, many in my grandparents’ and parents’ generation did not have the opportunity to obtain even an elementary education. Mustafa Kemal Ataturk led and won the War of Turkish National Liberation against the occupying European forces, a war that gave rise to the modern Turkish Republic. The new Republic gave priority to developing an education system available to all Turkish citizens. In a short period, schools were opened throughout the country, manned by teachers who were committed to Ataturk’s vision of an educated citizenry, idealistic about their country and optimistic about Turkey’s future. As a result, unlike my parents and grandparents, even in an underdeveloped, rural part of Turkey, I had access to excellent teachers and an excellent education that instilled in me pride in the history of the Turkish people and confidence that we could accomplish great things.  My mother was an illiterate woman who was the daughter of an Imam in a small village near Savur. Although she could not read or write, she was the most intelligent woman I have known. She was also very progressive and virtually worshipped Ataturk. It was at her insistence that all of her children got some degree of education. My father was the hardest working man I have ever known. He was, and still is, my role model. My oldest brother, Kenan, taught me how to read and write when I was 5 years old. Therefore, when I began school I was well ahead of my classmates. As importantly, Kenan was a role model for the pursuit of excellence and advancement through education and hard work. Kenan was the first of my family to attend college, specifically the Turkish Military Academy. Throughout his career, he was highly respected by his men and his colleagues for his fairness, hard work, and determination. He eventually rose to the rank of brigadier general in the Turkish Armed Forces. **Career decisions** I was the top student in my class throughout my primary education in Savur and my secondary education in Mardin. My favorite classes were math, Turkish, French and chemistry. In 10th grade an excellent chemistry teacher inspired me to become a chemist. However, academics were not my only love. Like every boy throughout most of the world, I grew up playing soccer. In high school, I played goal keeper for my high school (Mardin Lisesi), for Savur Spor (Savur), and for Mezopotamya Spor (Mardin). I was very good because I had fast reflexes and was fearless. More than once my teammates carried me off the field on their shoulders because I had made critical saves that helped win the game. During this period, I was asked by the Turkish Soccer Federation to participate in regional trials for the Turkish Under-18 team. Although playing for the Turkish National Team had long been a dream of mine, I chose not to participate in the trials because I thought that my height and weight were not sufficient for a national caliber player. Even though I quit playing soccer after the 10th grade, my love of the game remains, and I am an ardent supporter of Turkish and American national teams, the Galatasaray Professional Turkish soccer team, and the University of North Carolina–Chapel Hill Women’s Soccer Team.  When I graduated from high school I took the entrance exam for the B.Sc. Program in chemistry at Istanbul University and, at the suggestion of five of my friends from Mardin who were interested in becoming physicians, also took the Medical School Entrance Exam. I did well on both exams, but my friends prevailed on me to join them in medical sciences instead of continuing in Chemistry. I began medical school in November 1963. **Medical school** Coming to a cosmopolitan city like Istanbul had both advantages and disadvantages. I made friends with Turks of different ethnic backgrounds including Alevi, Armenian, Jewish, Greek, Kurdish, as well as the descendants of Turkish refugees from all of the Balkan countries. This enlightened my world view, especially with regard to the horrific effects of the Balkan Wars and World War I and the evil effects of religious and ethnic bigotry. Several of my professors, most of them Jewish, had fled Germany and nearby countries before or during World War II; despite the fact that many of them were leaders in their fields, they were rejected by many Western countries but were recruited to Turkish universities where they contributed to raising the education there to European standards. The Turkish nation owes a great debt of gratitude to these outstanding professors for their contributions to our science, education and even linguistics.  The main disadvantage of attending the top medical school in Turkey was my fear of failure. Despite finishing at the top of my high school class in Mardin, I was now in class with fellow students who had graduated from some of the best public and private schools in Turkey. I was determined to show my classmates that a student from the “backward” southeast could succeed and even surpass students from more cosmopolitan areas. I decided that I could realize this goal by totally immersing myself in my studies to the exclusion of all else. I never went to a movie theater, concert, or play in Istanbul. My only diversion during that time was my involvement in the Turkish Nationalist Movement, which was opposing the Communist/Internationalist movement that was gaining strength in the country. I never participated in physical violence but strongly believed that the “comrades” who occupied the main administrative building of Istanbul University and hung the hammer-and-sickle red flag on top were wrong; I still believe that communism, as it is practiced, is evil.  In my second year of medical school, I learned for the first time about the DNA double helix; I was fascinated and decided to become a biochemist when I graduated. My first thought was to begin research training as soon as possible, so in my final year of medical school I consulted the Chair of the Biochemistry Department, Mutahhar Yenson, about the possibility of joining the department upon graduation. He expressed the opinion that anyone obtaining a medical degree should practice medicine for at least two years before specializing in basic science research. So after graduation, at the top of my class, I returned to Savur to practice medicine in June of 1969. **Medical practice** For the first six months after I returned to Savur, I turned a room in my family’s house into a free clinic. Fortuitously, in the Fall of that year the Turkish Minister of Health passed through Savur, learned of my clinic, and suggested that I work for the Ministry of Health. Eventually, I was appointed Chief Medical Officer to a nearby village called Surgucu and was provided with a Jeep and a chauffeur. For the next year, I served people in Surgucu, in nearby villages and hamlets, and in a number of very remote villages. I was the first doctor that many of my patients had ever seen. I spent much of the salary I was paid by the Ministry of Health to buy drugs for my patients and toys for the small children whose families could not afford them. With simple medical procedures, I believe I saved the lives of many children.  One of the most challenging aspects of my medical practice was that some of my female patients spoke only Kurdish; during that period and in that part of Turkey, families did not send their daughters to school, so they did not learn Turkish. Local translators were usually men, and thus the women were often uncomfortable explaining intimate health problems to a man from their village. I tried to circumvent the problem by learning Kurdish, but I never became fluent. Nevertheless, I think the women appreciated the effort; they often kept the prescriptions I had written as a talisman after using the drugs I prescribed.  Looking back, I remember the 18 months that I practiced medicine as the happiest time in my life. However, I also found the practice of medicine intellectually frustrating; for example, I wanted to understand why streptomycin killed the tuberculosis bacterium, but penicillin did not. So throughout the time I practiced medicine, I also applied for fellowships to study biochemistry abroad. **PhD studies: cloning the photolyase gene** In 1971, I won a NATO fellowship to fund Ph.D. research in one of the member countries. I chose the United States, because it was the leader in scientific research in the world. I was admitted to the Department of Biochemistry Graduate Program at Johns Hopkins University and entered there in 1971. I was totally unprepared for the problems I would encounter there. Although, I had taken English classes during my final year of medical school, I could not communicate with my professors and fellow students. In addition, because of my previous academic success and patriotic upbringing, I was self-assured and confident to the point of arrogance, and people avoided me. It was like being in solitary confinement. As a result, I left Johns Hopkins in June of 1972 and returned to Savur to regroup. After practicing medicine again for about 6 months, and a brief detour to England, I returned to the United States more mature and reasonably proficient in English, and applied to Dr. Claud S. Rupert at the University of Texas at Dallas (UTD). I was accepted into the UTD Biology Program there in 1973 and joined Dr. Rupert’s lab in 1974.  Dr. Rupert is the scientist who discovered the enzyme photolyase; this discovery, in 1958, marks the beginning of the scientific field of DNA repair. In the bacterium *E. coli*, exposure to UV light kills the organism; however subsequent exposure to visible light reverses the killing effect. This is called photoreactivation, carried out by the enzyme photolyase. When I joined Dr. Rupert’s lab, the most outstanding question was “how does the enzyme absorb light.” To answer this question it was necessary to have the enzyme in large quantities and high purity, but no one had been able to purify it in sufficient amounts. About the time I joined the Rupert lab, molecular cloning was invented at Stanford University. I immediately saw the potential of this approach for solving the photolyase production problem. I would clone the *E. coli* photolyase gene, amplify the enzyme, and then purify it and characterize its chromophores and action mechanism.  The first step was to isolate a mutant defective in the photolyase gene so that I could use this mutant as a host for cloning. I devised a counter-intuitive experimental scheme to generate and select the mutant and performed the screen 1–2 times daily for 6 months before obtaining the first *phr* mutant. Along the way my self-confidence was challenged, not only by the difficulty of obtaining a mutant but also, during the period of repeated failures, by the comments of a labmate who told me that I did not have talent for lab research and should return to medical practice. The ultimate success of this experiment played a pivotal role in my evolution as a scientist because it required me to gather information from unrelated fields to create a method and because I persevered until the method worked. I believe that there are three characteristics essential for a successful scientist: creativity based upon knowledge, hard work, and perseverance in the face of failure. Although the paper describing this method has only been cited 6 times (including two self-citations), for me it is one of my most important papers because it gave me the confidence to carry on research and equally it helped convince Dr. Rupert that I was a good student so that he gave me the freedom to pursue my research goals.  Using the mutant I had isolated, I cloned the *phr* gene of *E. coli* in 1975, and began experiments to characterize the plasmid carrying the gene. However, in 1976 I was called back to Turkey to fulfill my military service obligation. I returned to Texas four months later with the rank of Second Lieutenant and resumed my work using the cloned gene to purify the enzyme. However, cloning a gene was such a major achievement at the time (I believe that *phr* was the first gene cloned east of the Rocky Mountains) that Dr. Rupert decided I had accomplished enough to earn a Ph.D. I started writing my doctoral dissertation in the spring of 1977 and, with the encouragement of Dr. Rupert, applied to three leading DNA repair labs. I did not receive an offer from any of them, probably because I had not published. I had been so engrossed in doing experiments that I had not taken the time to write up the 6–7 papers I had material for. Moreover, gene cloning was new and its utility was not appreciated yet by many in the field. Fortunately, I learned from a fellow graduate student that Dr. W. Dean Rupp of Yale University was planning on cloning the *uvrA*, *uvrB*, and *uvrC* genes responsible for nucleotide excision repair in *E. coli*. I applied to Dr. Rupp and, based upon Dr. Rupert’s strong personal recommendation, Dr. Rupp offered me a position in his lab. I defended in July of 1977 and left UTD in September to join Dr. Rupp’s lab, still not knowing how photolyase absorbs light. **Post-doctoral work: maxicells; dual incision I** When I joined the lab of Dr. Rupp, Yale University was one of the top three DNA research centers in the world and an exciting research environment. In addition to Dean Rupp, other pioneers in the field of repair and recombination there included Paul Howard-Flanders, Charles M. Radding and Franklin Hutchinson. I cloned the *uvrA*, *uvrB*, and *uvrC* genes in quick succession. While at Dallas, I had begun working on a method, which I called Maxicells, to identify the proteins encoded by cloned genes. At Yale, Dr. Rupp made suggestions to improve the method, which were crucial to its eventual success. It took almost a year to work out the details, but eventually the method worked. The paper describing Maxicells was published in 1979 and became an instant hit because it was applicable to identifying any plasmid-encoded protein. The method was widely used throughout the 1980s, and to this day it is my most cited research paper.  Having cloned the *uvrA*, *uvrB*, and *uvrC* genes, I used the Maxicell method with radioactive tracers to label, identify and purify the proteins encoded by these genes. Up to this point, the classical model for nucleotide excision repair was that a UV endonuclease incised the damaged strand 5′ to the damage and n exonuclease removed the damage in the 5′ to 3′ direction in the form of a 4–6 nucleotide fragment containing the damage. Much to my surprise, in the spring of 1982 I found that when I reconstituted the incision reaction *in vitro* using purified proteins, the UvrABC nuclease made concerted dual incisions, one 7 nucleotides 5′ to the dimer and the other 3–4 nucleotides 3′ to the dimer, releasing a 12–13 nucleotide long fragment carrying the dimer. I named the enzyme “ABC excinuclease” to emphasize the unique dual incision mechanism. This was a major discovery in the field of DNA repair; however because there were several other groups working hard on the same question, I could not tell anyone except a few lab colleagues about this result until we were ready to present it at a meeting and to publish it. Dr. Rupp presented the result for the first time at an international meeting on recombination and repair in France in the Spring of 1982. I still run into colleagues who say that this talk generated huge excitement at the meeting. Dr. Rupp’s talk was published in the meeting proceedings, and a full paper describing my work was published in 1983.  While I was in Dr. Rupp’s lab, other exciting events were also happening in my personal life. Back in Texas I had become a close friend of Gwen Boles, a graduate student in the same department at UTD. Gwen graduated three months before me and took a post-doctoral position in New York, working on the molecular basis of thalassemia. We continued to see each other on weekends when I moved to Yale, and we married in 1978. However, it was another 2 years before Gwen completed her work in New York, moved to Yale, and joined Dean Rupp’s lab to work on regulation of DNA repair genes in *E. coli*. Although living apart was not ideal, the additional time that Gwen spent in New York allowed her to eventually publish five papers from her post-doctoral work there.  In 1981, encouraged by my research successes, I began applying for faculty positions. I applied to about 50 universities and was turned down by all of them, some without even a reply to my application. Then I received a call from Mary Ellen Jones, the Chair of the Department of Biochemistry at the University of North Carolina at Chapel Hill. Dr. Jones was interested in recruiting molecular biologists to modernize the department. Gwen and I visited Chapel Hill, and we were both offered faculty positions in the spring of 1981. Because I was working on the reconstitution of ABC excinuclease and felt that I could not take a six-month break to set up a new lab, we accepted the positions on the condition that we could defer moving for a year. Dr. Jones agreed, and that enabled me to submit the paper describing the reconstitution and the dual incision mechanism in the fall of 1982, just before moving to Chapel Hill. This also allowed Gwen and me to write our first NIH grant proposal to work on photolyase. The proposal was funded, and as a result when we arrived in Chapel Hill most of our equipment was already in place, and we were able to start experiments three days after we arrived. **Photolyase: “As complete as any research study can be”** When I started my own lab at UNC-CH, I decided to resume working on photolyase, specifically on identifying the chromophore and solving the action mechanism. In a relatively short period of time, we overexpressed and purified the enzyme and discovered that the enzyme has not one, but two cofactors, FADH– and MTHF that absorb light. In a series of experiments with collaborators from around the world, we found that MTHF acts as an antenna which absorbs light energy and transfers that energy to the FAD cofactor which carries out catalysis. Over the next 20 years, we and our collaborators defined the molecular mechanism in great detail and have traced all of the steps of the repair reaction in real time, from light absorbance to splitting of the dimer and return of the electron to the flavin cofactor. My work on photolyase has, with interruptions, spanned over 40 years and involved collaboration with numerous colleagues who were leaders in cofactor chemistry, flavin photochemistry, crystallography and ultrafast chemistry. It was therefore gratifying when a colleague recently wrote in a commentary on a paper we published in 2011 with our collaborator Dongping Zhong that “with this paper … the story of PL (photolyase), originating 62 years ago, has come to be as complete as any research study can be” [2]. **Transcription-coupled repair; Yunus Emre destani** In 1985 and 1987, Philip Hanawalt and colleagues reported that transcription strongly stimulates nucleotide excision repair in human cells and in *E. coli*. They suggested that RNA polymerase stalled at a damage site increased the rate of damage recognition, which is the rate-limiting step in excision repair. We tested this model *in vitro* using purified *E. coli* proteins and found that RNA polymerase stalled at damage actually inhibited repair. From this we proposed that an additional factor recognized stalled RNA polymerase, displaced it from the damaged site, and simultaneously facilitated assembly of the excision nuclease at the damage. We identified and purified such a factor which we named TRCF (Transcription-Repair Coupling Factor). We went on to show that TRCF is the product of the *mfd* gene first described by Evelyn Witkin in 1956, and that purified TRCF, RNA polymerase, and ABC excision nuclease are sufficient to reconstitute transcription-coupled repair *in vitro*. I consider the paper describing this work to be our most aesthetically pleasing, both scientifically and stylistically. We made a hypothesis, obtained the necessary reagents to test it, and found the hypothesis to be correct. In the process we solved a mystery of 30 years standing (mutation frequency decline). The paper is well-written, states the problem concisely, and proceeds to describe the experimental results succinctly. The data is clear and unambiguous and the model has stood the test of time. To my Turkish colleagues who inquire about my research, this is my Yunus Emre Destani (Yunus Emre Opus), because Yunus Emre, a mystic poet who lived in the 14th century, is to the Turkish language what Chaucer is to the English language, and every Turk aspires to the perfection Yunus Emre achieved in his chosen field. **Excision repair in humans; Dual incision II (“Known only to God and me”); Molecule of the year** In 1987, I turned my attention to the mechanism of human nucleotide excision repair, which had remained poorly understood for over 20 years. We decided to pursue a biochemical approach to understand the reaction mechanism and focused initially on what we viewed as the most important question: do human cells utilize a UV endonuclease/exonuclease for excision or is there a dual incision mechanism similar to the one we had found in *E. coli*? For five years, we tried many assay systems, cell types, different cell extract preparations, and different types of substrates, to no avail. Finally on November 8, 1991 we captured the excised oligonucleotide: it was a 27-mer (“nominal 30-mer”) released by dual incisions. Yes, the mechanism was by dual incisions, but the dual incisions were different than *E. coli*. This discovery was one of the highlights of my research career. When I first saw the 27-mer, I told Gwen “there is an important biological fact about humans that is known only to God and me.” We followed up on this discovery, by isolating and purifying all of the proteins necessary for the dual incision reaction, and reconstituting the reaction *in vitro* from completely purified components. This work, combined with our elucidation of the mechanism of TCR, played an important role in the selection of DNA Repair as ‘Molecule of the Year’ by *Science* magazine in 1994. For this issue, Paul Modrich, Philip Hanawalt and I were asked to summarize the exciting discoveries in the field of DNA repair by our respective laboratories as well as those of a dozen other laboratories in the preceding year. **Brief map of the human genome; Piri Reis map** After the discovery of dual incisions in humans, we wanted to know the fate of the excised oligomer in human cells, but were unable to isolate the 30-mer from UV-irradiated human cells. After spending 20 years characterizing human excision repair *in vitro*, we finally captured the 30-mer produced in vivo. This has allowed us to map the sites of repair across the entire human genome at single nucleotide resolution. This repair map shows, in a geographic sense, repair mountains, valleys and canyons corresponding to regions of high, average, and low or no repair. This method will likely help us understand factors other than the primary repair proteins that affect repair efficiency and may have applications to improve chemotherapy. Personally, this is the most satisfying accomplishment in my lab in the last decade, and to Turkish colleagues I refer to it as “My Piri Reis Map.” Piri Reis was a Turkish admiral and cartographer who drew the world map in 1513 with a level of accuracy unrivaled by any other cartographer of his period. He is revered by Turks as a great scientist, arguably the last great scientist of the golden age of so-called “Islamic Science.” After submitting the paper describing this result, I went on a lecture tour of Peru and told Gwen that “if my plane hits the Andes and I die, I will die a happy man.” **DNA damage checkpoints** Cells respond to DNA damage by repairing it, by activating signal transduction pathways for arresting cell cycle progression, by changing the transcription profile, and by inducing apoptosis. These responses are important for cellular homeostasis and have been the subjects of detailed studies by many investigators. However, because of the very nature of the phenomena investigated, the biochemical analyses of these processes, with the exception of apoptosis, have been limited. With this general view, we decided to apply our experience in DNA repair to investigate the biochemistry of checkpoint activation. For the past 15 years, we have made significant contributions to the biochemistry of DNA damage checkpoints activated by UV damage. We developed several *in vitro* systems that captured specific steps in the signaling pathway. Perhaps our most physiologically relevant accomplishment has been the coupling of human nucleotide excision repair with the DNA damage checkpoint response in a completely defined system. I look at this work as the ultimate in reductionist biochemical research that aims to explain complex cellular phenomenon in a minimalist *in vitro* system. **Cryptochrome and the Circadian clock** Photolyase is not universally distributed in the biological world, and its presence in humans had been controversial for 35 years after its discovery in bacteria in 1958. In 1993 we conducted an exhaustive study on this subject and published a paper stating categorically that humans do not have photolyase. This result applied to both the classic photolyase that repairs cyclobutane-type pyrimidine dimers and another type of photolyase discovered by T. Todo that repairs pyrimidine (6–4) pyrimidone adducts. Then in 1995, Human Genome Sciences released the sequences for a number of partial human cDNAs, and among these was listed a photolyase homolog. We immediately obtained the cDNA for the entire gene, and shortly thereafter, discovered a second gene with high sequence similarity to photolyase. After cloning and expressing both genes, we found that neither of the recombinant proteins nor cells expressing the proteins had detectable photolyase activity of either type. We were still trying to decide what to do with these results, when “chance favored the prepared mind.”  In May of 1996, returning from a visit to Turkey, I read an article about the circadian clock and jetlag by Dr. William Schwartz in a flight magazine. I was most intrigued by the setting of the clock by blue light (wavelengths similar to those absorbed by the photolyase chromophores) and the fact that in some blind mice and people who lack conscious light perception, the circadian clock still responds to light because the “circadian visual system” is anatomically and physiologically distinct from the image-forming visual system. After reading this article I thought perhaps the human photolyase paralogs we had found might in fact be clock proteins that sense blue light. I discussed this with my lab and suggested that we call these proteins cryptochromes 1 and 2 (CRY1 and CRY2) in analogy with the plant blue light photoreceptors which also had sequence similarity to photolyase. The paper describing this work was published in *Biochemistry* in November of 1996, and it appears that it escaped the attention of the entire circadian clock community.  To test this claim I immediately set out to learn as much as I could about the circadian clock and neuroscience. By the end of 1997, we had shown that cryptochromes were highly expressed in the two anatomical locations critical to the clock, namely the ganglion cell layer of the retina, and the suprachiasmatic nucleus (SCN) in the brain, which is the neurological center of the clock in mouse and man. In particular, *CRY1* mRNA exhibited high amplitude daily rhythmicity in the SCN. This was sufficient circumstantial evidence for us to publish a paper in *PNAS* claiming that the mammalian CRYs are circadian photoreceptors. This paper electrified the circadian clock community, but still we needed evidence of causality.  To prove our contention we had to show that mutations in the *CRY* genes altered the clock. We constructed a CRY2 mutant, and when it was tested in the laboratory of our collaborator Joseph Takahashi, it was apparent that even though the mutation affected sensitivity of the clock to light, even in complete darkness, it had an effect on the clock. We concluded, that CRY2 had both lightdependent and light-independent effects on the clock. In the meantime, our first paper on the potential role of CRY in the circadian clock led to the identification of a CRY homolog in *Drosophila*, and a *Drosophila* CRY mutant with greatly reduced photosensitivity was also isolated. Our work, also led to re-evaluation of *Arabidopsis* CRY mutants, and experiments performed by plant biologists showed that CRY also plays a role in the *Arabidopsis* circadian clock. Our CRY2 mutant mouse paper and the *Drosophila* and *Arabidopsis* papers were published within a week of one another. This, along with other important progress being made in the field, led to the circadian clock as runner-up for *Science* Magazine ‘Molecule of the Year’ in 1998.  Later in 1999, our group, in collaboration with T. Todo and J.S. Takahashi and another group of Dutch and Japanese colleagues, made mouse mutants defective in both CRYs and found that they no longer had a functioning circadian clock. There was rapid progress in the field, and by 2000 there was a reasonably detailed model for the clock in which CRY plays the role of the primary transcriptional repressor in the clock circuitry generated by a transcriptional and translational feedback loops. Current evidence indicated that CRY is primarily, if not exclusively, a repressor in mammals with no photoreceptor function, while in *Drosophila* it is the primary circulating photoreceptor. The discovery of cryptochrome as a circadian protein has given me a profound sense of gratitude and personal satisfaction for providing me the opportunity to contribute to an entirely different field of research from DNA repair and thus interacting with a new set of colleagues and a new way of thinking. **Full circle** For the past 15 years, we have been working on the mechanism by which CRY participates in the circadian clock in mammals and its photoreceptor function in *Drosophila* and have contributed to the current clock models for both organisms. Our work has also led us to discover that the circadian clock regulates excision repair in mice and that the carcinogenesis of UV light exhibits a circadian pattern. We are currently analyzing the circadian effect of repair in humans and the potential applications of this knowledge to chemotherapy regimens. **Concluding remarks** I have had the good fortune of having parents who instilled a strong work ethic in me and a belief in the value of learning. I have been fortunate to have had excellent teachers throughout my education from primary school in Savur through high school in Mardin and medical school in Istanbul, and excellent mentors in graduate school and post-doctoral work in Texas and New Haven. I thank my family for their love. I am grateful to my wife, Gwen, for her love and support. In the words of one of my mentors, “Aziz, I don’t think you would have survived without Gwen.” I thank my goddaughter, Rose Peifer, who has added joy to my life and makes me feel young. Finally, I thank Gwen and Rose for keeping me on the straight and narrow. |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** | [Aziz Sancar]  [Aziz Sancar] Hello.  [Adam Smith] Oh hello, Professor Sancar, this is Adam Smith from Nobelprize.org. Many congratulations on the award of the Nobel Prize.  [Aziz Sancar] Thank you.  [Adam Smith] How did you hear the news?  [Aziz Sancar] I just got a call half an hour ago. My wife took it and woke me up. I wasn’t expecting it at all, I was very surprised.  [Adam Smith] [Laughs] I can hear it in your voice. What was the first thing you did on hearing the news?  [Aziz Sancar] I tried my best to be coherent, I was sleeping, and it was a pleasant experience.  [Adam Smith] It must be quite extraordinary, what an amazing phone call to receive. I believe I’m right in thinking that you’re the first Turkish born scientist to receive the Nobel Prize?  [Aziz Sancar] Scientist. Orhan Pamuk got it in Literature a number of years ago.  [Adam Smith] Exactly, yes, but scientist yes. I imagine that not only will there be celebrations in Chapel Hill but there will be big celebrations in Turkey today.  [Aziz Sancar] I’m sure there will be. Yes they’ve been asking over the years and I was tired of hearing ‘when are you going to get the Nobel Prize?’ so I’m glad for my country as well.  [Adam Smith] Yes indeed. The Prize is of course for mechanistic studies of DNA repair and I suppose it’s been a mammoth task, and is still a mammoth task, mapping all the systems that protect our DNA.  [Aziz Sancar] Right.  [Adam Smith] And these repair mechanisms mostly protect us from cancer but presumably they also end up protecting cancer cells as well sometimes.  [Aziz Sancar] That is correct and they’re also important in cancer treatment because many of the anti-cancer drugs do damage DNA and whether cancer cells can repair it or not could influence how cancer is treated.  [Adam Smith] What do you think is going to happen to you now?  [Aziz Sancar] Well, my lectures start at the end of this month and go through December but I think I will try my best to go through with my lectures, but there will be some disruptions I think.  [Adam Smith] I imagine many. Are you looking forward to the attention that is about to descend on you?  [Aziz Sancar] I am of course honoured to get this recognition for all the work I’ve done over the years, but I’m also proud for my family and for my native country and my adopted country, and especially for Turkey it’s quite important.  [Adam Smith] Thank you very much indeed, well when you come to Stockholm in December for the awards ceremony we will have the chance to speak more about this.  [Aziz Sancar] OK, thank you.  [Adam Smith] OK, thank you. And my many, many congratulations on the award.  [Aziz Sancar] Thank you very much.  [Adam Smith] Thank you, bye bye. |
| **Interview** |  |
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| **Biographical** | I was born and raised in Ann Arbor, Michigan, a university town. Even though my parents were not affiliated with the university while I was growing up, I think that environment and the people I encountered there really contributed to my latching on to science.  My Dad went to the University of Michigan as a physical education major right after World War II. He became the captain of the wrestling team (Figure 1), and after graduation, he was asked to stay on as an assistant coach. Eventually, to make more money, he started working as a junior draftsman at a machine tool business, and my parents put down roots in Ann Arbor.  My Dad taught me the value of hard work. He came from very humble beginnings, but eventually started his own company and grew it to 300 employees and 75 million dollars in annual sales. My mom raised my two older sisters, my younger brother, and me. Both my parents were quite intelligent, as well as extremely competitive. My Dad was an All-American wrestler who just missed the 1948 Olympic team. My Mom didn’t have any outlet for her intelligence, and I think she was unhappy being locked into her role as a housewife in the 1950s and 60s. But she loved to trounce all the contestants on Jeopardy when it came on TV. Genetically, I think my parents’ competitiveness coherently interfered in me to create something four times as competitive as either one of them. I don’t like to lose.  I had a happy childhood. I was in Boy Scouts and I’d play a bit with other kids, but nothing really interested me as much as reading and learning. My siblings say I was self-absorbed. I latched on to the space program around the time I was in kindergarten, drawn to the exploration and the excitement, the rockets and the power. I drew elaborate designs of spacecraft and other nonsensical machines that my fifth grade teacher hung in the corridors of the elementary school, and when I was a bit older, I was really into building model rockets. When I was talking about science I could be engaging, but outside of that, I was very shy.  In the third grade, I made friends with a boy whose Dad was a scientist at the university, and he infected me with his enthusiasm for science. We had a subscription to the Science Service, and waited with baited breath for the company to mail us a new kit each month so we could get started building a battery or doing the next experiment. By the end of fourth grade, I had exhausted every science-related book in the library and was looking for more to learn. I remember writing a letter to a scientist at the university right after quarks were discovered. I asked him about the mass and charge of quarks, and I was so excited when he wrote back with answers to my questions. By middle school, I wanted to be a theoretical astrophysicist.  In seventh grade, I’d spend most afternoons messing around with a couple of friends in the science teacher’s back room, which had everything you would need to make everything from fireworks to a Van de Graaf accelerator. We usually stayed until dinnertime, making gunpowder or mixing chemicals to see what colors they gave off when you added various metals. That guy would probably be arrested if he allowed that today, but that freedom to explore was so valuable.  By high school, I became a machine of studying. I took advanced placement everything, whether it interested me or not, and I pulled innumerable all-nighters working on assignments. My attendance was probably barely enough to pass, but man, I learned a lot. My biology teacher senior year was Mr. Young. Knowing he had never given an A, I made it my mission to get an A+ in his class. Every week, we had another complicated and extremely detailed lab, and that’s where I realized I liked experimentation and doing things with my hands. I turned in a 50–100 page lab report every week, and I got the A+.  After high school, I went to Caltech. I went with much trepidation, afraid I wouldn’t measure up to my classmates. I didn’t realize that my public high school was probably one of the best in the country, and it turned out I was better prepared than most of the kids.  I threw myself into my coursework, taking harder and harder classes. By my junior year, I found my limit. It felt like an infinite loop of homework and studying and test taking. I had to take the third trimester off because of my health – my hair was falling out and I had eczema so bad I looked like a lobster. I’ve never worked that hard at any other time in my life.  I got a great education at Caltech but it was extremely theoretical. It was an independent project in a fluid mechanics lab that hooked me on doing experimental research. My advisor, Garry Brown, encouraged me to present my research at an undergraduate competition held by the American Institute of Aeronautics and Astronautics. My practice talk was incredibly dense and full of equations, and he ripped it to shreds. He taught me that when you give a talk, you are telling a story. That was incredibly helpful in learning how to communicate science, and in the end I won the nationals of that competition. That experience convinced me to be an experimental scientist.  So, when I graduated from Caltech in 1983, I wanted to find practical applications of my physics. Cornell offered one of the few applied physics programs in the country at that time, and its student population was 50 percent female. Although I was still very shy, I knew if I went there I would be forced to confront the opposite sex. So I went to Cornell.  The path to the rest of my career was set almost immediately. After the first semester, I met Mike Isaacson and Aaron Lewis. Aaron had been trained as a chemist in Raman spectroscopy, and Mike was one of the first guys to directly image atoms in an electron microscope. He had turned that microscope around and made it into a lithography tool that could make holes as small as 30 nanometers in a thin membrane, which you could then coat with metal to make it opaque.  He and Aaron thought that if they shone light through those apertures and scanned it across living cells, they could illuminate just a 30 nanometer region and produces images with the resolution of an electron microscope. This sounded like it could be something big, and I wanted in.  Once I got started, I couldn’t wait for classes to end. I wanted to be in the lab all the time. The first couple of years were really hard. We had no money. Fellow graduate student Alec Haratounian and I were able to make the patterns at the sub-micron facility, but we had to borrow or build just about everything else. So I learned how to make things work when you don’t have anything to work with. My advisors mostly left me alone, so once we got a grant a few years in, I was free to make my own mistakes. I made plenty of mistakes, but you learn by failing, and I learned a lot.  I did a lot of work characterizing the apertures, and Alec started putting together a test rig. But to make those apertures, the membrane had to be 100 nanometers thick, and if you looked at them the wrong way they would shatter. After the first couple of years, we figured out we could pull glass pipettes like people were doing for patch clamping to get the tips we needed for the probes. Alec got his thesis, and I built this crazy, elaborate, expensive microscope that kind of worked (Figure 2). I never looked at much beyond test patterns, but it was enough to prove that the idea was valid.  In that era, Cornell was at the forefront of many aspects of cryogenic condensed matter physics, which made it a recruiting conduit to Bell Labs. I wasn’t salivating to go there, but I got an interview and I went to visit in early 1988. By the time I left, I knew it was where I really wanted to be. Everybody was so bright, and they didn’t hold anything back. I had prepared a 45 minute talk and it took an hour and a half because I was just peppered with questions. It was fantastic.  During that visit, I met [Horst Störmer](https://www.nobelprize.org/nobel_prizes/physics/laureates/1998/stormer-facts.html), head of the semiconductor physics research department (Figure 3). Horst radiated enthusiasm and energy out of every pore, and he was just brilliant besides. I knew next to nothing about semiconductor physics, but Horst thought near-field was a really cool idea and it could go places. He wanted to hire me, even though what I was doing was completely outside of what everyone else in the department was doing. Except for one guy – Harald Hess, who I also met during that visit. Harald had built a low temperature scanning tunneling microscope to study superconductors, and he and I hit it off immediately.  I was hired in Horst’s department, and I picked up where I’d left off with near-field. I had enough resources to build my microscope, but the damn thing wasn’t working any better for me than it did at Cornell. Because of Bell Lab’s history and the brilliance of everyone around me, I felt like I was on probation from the time I got there. Two years in, I wrote in my self-evaluation that if I didn’t have a breakthrough in the next year, they wouldn’t need to fire me because I would quit.  Harald really kept me afloat both personally and professionally during that time. We both worked insanely hard during those years. I would come into work at 4:30 in the morning, and if I saw Harald’s car, I would put my hand on the hood to find out if the engine was still warm. He did exactly the same thing. We were both really competitive, but we played tennis every morning and ate dinner together every night. We were best friends and still are.  During my third year, I stopped just trying one thing after another, and started thinking like a physicist about why things weren’t working. Once I understood the physical problems of the pipette tip I was using, I realized I could replace it with an optical fiber, which would deliver more light to the tip. I also came up with a method of using dissipation force feedback to regulate the tip’s distance from the surface of a sample, which didn’t break tips like my old method and could be used on cells as well as semiconductors.  With those breakthroughs, the next few years were the golden age for nearfield micoscopy. I tried the technology everywhere I could think of. Sometimes it worked and sometimes it didn’t, but the papers came quick. In 1992, we applied it to data storage – at one time we held the world record for storage density – and in the following year I demonstrated super-resolution fluorescence imaging of cells for the first time.  W.E. Moerner had been the first to see the spectral signature of single molecules at cryogenic temperatures in 1989, but no one had yet imaged single molecules at room temp. You needed focused light, because otherwise the background would obscure the signature of a single molecule. At the time, there was no better means of focusing light than near-field microscopy, and as soon as I attempted that experiment, it worked. Surprisingly, the molecules looked like arcs instead of round spots – the molecule was acting as the light source, and its dipole moment was mapping out the electrical field inside the near-field aperture. It was an afternoon experiment that was a shock on many fronts.  For my last hurrah with near-field, Harald and I put my near-field probe on his low-temperature tunneling microscope to study quantum well structures, which are the basis of semiconductor lasers, like those in laser pointers. With standard diffraction-limited optics, their spectrum looks like a smooth hill of emission, but we saw a crazy series of super sharp lines. Our probe volume was so small, the light could only be emitted at certain discrete sites. And the wavelength of that light was very sensitive to the local thickness of the quantum well, so they glowed in different colors, which meant we could study them individually.  That was a stunning paper, but by this time I was fed up. Although nearfield has proven to be a valuable tool for materials characterization and studying light-matter interactions at the nanoscale, my original goal was to make an optical microscope that could look at living cells with the resolution of an electron microscope. But near-field only worked on samples that were ridiculously flat, where the thing that you wanted to see was ridiculously close to the surface. If you’re 20 nanometers away, you lose significant resolution. I knew a cell was a bit rougher than 20 nanometers, so it just wasn’t going to happen.  Meanwhile, the field had blown up. There were hundreds of people doing near-field by this time, and much of it was crap. People were fooling themselves with images that had sharp-looking but artifactual structures, and they just didn’t want to hear it. I felt like every good result I had provided justification for a hundred lousy papers to follow, and that was a waste of people’s time and taxpayers’ money.  On top of that, it was clear by 1994 that Bell was coming to an end. The phone monopoly had been broken up in 1984, and it was hard for AT&T to justify all the spending on basic science. We could feel the weight of the world on our shoulders. I was exhausted.  So I quit. While my wife worked, I stayed home with our daughter Kriya, who was born in 1993, and became a house husband. I really didn’t know what I wanted to do.  My Dad had worked for the same company until he was 60, then used his retirement savings to start a competing company. He had always wanted me to come work for him. So I made occasional trips to Michigan to consult for him while I raised my daughter in New Jersey and continued thinking about science.  A few months after I left Bell, I was pushing Kriya around in the stroller and it popped into my head that if you could somehow isolate different molecules in multiple dimensions, you could localize each one and do super-resolution imaging that way. I was excited about this for a couple of months, and I published the idea. But I knew using it for biology was going to be very difficult, because there could be hundreds or thousands of proteins in a single diffraction-limited spot, and there was no easy way to distinguish them at room temperature. As an engineer, I didn’t want to do a hero’s experiment; I wanted to do something useful.  When Kriya was three, and started speaking with a Jersey accent, I knew we had to get out of New Jersey. I eventually became convinced from the consulting I did that I could have an impact in my Dad’s company, so we moved to Michigan in 1997 and set down roots.  My Dad gave me as much freedom as I had at Bell. My proudest development was a servo-hydraulic machine tool that combined old hydraulic technology with modern control theory and the energy storage principles that are in today’s hybrid cars (Figure 4). It could move four tons at eight Gs of acceleration and position to five micron precision. It was much smaller, much cheaper, much faster, and much better than any previous technology. It was also too different, and after three or four years developing it, I couldn’t sell it worth beans.  You work under so many more constraints in the business world than you do in academia – anybody who can make a profit has nothing but my utmost respect. But I was very bad at it, and I felt like I was only using a small fraction of what I knew and was good at, which was physics. So in 2002 I quit.  That was probably the hardest part of my life. I had pissed away my academic career and I had pissed away my backup plan of working for my Dad. Once again, I didn’t have any idea what I wanted to do. Fortunately, with money in the bank, I had some time to think of a solution.  I reconnected with Harald, who had also gone into industry in San Diego, but wasn’t completely satisfied. We started meeting in various national parks (Figure 5) and confronted our respective mid-life crises, asking: What do we want of life? What’s important? How can we have an impact? The rest of the time, I would go to a cottage we had on a lake in Michigan to think while Kriya and her brother Ravi were in school.  I started reading the scientific literature again, and quickly came across [Marty Chalfie](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/2008/chalfie-facts.html)‘s paper on green fluorescent protein, which he had published in 1994 as I was leaving Bell. It was like a religious revelation to me. Part of what made imaging with near-field so difficult was that it was hard to label proteins densely enough without also putting the fluorophore on a bunch of nonspecific crap. Here was a way to label with 100 percent specificity, and you could do it in a live cell. I couldn’t believe how amazingly elegant it was. I hadn’t wanted to go back to microscopy, but once I learned about GFP, I felt like I had to.  I wanted to take advantage of GFP to do live cell imaging, but my physics knowledge had atrophied. So I pulled out my old textbooks and started redoing old homework problems. I was really motivated to understand it this time around, because I figured this was my last chance to make a scientific career. The knowledge was all in my head, it was just kind of stuck behind a wall, and that wall came down quickly. Robert Heinlein in *Stranger in a Strange Land* has this word called “grok,” where you know something so well that you love it and hate it and it’s part of you. Within three months, I grokked diffraction and light and formation of foci.  I started to think about using multiple foci to image more quickly. I learned about optical lattices, which had been developed several years earlier, and came up with a theory for new lattices that would allow for faster, less damaging imaging. After thinking through all the potential applications, I filed a patent that was more than 300 pages long.  I tried to convince Harald to come make this lattice microscope with me. He was interested, but unsure. I also contacted Horst, who had won the Nobel in 1998, and was now at Columbia. He invited me to present the idea to the biology department there in April 2005. Marty Chalfie was one of my hosts during that visit, and he turned to me in the cab on the way to dinner and said, “It sounds like you really believe in this idea. How are you going to get back in the lab?” I said, “I have no idea, but I read in *Physics Today* that there’s a guy named Gerry Rubin who wants to make a biological Bell Labs,” and we left it at that.  I stayed focused on finding a way to do the lattice microscope, and in the same month went with Harald to meet Mike Davidson at Florida State University. Mike had one of the biggest libraries of fluorescent protein fusions in the world, and that’s where we learned about photoactivatable fluorescent proteins. In the Tallahassee airport on our way home, it became obvious to Harald and me that this was the missing link for the idea that I had pitched after I left Bell: we could isolate a few molecules at a time by activating limited subsets of photoactivatable proteins. It seemed so easy. We immediately abandoned the lattice idea and started writing claims for patents. We continued to meet in various national parks, and planned our research and patent strategy.  Harald and I didn’t know any biology, so we needed help. I arranged to meet the developers of the photoactivable fluorophores, Jennifer Lippincott-Schwartz and George Patterson at the National Institutes of Health and told them our idea. Jennifer told us to build the microscope and bring it by.  Harald and I built the first PALM microscope in his living room in La Jolla (Figure 6). We were both unemployed, but Harald had some of his equipment from Bell. We pulled that out of storage, and each put in $25,000 to cover everything else we needed. We worked hard, and in September shipped all the parts to rebuild the microscope in the darkroom of Jennifer’s lab at the NIH. The first time we put a cover slip coated with molecules into the microscope and turned on the photoactivating light, the first subset popped up and we knew we had it.  By limiting the photoactivating light so that only a few labeling molecules appeared in each image, we could find the center of each spot. Repeating this 10 or 20 thousand times built up the super-resolution image. By early 2006, we had 20 nanometer resolution images of actin filaments, focal adhesions, mitochondria, and lysosomes. We submitted the work to *Science* in March, and it was published that August, after a lengthy fight with a reviewer who demanded correlative EM data, and then pushed for rejection even after we supplied it.  Meanwhile, Marty had told Gerry that I was interested in that “biological Bell Labs,” HHMI’s new Janelia Farm Research Campus. The campus wasn’t built yet, but I was invited to interview in a little building off site in August, and was on the payroll in October 2005.  Once the building opened in 2006, postdoc Hari Shroff and I lived and breathed PALM for the next few years. It was a very competitive time in super-resolution. We developed multicolor capability, and demonstrated live-cell PALM. We also developed with Jennifer a method to study cellular transport by watching subsets of molecules diffuse in a cell, and we had a few other successes here and there.  In 2008, *Nature Methods* named super-resolution “Method of the Year.” Everyone and his kid sister were doing super-resolution by that time. Just like when near-field was at its peak, people were making all kinds of claims that I knew were impossible. Although we had demonstrated live cell imaging, PALM is too slow and throws too much light at a sample to be a practical solution for that. The field was getting crowded, and I’ve always found it most productive to go where the people aren’t. It was time to do something new.  Many of my neuroscientist colleagues at Janelia were trying to peer inside the brains of flies and mice, and I knew that imaging gets pretty crappy when you try to look deep below the surface of the tissue. We needed adaptive optics to correct for distortions caused by heterogeneity of the tissue. Astronomers deal with this problem in telescope images by shining a laser high in the atmosphere in the direction of the object they are observing, then measuring with a special sensor how the light from that guide star is distorted as it returns to Earth. We couldn’t use quite the same approach because scattering in the brain obscures the guide star, so in 2010 postdoc Na Ji and I turned the sensing principle on its head and used image displacements in the sample itself as the sensor. Na has since improved this idea greatly in her own lab, and uses it to record neural activity deep in the cortex with much greater accuracy and reliability.  Meanwhile, Ernst Stelzer had come to Janelia in 2008 and spoke about using a sheet of light to image a single plane at a time within a specimen while avoiding illuminating the regions above and below. I thought that was an elegant solution to the problem of photodamage, and wanted to contribute something new. A light sheet is typically too thick to see detail inside of cells, so with postdocs Liang Gao and Thomas Planchon, we used something called a Bessel beam that we scanned across the sample to create a much thinner light sheet. Within a year or so, we were imaging dynamics within living cells with good resolution in all three dimensions.  One of the problems we encountered was that the Bessel beam had side lobes of weaker light, which created out-of-focus excitation. Liang eventually overcame that problem by stepping the beam instead of sweeping it, and using structured illumination microscopy (SIM), originally developed by my Janelia colleague Mats Gustafsson, to exploit the resulting periodic excitation pattern and extend the resolution a bit beyond the diffraction limit in two of the three dimensions.  To not sacrifice speed when stepping the beam, we generated seven Bessel beams in parallel. To our initial surprise, spreading the energy seven-fold significantly cut the photodamage. What we learned was that while the total dose of light you put into the cell is important, what’s far more important is the instantaneous power delivered to the cell. I then realized that this was consistent with what Na and I had found earlier in 2008 when we reduced the damage associated with two-photon imaging by splitting ultrafast light pulses into a series of sub-pulses of much lower peak power.  Why stop at seven? I modeled the interactions of additional beams, and found that as they become crowded and the side lobes start to interfere, you get crazy resonances and anti-resonances – but there are magic periods where all of a sudden the side lobes destructively interfere. It’s a triple win: You spread the energy out, get a very thin light sheet by eliminating the nasty side lobe problem, and you create a high contrast light sheet ideal for SIM.  That brought me back full circle to the optical lattice theory I had published in 2005. That theory predicted exactly what types of light patterns would create these magic periods. Postdoc Kai Wang figured out how we could use a spatial light modulator to produce these patterns in the lab, and my other postdocs Bi-Chang Chen and Wesley Legant built lattice light sheet microscopes to discover what we could do with this technology.  As it turns out, a lot. The light sheet is so thin that only in-focus molecules are illuminated, making it the perfect tool to push all single molecule imaging methods, including PALM, past their previous limitation to thin samples. Ditto with SIM. When used in a diffraction-limited mode, we can often record several image volumes per second or, at slower speeds, image many brightly labeled samples indefinitely. We worked with over thirty different groups on everything from the kinetics of single transcription factor molecules in stem cells to cell division, 3D cell migration, and embryonic development before publishing the method in *Science* shortly after I received the Nobel.  I think the super-resolution field is still sorting itself out, but I have a suspicion that the lattice light sheet microscope, and not PALM, will be the high water mark of my career. I’ll never be a biologist, but I get a kick out of the beauty of the movies, the craziness of the cell, and the opportunity to learn from dozens of the best biologists in the world. Every week it’s a new adventure.  Mats passed away in 2011, but we also continue to push the limits of SIM. My postdoc Dong Li has extended live cell SIM to 50 nm resolution at subsecond frame rates. Because it is so much faster and uses so much less power than PALM, STED, or RESOLFT, I think there’s a good chance that SIM will be the super-resolution method that will have the greatest impact in live imaging.  I feel like I’ve been incredibly lucky to have had the career I’ve had. Everywhere I’ve been, I’ve been able to focus 100% on my work – I’ve never written a grant in my life. I doubt I would have been as successful in a more traditional academic career path. My group at Janelia has never been larger than five postdocs, and has averaged three. It’s tremendous fun to be able to work closely with them, and it’s exciting to feel like I have a real intellectual stake in what comes out of the lab. I doubt I’d have the same rush with a larger group such as is common elsewhere. In fact, I think that our research model gives us an almost unfair competitive advantage over our peers.  I’m also lucky in that I have a second chance to be a better husband and father. While I’m close with Kriya and Ravi, one of my regrets is that I didn’t spend more time with them when they were growing up. Na and I have two happy and beautiful little hellions, Max and Mia, and I have the opportunity to be with them more. I don’t know, though, if I’ll ever figure out how to optimally balance my responsibility and desire to be at both work and home.  Being fundamentally a pessimist, I still have two fears. One is that the distractions from the Nobel will disrupt our research model and hamper our productivity, as it has already begun to do. The other is that I feel we’ve been too successful. There’s important work still to be done, such as in a project by my postdoc Tsung-Li Liu to combine an adaptive optics method for transparent specimens developed by Kai with the lattice light sheet tech developed by Bi-Chang and Wes. This would allow us to take cells away from the cover slip, and place them back into the multicellular environment in which they evolved. However, this too is likely to succeed. I think it’s my obligation, given the resources at Janelia and the prestige and security of the Nobel, to throw the dice again, and do crazy, risky stuff. Harald and I are working together again with our respective groups in this direction. Only time will tell if anything comes of it, which is just the way I like it. |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** | [EB]  [Eric Betzig] Hello  [Adam Smith] Oh, hello. My name is Adam Smith, I’m calling from Nobelprize.org, the official website of the Nobel Prize.  [EB] Do you know what time it is right now?  [AS] Yes, it is just coming up to twenty to two in the afternoon.  [EB] OK, twenty to two good. If I ramble on can you cut me off at ten to two ’cause I have to give a talk at two, and set up my slides.  [AS] [Laughs] Of course.  [EB] You know, I have a keynote at a conference here I’m giving at two. Yeah.  [AS] Quite right, well I can bet you’ll get a stunning reception. How nice that you’re sticking to schedule. Well, first of all, you’re in Germany now so how did the news reach you?  [EB] Just the committee themselves, they called me around 11:30.  [AS] And what was your first reaction?  [EB] Well, I mean, shock, a little bit of quakes for about 20 seconds, then equal measures of happiness and fear.  [AS] [Laughs] What’s the fear about?  [EB] The fear is, you know, your life being changed. You know, I mean I really like my life the way it is now. And I don’t need… you know… I’m busy enough as it is. [Laughs] So I don’t like saying no to people and I’m going to have to learn how to say no more. And I mean obviously I’m happy with it but I am a little bit scared about how much it will, particularly over the next three months, affect things.  [AS] Yes indeed.  [EB] It comes with the territory, right?  [AS] You yourself have tended to tread a fairly unconventional path. I mean you resigned from Bell Labs, you stepped away from academia. Quite a risky strategy.  [EB] Well, yes and no. I mean, in my opinion the only real asset one has is one’s reputation, right? I mean any company, and institution can go belly up at any time. But if you have a good reputation, you know, you can usually find somebody who can, who thinks they can use what you have to offer. So, I never really viewed it as all that risky at some level. Frankly, I guess, I don’t really understand why people, why so many people, are so risk averse. You know there’s always ways to wiggle your way out of any situation if you’re motivated enough.  [AS] This is a chemistry prize, do you consider yourself a chemist, a physicist, what?  [EB] Ha! I already said to my son, you know, chemistry, I know no chemistry. [Laughs] Chemistry was always my weakest subject in high school and college. I mean, you know, it’s ironic in a way because, you know, trained as a physicist, when I was a young man I would look down on chemists. And then as I started to get into super-resolution and, which is really all about the probes, I came to realise that it was my karma because instead I was on my knees begging the chemists to come up with better probes for me all the time. So, it’s just poetic justice but I’m happy to get it wherever it is. But I would be embarrassed to call myself a chemist.  [AS] Last question. You’ve changed fields a few times in the past. Do you think you’ll change field again?  [EB] Well, I was almost certain I would before this prize happened. Now it’s going to be, now people are going to want to keep me from changing too much. But, you know, it’s probably a quixotic dream but, you know, I’ve always been… when I was a kid I wanted to be an astronaut and I’ve been watching with jealousy the development of the private space transportation companies. You know, if I could ever get away from this, it might be fun some day. Hell, if I was just sweeping the floor of the assembly bay while they were putting the rockets together I just think that would be a blast. You know? I don’t know, I’m an engineer at heart so that impresses me – like super-resolution it’s just a fascinating engineering challenge.  [AS] It’s been a great pleasure to speak to you. Thank you very much indeed. Congratulations again.  [EB] Alright, good, thanks a lot. Bye, bye.  [AS] Thank you, bye bye. |
| **Interview** |  |
| Q4 | Could you describe your Nobel Prize-awarded work in simple terms? |
|  | Eric Betzig: My work and the work of my colleagues for this prize is about trying to see small things, particularly living things in cells. So, your body is composed of cells and the cells themselves are composed of molecules, and in particular proteins come together to create the life inside of cells. There is about 10,000 different kinds of proteins but they are about 100 times smaller than old microscopes can look at. The microscope we developed is a microscope to allow you to see much closer to the level of the individual molecules that make up single cells. |
| Q2 | At what point did you realize your work was a breakthrough? |
|  | Eric Betzig: When did I knew it was a breakthrough … My feeling is that most of the time for many awards, I think, including my work, is that there are several steps that seem like big jumps but there is not a single step. But probably the biggest small step was when my friend and I, we built the microscope that ultimately won me the prize in his living room and when we first put a sample in, it would turn on single molecules and we saw these molecules come on, I knew that the idea we had was likely going to work. So, 2006 was when that happened. |
| Q3 | What brought you to science? |
|  | Eric Betzig: The space program, because I wanted to be an astronaut when I was a kid because the Apollo program was going on then and that captured my imagination. That led me even in elementary school, by third grade I was captivated by science, particularly physics. |
| Q5 | Who is your role model, and why? |
|  | Eric Betzig: I am egotistical enough to consider myself as my primary role model, but there have been people, particularly system integrators of the past. I consider myself much more of an engineer than a physicist or certainly a chemist, like Jo (Joseph) Shea. He was the program manager for the Apollo program and he is the guy who brought together all the technical threads to make the command module and the lunar module and riding herds of 30,000 engineers across the country at the time. Or a guy like Elon Musk, building space axe very quickly out of nothing and Tesla. Guys like that inspire me. I would not necessarily call them role models, but it is nice to know that there are other guys out there who just don’t give up and put everything they can and all their passion into a project. |
| Q10 | Do you see a difference between academia and industry? |
|  | Eric Betzig: It is different in some ways and the same in other ways. I worked after I got my PhD, I worked at Bell Labs a sort of industrial but really basic research place for six years and was working on technologies that ultimately lead to this prize, but I got fed up with the limitations at the time and I quit science. Then worked in my father’s machine tool company, which is a much smaller enterprise, a few hundred guys. But although, in the academic world oftentimes they looked down their noses at what happens in the industry. It has been my experience that many of the people I have met working in my father’s company were as smart, if not smarter, than many of my colleagues that I have had in academia. People are just smart in different ways and different fields and they peak at different times. Oftentimes, guys in industry are later bloomers and the sort of young kids who latch to science early, but it is all about problem solving, either endeavour, and clever people find ways to solve problems in all walks of life. My father is now retired, he is 90, but I worked with him up until, let see, until he was about 80 years old. |
| Q14 | What are your future plans? |
|  | Eric Betzig: That is a good question. The prize makes it harder leave the academic world but about every seven years I have an itch about try something new. One of my fears with the prize is that you get complacent and I always want to be pushed and scared because I feel I am most productive when I am scared about being able to provide for my family or do whatever I think, that’s when the creativity is the highest.  I feel like I have probably about two or three more years – I have actually been working on other microscopes since 2008. About four or five years ago I stopped doing the work that lead me to the prize because I was frankly bored of it. I have been working on other kinds of microscopes and answered other kinds of questions, but I think I have a couple of more years of that before I’ve said everything I have to say about microscopy. I honestly like to go work for one of the private space transportation companies if I could. |
| Q9 | What were you doing when you heard you had been awarded the Nobel Prize? |
|  | Eric Betzig: It is nice to win something like the Nobel Prize, but I feel a bit uncomfortable and, in some ways, hypocritical about accepting it, because I have always believed that accomplishments are objective, but accolades are subjective. The accomplishments are things like the idea for the thing that got me the prize, I got it right after I quit from Bell Labs and was walking my daughter around in a stroller in the neighbourhood. You can always remember those moments like the were just five minutes ago, I can remember that flash that I wasn’t even thinking about the problem, but it just pops into your head about how you can combine elements of your previous work to do something new.  The idea laid fallowed for ten years while I was in industry and then when my friend and I were visiting another lab, we found about this photoactivated protein which was the missing link. So that is another time that again will always feel like it is just a few minutes ago that you just remember “Oh my god, this is exactly what will make that idea work”. A then a year later, when we actually saw that work in the microscope, and we turned on this one light and these molecules popped on all of a sudden. We said: “We have got it; it is going to work”. Those three events that lead to this prize, those are the thing that you remember when you are dying. You won’t remember exactly what happened this week, but you will remember those actual accomplishments and when they happened. |

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| **Chemistry\_2024-2000** | |
| **ID** | 0329 |
| **Biographical** | I was born on 23 December 1962 in Arad, a medium-sized, ethnically diverse city in the western part of Romania, directly on the border to Hungary. In those days, Romanian, Hungarian and German were the languages that could be heard on the street in a frequent mix, and most locals – including simple folk – spoke two or three of these languages fluently. Ethnic conflicts were unknown, because until 1918 the area was part of the Austro-Hungarian Empire, and linguistic and religious diversity was the normal state of affairs. My parents originated from a place a few kilometres further north, called Santana (German: Sankt Anna), which was founded by German immigrants in the 18th century. Most people in Sankt Anna, including my parents, spoke German as their mother tongue, or, more precisely, a dialect spoken in south-western Germany at that time. This is where I spent most of my childhood.  My father worked as an engineer in a managerial position in a company. My mother was a primary school teacher. Actually she would have liked to study mathematics, but in communist Romania in the 1950s this wasn’t possible due to her allegedly ‘bourgeois’ background. She was expelled from school several times, and only later was she able to obtain her school-leaving certificate with considerable effort. This circumstance, as well as several other calamities that befell the generation of my grandparents in 1945, including ethnically based material dispossession and deportation to Soviet labour camps, eventually led to the view: ‘No one can take away what you have learned. And you always carry it with you wherever you go.’ Education was about the only asset worth achieving. For this reason, our house was full of books. My parents acquired anything that even remotely seemed interesting. And they liked to travel – but that was only possible within the borders of the country. Nevertheless, we were aware of what was happening outside Romania, as we were well informed from listening to Western radio stations.  My mother being a teacher, who understandably did everything in her power to educate me early, I learned to read at a young age. And because I didn’t particularly like kindergarten, she often took me along to her classes. Things were more exciting there. I had no siblings, and I spent many hours with books such as an encyclopaedic lexicon from West Germany, which I studied in detail. I was especially fascinated by things such as the chain reaction, even though I didn’t quite understand it. And I still vividly recall watching the moon landing on television which was otherwise full of communist propaganda. But this made the highlights all the more interesting: science fiction thrillers from America that were aired on Sundays in English with Romanian subtitles. That was very exciting, and somehow the aspiration grew in me that I later wanted to become a scientist.  Our classes were held mostly in German, because Romania maintained basic education in all the minority languages. We learned French as a foreign language. In retrospect, I believe I was very fortunate that many of my teachers at the time were in their twenties or thirties and that they were highly motivated to inspire their pupils. I still remember how my chemistry teacher (Figure 1) explained the basic principles of atomic structure in a compelling way, and how amazed I was to learn that most of the atomic mass resided in the much smaller nucleus.  After grade eight, at the age of fourteen, I was able to obtain one of the few places at the Nikolaus Lenau Lyceum in Timisoara, one of the best secondary schools in the country. There you could specialise in mathematics and physics, and it was there that I was first propelled towards physics, as I had won a local competition and realised that physics was fun. On the other hand, daily life was difficult, and I associate my time in the school dormitory in Timisoara with going to bed with a grumbling stomach. It was, after all, communist Romania, and Ceausescu was in the process of expanding his dictatorship. The regime in Bucharest – unlike the normal people on the street – was growing increasingly nationalistic and bizarre. The flood of propaganda let the feeling grow that it’s not good to live under a dictatorship – especially with a minority background. And it was easy to conclude the latter from my last name.  And another feeling took root in me: things that are publicly asserted and constantly repeated aren’t necessarily true. Quite the contrary: I became sceptical about accepted opinions. Coupled with having no prospect of improvement, all this meant that most of the people who could even remotely claim a German or Jewish background tried to leave the country. But that was far from easy.  When a classmate emigrated with her family, I convinced my parents that they too should apply for an exit visa. Besides, my mother had been diagnosed with a disease two years earlier, and one of her doctors recommended emigration to Germany, where she could receive better medical care. After two years of uncertainty and inconvenience with the officials, we were allowed to leave for West Germany with a few belongings. It was on April 8, 1978; I was fifteen. We had no close relatives in Germany and settled in Ludwigshafen, an industrial city west of the river Rhine, far away from the iron curtain. I also found Ludwigshafen to be good, because I had seen on the map that the university town of Heidelberg was just a few kilometres away, and that struck me as a goal worth pursuing.  I was thrilled about the opportunities in the West, though this was also accompanied by my parents’ struggle to settle in Germany. In Ludwigshafen I attended a secondary school, and soon realised that I was far ahead of my classmates in the sciences. I also had a fantastic physics teacher, Mr. Ecker, who gave me great encouragement. Then again, my English was limited to what I had picked up from non-dubbed American and British films in Romania. Finally, I learned that I could graduate from secondary school with only French as foreign language, and I took advantage of a rule that allowed me to graduate one year earlier than usual. I did that and began to study physics at the University of Heidelberg in 1981.  Studying physics was the next great liberation, because the material to study was not dependent on *zeitgeist* or politics. At the same time, the atmosphere in Heidelberg was very conducive. On Friday evenings there was a colloquium, followed by wine and pretzels for all. The first speaker I heard in the colloquium was [Isidor Rabi](https://www.nobelprize.org/nobel_prizes/physics/laureates/1944/rabi-facts.html). Unfortunately, it wasn’t easy for me, because after briefly starting in German, he switched to English at some point. Nonetheless, seeing and hearing one of the greatest scientific minds of the 20th century was an important and highly motivating experience.  I don’t know if I stood out as a student. In any case, I was always dissatisfied when I had the impression that the lecturer failed to get to the heart of the matter. I could never accept arguments such as “if you do the maths, you’ll know why this is so.” I firmly believed that everything could be boiled down to simple principles. And if that wasn’t possible, one simply didn’t understand the matter. Be that as it may, a consequence of this attitude was that during my studies I spent hours and hours thinking about how I could distil down phenomena and concepts to their essence. During the vacations, I managed to hide out in my room for months – much to the concern of my friends – ‘picking apart’ textbooks from morning till late and writing my own version of the subject in stacks of notebooks. Some days I only progressed by one or two pages, and it was frustrating when I still hadn’t grasped the core of the matter. But it was fantastic to eventually ‘discover’ what the core was. I was also of the opinion – and it’s probably true – that I am terribly bad at memorising things, and if I didn’t understand something exactly, I would forget it and fail my oral exams. Fortunately, that did not happen.  Like many physics students, I had planned to specialise in particle or nuclear physics, and Heidelberg was the place to do it. On the other hand, I heard that it was disillusioning to work on large projects and that job prospects were not good. The latter consideration proved decisive, because my father’s job was becoming increasingly uncertain, and my mother was again diagnosed with a serious illness. As the time to work on my diploma thesis approached (a final master’s thesis lasting up to 2 years), I opted – against my inclination – for a topic which I believed at the time would provide good prospects of finding a job. It was about microlithography, the production of fine structures in photoresist material for computer chips. Professor Siegfried Hunklinger from the Institute of Applied Physics, a low-temperature solid-state physicist who had just moved to Heidelberg from the Stuttgart-based Max Planck Institute for Solid State Research, wanted to produce piezoelectric surface-wave transducers lithographically and had teamed up with his colleague, Professor Josef Bille, to construct a laser scanner that could be used to write microstructures.  I must have done my diploma thesis work reasonably well, because I was one of the few students Professor Hunklinger planned to keep for doing a PhD. But, for my doctoral thesis, I wanted to focus on something less applied – which wasn’t so particular, because most of the other students were concerned with low temperature solid-state physics. Actually, Professor Hunklinger had kind of planned that for me as well, but in the end it turned out to be a subject which again had a touch of applied physics. And I didn’t have the courage to say that I would do it with little passion.  As it happened, Professor Bille and Professor Hunklinger had just founded Heidelberg Instruments GmbH, a start-up company developing laser-scanning optical systems for a broad range of applications: optical lithography, ophthalmology, and confocal microscopy for biology, as well as microlithography inspection. Confocal microscopy was about to emerge as a new microscopy technique, having the advantage of suppressing light from above or below the focal plane. In the mid-1980s, it was therefore believed that this could be used to measure transparent 3D photoresist microstructures more accurately, which was important for the mass production of computer chips. My task was to find out if and how this would work. However, that wasn’t easy, because the structures on the silicon wafer were transparent and had about the same width and height as the wavelength of light. The confocal principle was not really able to solve the problem; rather it produced complex images that changed drastically with minute changes in the dimensions of the structures. I called the images ‘aliens’, because they reminded me of the figures of a popular computer game at the time. At first, I wanted to find a mathematical model to predict them, but there were too many process parameters to deal with, and ultimately such an approach would be impractical for a semiconductor manufacturer.  As the only physics graduate student at Heidelberg Instruments, I was more or less on my own. Occasionally, I was able to turn to the company’s development manager, Roelof Wijnaendts van Resandt, who had run a group on confocal microscopy at the Heidelberg-based European Molecular Biology Laboratory (EMBL) a few years earlier. But he had little time for me, because the company was struggling to survive. There was also a biology graduate student, Werner Knebel, who was investigating the suitability of confocal microscopy for cell biology. We often talked to each other. I explained to him the physics of image formation and he introduced me to fluorescence imaging in biology. Otherwise, my routine was interrupted only by my walks to the weekly seminars on solid state physics, teaching duties, group meetings, and the colloquia on Friday evenings. I was quite frustrated. Actually, I wanted to do something more exciting than optical microscopy – which I perceived as a boring physics subject of the 19th century, which had nothing to offer apart from diffraction and polarisation.  In the interim, I had received a stipend from a foundation, meaning that I wasn’t dependent on the company. I also knew that my thesis advisor was a ‘real’ physicist with a passion for physics. So I started to ask myself whether there might be an interesting problem left in optical microscopy after all. The only thing that still seemed interesting in my view was the diffraction limit of resolution. So I figured that breaking this limit would be really new and exciting! All of a sudden, everything looked brighter, because thinking about light microscopy took on a new meaning.  So I decided to pursue the thesis work as initially requested, but what really motivated me was the resolution problem. I knew of course that near-field optical microscopy existed, but it seemed to me like a kind of scanning tunnelling microscopy. In contrast to that, I wanted to come up with a light microscope that looks and operates like a light microscope – but without the limits set by diffraction. So I began to comb through my textbooks again, searching for phenomena suitable for overcoming the diffraction barrier. I pondered all kinds of options from the Stark to the Zeeman effect. I even checked textbooks on nuclear physics. My efforts weren’t initially met with success.  But one thing came up most naturally: Virtually isolated from the optics community, I had figured out how to calculate the focal light field at large focusing angles, and had written a computer program to do so. I had solved the problem in my own way and had lots of fun playing around with the field calculations, which worked beautifully. The largest focusing (i.e. aperture) angle of the best objective lenses at that time was around 71°. Of course, I also plugged the theoretically largest value of 90° into my program, which corresponded to a converging hemispherical wavefront. I also calculated what would happen for a complete sphere. While the last two cases were interesting but impractical, it was far more realistic to calculate what would happen if one juxtaposed two lenses with a 71° aperture angle and caused their wavefronts to add up constructively at a common focal point. That the main diffraction peak would become three to four times sharper along the optical axis (*z*) than with the best single lens was to be expected. However, less obvious was the outcome that the secondary diffraction peaks along the axis were small enough to be discriminated against in a potential image; they would not produce ambiguities or ‘ghost images’. So it seemed feasible to improve the resolution along the optic axis by 3–4 fold, by using two counter-aligned ~70° lenses in a coherent manner. That was the idea behind what was later to be called the 4Pi microscope.  Back then I called it the double-lens microscope and presented the results sometime in 1988 in Professor Hunklinger’s seminar series – as an addendum to what I was actually supposed to do. The idea was perceived as interesting, but the difficulties in aligning two lenses to focus at the same point and controlling the phase of the wavefronts were thought to be daunting. And, of course, the concept wasn’t suitable for silicon wafers – only for transparent specimens such as biological cells. Actually, I set off to try it out, but Heidelberg Instruments disintegrated into several subunits in 1989, and Prof. Hunklinger resigned from it. It is left to be noted that the subunit dealing with confocal microscopy was purchased by the company Leitz which later became Leica Microsystems GmbH, a leading supplier of confocal microscopes.  By the time I had completed my doctoral thesis in the summer of 1990, I was convinced that there must be a way to improve resolution in a more fundamental way. With the two-lens approach I had at least found a beginning, albeit only within the limits imposed by diffraction. But the mindset that I had constructed for myself, picking apart textbooks, told me that physical phenomena must exist that should be suitable to overcome the barrier radically. So much progress had been made in physics in the 20th century that there had to be at least a single phenomenon that should enable lens-based optical microscopy with resolution at the nanometer scale.  My stipend had run out, and I had asked Professor Hunklinger if I could stay on another year to work on the resolution problem. But optics wasn’t his field. It was clear that I would have to go my own way. This wasn’t easy because at that time there were no structures in Germany to give young researchers a start. Usually, you needed a professor (mentor) for whom you would work for several years while working towards your *habilitation*, a postdoctoral degree required for having one’s own students and to lecture. I neither had such a mentor nor was applying for a postdoctoral position in the USA an option. First, I didn’t know anyone there; second, my English was rather modest.  Fortunately, my grandparents, who had meanwhile followed my parents to Ludwigshafen, had saved 10,000 Deutschmarks, which they gave me as a present when I was awarded my doctorate. I sat for a couple of weeks thinking about how I could build a ‘double confocal microscope’ with two juxtaposed lenses and used the money to pay an attorney to file a patent on it. Since I had worked in the setting of a start-up company, I thought that I may be able to persuade Leica or another big company to support the development. But things worked out differently: Roelof Wijnaendts van Resandt introduced me to his former PhD student Ernst Stelzer, who had succeeded him as head of the microscopy group at the European Molecular Biology Laboratory (EMBL) in Heidelberg. I indicated to Ernst that I wanted to work on the resolution question, and he offered me a stipend for a few months, on the condition that I would apply for external stipends for the rest of my stay. One has to appreciate that at the time there was a surplus of physicists in Germany, and the prospects of doing academic research were poor. However, I had just learned the hard way that it is a mistake not to do what you really enjoy.  I therefore wrote up a small application for a stipend to the German Research Foundation (DFG), the main funding body in Germany. Essentially, I described the double-lens microscope and my view on the prospects of improving the resolution in a lens-based light microscope. Although located in Heidelberg, the EMBL is legally outside Germany, which meant at that time that I could not be funded by the DFG unless my application was formally supported by a German university. Since I could no longer appeal to Professor Hunklinger, I consulted the directory of physics professors at Heidelberg and picked out two whose interests seemed most closely related to the subject.  I wasn’t familiar with either of them. One was Reinhard Neumann, a lecturer from Prof. Gisbert zu Putlitz’s chair on atom spectroscopy; he asked me whether I wanted to do near-field optical microscopy. I replied with ‘far-field only’, whereupon he looked at me with a stare. But he read my essay and finally wrote a letter of support. The other was Professor Christoph Cremer, who worked on flow cytometry and chromosome organisation, the only biophysicist in the directory. He also read my little essay with interest. When I came back a few days later, he was excited and showed me a paper that he had published in 1978, which he jokingly referred to as a *jugendsünde*, i.e. a peccadillo of youth. The paper suggested a hypothetical hologram producing a freely propagating elliptical wavefront which was predicted to converge in a single point of light that would possibly become infinitely sharp, at least much smaller than the diffraction barrier. Scanning this ultrasharp point across the sample was supposed to produce images with resolution well beyond the diffraction barrier. He called it the “4π microscope.”  I instantly realized that even if you could build the desired hologram, it would not produce an infinitely sharp point of light. The concept was not congruent with the laws governing the propagation of electromagnetic radiation. But Professor Cremer was supportive too, and wrote the other letter. The stipend was later approved on the condition that I spend six months abroad. I opted for Oxford, to work with Professor Tony Wilson, an early confocal microscopy pioneer. (I finally did that four years later, in 1995.)  The EMBL was a great place. It was international, and the working language was English. I took advantage of this time to learn English, and after I had listened to many presentations, I eventually plucked up enough courage to present in English myself. I had no choice after all. With Ernst Stelzer I had agreed to build the microscope with the two counter-aligned lenses, to see if the axial resolution increase could be realized. It wasn’t easy. I remember that in December 1991, one day before my birthday, I had the first clear indication that it was feasible. The key was that I could exactly predict what the experimental data should look like, so I was able to discriminate against misalignment. In the publication, Ernst suggested that we call it the “4π microscope,” which I wasn’t particularly happy about. For one thing, the solid angle of the double lens arrangement was far from 4π. Furthermore, the actual discovery was that ‘4π’ wasn’t needed to increase the axial resolution; two high-angle lenses were sufficient. Moreover, the Cremer paper had drawn an improper physical conclusion (i.e. a point-like spot of light) and had completely missed the axial resolution increase as the actual benefit of adding the other side of the solid angle. Ernst and I finally compromised not to use the Greek letter π, but the Roman letters Pi. Whether I liked it or not, the name 4Pi stuck. The group was later reinforced by two talented physics diploma students, Gernot Reiner and Steffen Lindek. Since Ernst did not have the *habilitation*, the thesis works were officially handled by Professor Cremer, who became increasingly interested in the resolution topic.  In this quest for increasing axial resolution using two lenses, it was not enough to produce a focal interference pattern with counter-propagating waves. The challenge was to create a main focal diffraction peak with negligible secondary ones, i.e. an optical transfer function of the microscope that was both expanded and contiguous along the optic axis. Otherwise, one would end up with image artefacts. With the use of the two-photon excitation modality introduced in microscopy by Winfried Denk and colleagues, making contiguous transfer functions became reliably possible. But there were still no images of biological specimens taken and, of course, using two opposing lenses didn’t break the diffraction barrier. The latter particularly vexed me. However, the good thing was that the resolution question in far-field microscopy had been raised for all to see, and, importantly, I had a foot in the door.  Ernst Stelzer and I ended up with very different views on how realistic it would be to overcome the diffraction limit. We parted ways in 1993. He went on to tilt two low-angle lenses so that they were at almost 90° to each other and called it confocal theta microscopy. Later he refined this arrangement into what is now called the light-sheet microscope.  In the spring of 1993, the stipend ran out, and I could no longer stay at the EMBL. The DFG, which had just set up a special funding program called ‘New Microscopy for Biology and Medicine’, told me that I couldn’t apply for research funds because I had no job and no laboratory to work in. They funded a couple of near-field optical microscopy projects though.  But once again I was lucky: Also working in the Stelzer group was a Finnish colleague, Pekka Hänninen, who planned to return to Finland. Pekka had realised the timeliness of the resolution topic and introduced me to his future professor, Erkki Soini of the University of Turku, who offered to submit a research proposal on 4Pi microscopy to the Academy of Finland, basically on my behalf. The Academy agreed to fund the project, on condition that I worked in Turku. So I arrived in Turku in the summer of 1993, and Erkki Soini, Pekka, and I worked very hard to set up a small optics laboratory. We started where I had left off at the EMBL, namely with 4Pi microscopy – first, because it was the only tangible approach at the time, and second because the credibility of the whole endeavour was at stake. Rumour was that my efforts would end up like all other far-field optical ‘superresolution’ efforts before, namely as an academic curiosity. The situation was not helped by the fact that Ernst Stelzer started to distance himself from the ‘4Pi’ work carried out in his laboratory in publications.  At the same time, I felt that simply changing the way light is focused or re-arranging lenses will not change matters fundamentally. The only way to do so would be either via some quantum-optical effects or – what appeared more promising – via the states of the molecules to be imaged. The molecules whose states could be most easily played with were fluorescent ones, which, fortunately, were also those of interest in the life sciences.  On a Saturday morning in the fall of 1993 I was browsing through Rodney Loudon’s book on the quantum theory of light in the hope of finding something suitable. A few weeks earlier I had imagined what would happen if the fluorescent molecules would be re-excited from the excited state using slightly offset beams. When my eyes caught a chapter dealing with stimulated emission, it dawned on me: Why excite the molecules, why not de-excite them, i.e., keep them non-fluorescent in order to separate them from their neighbours. I was electrified by the thought and immediately checked Fritz Schäfer’s book on dye lasers to see what was reported about the stimulated emission of fluorophores such as rhodamines. A quick assessment showed that an image resolution of at least 30–35 nanometres could be achieved in the focal plane, i.e. 6–8 times beyond the diffraction barrier. That was amazing. It was also instantly clear that the achievable resolution only depended on the intensity the sample would tolerate, and in principle was unlimited.  What also intrigued me was the fact that the resolution could be obtained without *a priori* assumptions about the distribution of features to be imaged. This was because at that time, it was widely believed that the route towards higher resolution in the far-field was data processing, which typically required some assumptions about the object. However, in my case, mathematical processing was not needed. The concept was based just on the use of a basic state transition, i.e. “just on physics.” I finally had an example of the type of approach I had been seeking for. It was the concept of STED microscopy.  But it wasn’t so easy to test this idea in Turku. I also thought that a tunable dye laser would probably be needed to optimise for de-excitation. But there was no dye laser to be had far and wide. After explaining the concept to Pekka, Erkki and other friends in the laboratory, I called up a former student friend from the Hunklinger laboratory in Germany, Leonore Hornig, who had become a patent attorney in the interim. I explained the idea to her and briefed her on filing a patent. I also felt that I should publish the idea in theoretical terms in such a way that it was as close as possible to reality and therefore hard to challenge. Before I left Heidelberg, Jan Wichmann, a physics student whom I knew privately, had expressed his desire to come to Turku for two weeks in December to work with me as an intern after finishing his diploma work with Prof. Jürgen Wolfrum. I explained the concept to him and asked him to model it numerically to be sure that the numbers were as close as possible to a real experiment. Jan’s preference was to use Gaussian beams because those could be handled relatively easily by the algebraic program *Mathematica*. The numerical evaluations of the rate equations largely coincided with my initial assessments. In any case, the paper proposing STED microscopy eventually read like a recipe: it was full of numbers. I tried hard to omit anything that could be interpreted as an oversimplification or exaggeration, because, not having a mentor and knowing that it was just a theoretical proposal, I was very much concerned about a total rejection.  On the other hand, the paper was written to convince the community that nanoscale far-field fluorescence microscopy is viable, as well as in the hope of getting a job and the funds to do it. Whether I would ever be able to realise it myself was indeed doubtful at that time, because the Finnish Academy grant was gradually nearing its end. Yet, in retrospect, I must say that the time in Finland was really exciting and decisive (Figure 2).  I also quickly realised that stimulated emission is not the only state transition that can be used to the same end. After all, the basic idea was to ensure that a part of the features illuminated by the excitation light remain briefly dark so that they can be separated from other features residing within the diffraction range. So I had the idea of parking the fluorophores in a dark metastable state, something dye laser operators were trying to avoid at all costs. This also had the important benefit of requiring less intense light. Since all my papers were published in specialised optics journals – which didn’t make my CV look particularly impressive – I submitted this proposal to a more general physics journal. When I received no response after months, I mustered all my courage and called the editor, who happened to be German. He told me that he had doubts about whether the diffraction limit could actually be overcome. He had sent the manuscript to three experts in near-field optical microscopy (!) – among them a famous one in the USA – and only one of them had replied. The reply was not favourable. It would all have to be demonstrated experimentally before making such claims, the editor said. When he realised my despair and that I didn’t really have the means to do that, he advised me to go back to Professor Hunklinger, so that he submits an application to the DFG on my behalf. I was terribly disappointed about the German academic system.  Today, it’s perhaps hard to understand, but the 1990s were not particularly receptive to the notion of obtaining nanometre-scale resolution in a lens-based optical microscope. This can be readily concluded from the fact that no laboratory had tried STED, although I had advocated the concept with much passion since April 1994. In my opinion, there were two reasons for this. First, near-field optical microscopy seemed the way to go at the time, including for the life sciences. Eric Betzig, who worked at Bell Laboratories in the early 1990s, had published prominent papers, such as a *Science* paper in 1993, showing the near-field optical recording of single molecules at room temperature. The second reason was probably even weightier. In the 20th century, various people had repeatedly proposed concepts to overcome the diffraction barrier in the far-field, most prominently Toraldo di Francia and Lukosz. Yet, none of these concepts were practical, or got beyond a factor of two. So it was therefore natural not to take a far-field method like STED and related ideas seriously either.  I was convinced that this time it would be different. My reasons were simple: STED fundamentally differed from other concepts in that it relied on separating features via the molecular states of the sample, rather than on tackling diffraction itself. But even more importantly, I could not find a basic physical oversight in my concept – in contrast to all of the ones reported until then. If problems were encountered in the realisation, they would only be technical, not conceptual in nature, which meant that they could be overcome through development. With the right transitions, one can transfer fluorophores between two states, such as a bright and a dark state, as one likes. When the molecule is in a dark state, that doesn’t mean that the (fluorescence) signal is lost; it simply isn’t produced. In other words, you can discern adjacent molecules by keeping some of them silent without losing anything, except time. If some signal is nevertheless lost, that is not due to the approach, but to the fact that something else takes place as well – something that is outside the conceptual framework. By discriminating against that, one can make the concept work. This insight gave me the courage to carry on with the development.  However, a first research proposal submitted from Turku in 1995 to a European grant agency with a view to implementing STED was rejected. But fortunately, a Marie Curie individual postdoctoral stipend came through at the last minute. In this precarious situation, Prof. Soini advised me to license my 1990 privately owned patent for the double-lens microscope (a.k.a. the 4Pi) to a company in Turku, Wallac Oy, in exchange for research funding. The company’s CEO agreed to transfer 100,000 dollars to a university account. To this day, I believe that compassion played a role.  Those funds were crucial, because they bought me time for a very fortunate event in my life: Dr. Thomas Jovin, the Managing Director of the Max Planck Institute for Biophysical Chemistry in Göttingen at the time, had become aware of my activities. An accomplished and open-minded scientist with Ameri- can background, who successfully kept abreast of the latest developments in molecular biology, fluorophore chemistry, and optics alike, he convinced Erwin Neher, Herbert Jäckle, Peter Gruss, Klaus Weber, Jürgen Troe and the other directors of the institute, to invite applications for setting up a small microscopy research group for five years. They had Winfried Denk (then at Bell Labs) or me in mind. In the spring of 1996 I spoke to Winfried on the phone. When he said that he wasn’t interested in this type of non-tenure track position, it came as a big relief. I had a good chance of securing the job.  In the meantime, we had made progress with STED microscopy in Turku. After testing a few dye solutions in a cuvette with Ignacy Gryczynski of Joseph Lakowicz’ group in Baltimore that showed some fluorescence modulation, I found out that one could apply a heavily chirped Titanium Sapphire laser to turn off a dark red fluorophore (with the trade name Pyridin2) under microscopy conditions almost completely. This was not easy to work out, because unlike in a cuvette, in a microscopy sample, stirring is not an option to get rid of radicals and bleaching, and the intensities are by orders of magnitude higher. It was also difficult to demonstrate the resolution increase directly, because Pyridin2 could not be coupled to biomolecules. Fortunately, it occurred to me how it could be done indirectly: slightly offsetting the STED beam with respect to the excitation beam was expected to reduce the focal fluorescence region to subdiffraction dimensions. Translation of a confocal point detector across the image plane then proved that this reduction indeed occurred. The measurements were done together with a diploma student, Franziska Meinecke, in 1995. From that point on, I knew that STED microscopy would work – at least under certain conditions. Franziska was less optimistic. She gave up science finally, saying that she felt sorry for me: difficult research subject, little support, no real prospects, and lots of sacrifices. It was sobering to hear that from a student, but I decided to carry on.  I didn’t write up those initial STED results because I thought that it may end up in a low-ranking journal again. However, in January 1996, I showed the data at the Friday physical colloquium in Heidelberg, where I gave a talk in front of my former professors including Otto Haxel, Franz Wegner, Joachim Heintze, and Dirk Schwalm, who asked questions at the end. It was my *habilitation* lecture, and *habilitation* was important to carry on in science and supervise one’s own diploma and PhD students (officially). Until then, Professor Cremer was taking care of the formalities. He thus also became co-author of some of the papers and advised me how to steer clear of political issues during the *habilitation* process. Today, I am very grateful that the physics faculty allowed me to habilitate in Heidelberg despite the fact that all the work was done in Turku. But contrary to many public assertions, I never was a student or a postdoc of Prof. Cremer. Nor did I work under his intellectual guidance. Rather the relationship reflected in part the inability of the German academic system of the 1990s to provide true indepencence to young researchers.  In December 1996 I took up the position in Göttingen. It was just in the nick of time, as the money from Wallac Oy had run out. The Max Planck Institute in Göttingen was incredible because, for the first time, I was able to plan a little ahead and submit my own research proposals. I submitted a grant for STED to an agency of the German Federal Ministry of Research, which was promptly rejected. However, the officials in charge accepted my appeal and approved the grant against the scientists’ recommendations. Shortly thereafter, Thomas Klar applied to work as a doctoral student in my laboratory. Thomas grasped the STED concept quickly and was exceptionally talented. Combined with the much better equipment now available, in a few months we reproduced and outperformed the experiments carried out in Turku. 4Pi microscopy had meanwhile yielded compelling images, too.  In 1999 Stefan Jakobs joined in as the first biologist postdoc, greatly extending the group’s interdisciplinary expertise. He had realised that the resolution was undergoing a transition and was attracted by the idea to pioneer its use in the life sciences. We were thus able to show beyond a doubt that the resolution of far-field fluorescence microscopy can be drastically improved, and also used in biological imaging. The paper was initially written up for the journal *Nature*, which decided not to send it out for review. I resubmitted it to *Science*, where it had the same fate.  Eventually, it got published in the *Proceedings of the Natural Academy of Sciences of the U.S.A.* in 2000. This time we had been more fortunate. As we learned later, the manuscript ended up with Shimon Weiss of the Lawrence Berkeley National Lab, who had participated at a symposium a couple of months earlier, where I had presented the data for the first time. He and the other reviewers accepted the paper and Shimon wrote a commentary in *PNAS* pointing out its implications. Given its history, it was very pleasing to see this paper being highlighted in Prof. Måns Ehrenberg’s presentation of the 2014 Nobel Prize in Chemistry.  The year 2000 was also fortunate in another aspect: I married my wife, Anna, a pediatric orthopaedic surgeon at the Göttingen university hospital, whom I had met in Göttingen in 1997.  In 2002, to my surprise, the Max Planck Society offered me scientific membership at the Göttingen Institute, which meant tenure and a stable funding contribution to my science.  Since 1994 it had been clear that any reversible transition between a fluorescent and a non-fluorescent molecular state is a possible candidate for overcoming the diffraction limit. In fact, everyone in my laboratory was instructed to keep eyes open for unexpected ways to modulate the fluorescence capability of a molecule. It was also clear that resorting to reversible on-off-transitions with long-lived state pairs would reduce the intensities required to overcome the diffraction barrier.  The intensity issue was often cited against STED. Therefore, in 2003, to make chemists and fluorescent protein designers aware of the transformative potential of such on-off state transitions for microscopy, I wrote up a little communication to *Nature*. The communication highlighted the – in my view – historical opportunity to design switchable fluorescent markers for the purpose of breaking the diffraction barrier.  This time, *Nature* sent out the communication for review, but all three reviewers rejected the paper outright, in fact with improper arguments and contentions. In my view, the actual reason for rejection was that “experts” in the fluorescence microscopy field did not (want to) accept that the resolution was about to undergo a historical change. And they did not understand that the fluorescent molecules were the key players in this change. They rather saw the field centred around multiphoton excitation, fluorescence lifetime imaging, and single-molecule detection, which no doubt were important, too. In any case, the paper ended up in *Appl. Phys. A*, where it was seen only by those who screened explicitly for it. Later, I asked myself what would have happened if the power of using photoswitchable molecules would have become apparent to the greater chemistry and biology community much earlier.  In this situation, I felt that I had to advance photoswitchable fluorophore synthesis myself, which wasn’t so easy since organic chemistry and molecular biology was not my background. So, I expanded the laboratory to include organic chemistry (with Vladimir Belov), and switchable fluorescent protein development (with Stefan Jakobs). This allowed me to follow a more systematic approach for playing the “on-off game,” harnessing other state transitions as well, such as cis-trans isomerisation. The STED idea could thus be expanded to encompass other state transitions, and particularly to operation at low light levels (RESOLFT). Therefore, starting from 2003 I strongly advocated the development and use of photoswitchable fluorescent proteins and organic fluorophores, because I felt that they would have the potential to provide the ultimate solution to the resolution problem in fluorescence microscopy.  STED ‘proper’ progressed as well. In 2003 we reported the first nanoscale far-field immunofluorescence images using STED. There were still hurdles to overcome. But many could be taken one by one – or the technological developments around us worked to our advantage.  In early 2004 my mother passed away in Ludwigshafen, after a twenty-year battle against cancer. At around the same time, I also started to set up a small group at the German Cancer Research Center (DKFZ) in neighbouring Heidelberg to give researchers in this field direct access to the novel developments in microscopy.  In the same year, the Howard Hughes Medical Institute (HHMI), a large philanthropic organisation in the USA, started to set up Janelia Farm Research Campus, a new type of institute where scientists are given ample resources and freedom to concentrate on important scientific problems. In 2004, HHMI and the Director of Janelia Farm, Gerald Rubin, asked the Max Planck Society and other organisations to help identify important problems to work on. I took part in two symposia for identifying such research topics, one of which I organised together with another Max Planck Society member in Munich. At this meeting, superresolution fluorescence microscopy was represented by myself and Mats Gustafsson, a spectacular Swedish colleague from the University of California at San Francisco. Mats had joined the field in about 1996–97 by introducing a widefield version of the two-lens (‘4Pi’) arrangement. A hallmark of Mats’s approach was to describe resolution and image formation in the spatial frequency domain. In fact, I never met a person who could think in frequency space as effectively as Mats. While I had not excluded obtaining superresolution in a widefield layout, I had felt that it would be easier to overcome the diffraction barrier first in a single-spot arrangement. This thinking was not wrong, but Mats advanced much further with widefield camera-based layouts than I and anyone else would have imagined. This applied not only to axial but also to lateral resolution improvements. He was of historical calibre.  Mats and I were about the only ones pushing far-field optical superresolution in those days. At scientific meetings we would present our latest data right from the optical table – usually many months before submission. This aspect gave the meetings a certain flavour – to the point of occasionally being marked somewhat by our friendly competition. This applied also to the HHMI-Max- Planck meeting in Munich. It then became obvious to anyone that far-field superresolution fluorescence microscopy was a hot topic. It is left to be noted that Mats was later hired to Janelia Farm and sadly passed away in 2011 after having left a huge legacy in microscopy.  In 2005 I received a very complimentary email from Eric Betzig saying he was entering the superresolution field again, attracted by my and Mats’s work. I had not met him personally, but I was aware of his eminent role in near-field optics in the early 1990s. However, this time Eric set out to work in the far-field. In fact, I had been asked by Janelia Farm seniors whether I felt Eric could still make a difference. I was very confident about that, given his accomplishments in near-field optics. And this turned out to be true, when I heard from him again about a year later.  In 2005, my wife Anna gave birth to our twin boys Sebastian and Jonathan.  The year 2006 was to become an *annus mirabilis* for the field. In 2005 my group had carried out three studies demonstrating for the first time that far-field superresolution fluorescence microscopy was able to give new insights in biology, (e.g. with Katrin Willig, Silvio Rizzoli, Thorsten Lang and Robert Kellner); they were published in early 2006. In this context, I am particularly grateful to my colleague Reinhard Jahn and Stephan Sigrist, now a professor in Berlin, who came up with interesting biological questions. In 2006, the development of the first commercial STED microscope was also completed. And, importantly, Eric Betzig and Harald Hess first realised and presented another major concept for far-field super-resolution, called PALM. Unlike STED or RESOLFT which briefly switched the fluorophores off using a pattern of light, PALM followed a ‘bottom-up’ approach: the molecules of the features to be resolved were stochastically and individually switched on and off, followed by localisation for position determination.  The art of detecting individual molecules had been pioneered by W.E. Moerner and Michel Orrit and had co-existed with far-field superresolution imaging for about 15 years. Superresolution and single-molecule detection were in fact two different fields, each having their own dynamics and proponents. For example, until 2006, single molecules had been used in superresolution microscopy for testing the resolution only. The systematic use of on-off-switching for separating molecules individually in a spatially stochastic manner, as first done in PALM, added a new dimension to superresolution fluorescence microscopy.  Eric’s work became public slightly before identical concepts were published by the groups of Xiaowei Zhuang (Harvard) and Sam Hess (U Maine), who called them STORM and FPALM, respectively. One year earlier, the groups of Paul Selvin (Urbana-Champaign), Nobert Scherer (Chicago), and Rainer Heintzmann (King’s College London) had come very close to this concept as well, bearing witness to the fact that, in 2005, far-field fluorescence nanoscopy was no longer an exotic topic. In any case, the works published in 2006 by Eric, who meanwhile had moved to Janelia Farm, Xiaowei Zhuang, Sam Hess and their teams gave the field an enormous boost.  ‘Superresolution’ fluorescence microscopy or ‘nanoscopy’ as we understand it today, fundamentally differs from the diffraction-limited one in that the separation of adjacent structural details is not accomplished just by focusing the light in use, but through the transient occupation of two different molecular states. In my view, this principle is so fundamental that it offers many opportunities to develop a whole range of powerful superresolution variants. I am delighted to see how this field is unfolding and how it is advancing the life sciences as well as other areas.  While 4Pi microscopy did not overcome the diffraction barrier *per se*, both STED-like and stochastic single-molecule-based variants of subdiffraction resolution fluorescence microscopy have now been implemented with ‘4Pi’ arrangements in order to provide the largest axial and hence 3D-resolution possible. Meanwhile all major microscope manufacturers offer ‘superresolution’ microscopes as their flagship products.  In 2009 our daughter Charlotte was born. We are so grateful for having three wonderful children who enrich our lives and give us huge inspiration and motivation for the work that we do.  In September 2014, I shared, with Thomas Ebessen and Sir John Pendry, the 2014 Kavli Prize in Nanoscience. The celebrations in Oslo were highly memorable for me, my wife and the children. As it turned out a month later, they were actually an exquisite “practice” for my family since another big event was to come. On October 8, I was informed by the Secretary of the Royal Swed- ish Academy, Prof. Staffan Normark, that I would share the 2014 Nobel Prize in Chemistry with Eric Betzig and W.E. Moerner. The Nobel week was a truly unique experience not only for my family but also for many members of my group and friends who joined us in Stockholm.  I was fortunate over the years to be accompanied by further outstanding students and postdoctoral scientists who have joined this quest, each making important contributions: Martin Schrader, Alexander Egner, Andreas Schönle, Jörg Bewersdorf, Volker Westphal, Lars Kastrup, Jan Keller, Gerald Donnert, Johann Engelhardt, and Christian Eggeling, to name just a few. Although the work done by my colleagues and myself has received the utmost recognition, there is still much to be done, and I still have a lot of passion contributing to the advancement of this field.  Today, now co-responsible for the new generation of scientists, I often wonder whether the way in which science is organised sufficiently encourages young researchers to pursue unusual research topics. So far I have kept myself well out of administrative duties and science policy-making – to the delight of my group, but not always that of my colleagues. But one thing remains close to my heart: I have recently launched an initiative to explore new ways of helping young researchers to embark on risky projects at an early stage of their career. And since many of my colleagues in the Max Planck Society also find this idea very interesting, I am optimistic that this endeavour will work out as well. |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** | [SH]  [Stefan Hell] Ja, hello  [Adam Smith] This is Adam Smith calling from Nobelprize.org  [SH] Hi, Adam, hello.  [AS] Congratulations of course on the award of the Nobel Prize.  [SH] Thanks, thanks.  [AS] May I ask just what you were doing when the news came?  [SH] I was reading a paper actually, and going through the details of a paper.  [AS] And, your initial reaction on hearing the news?  [SH] It was a total surprise. I couldn’t believe it. The first moment I thought it was perhaps a hoax or so. But I remembered the voice of Professor Normark, and I realised there were other people around and he said he would confirm by email, and so it’s serious. First of all I couldn’t really believe it. But then I gradually realised that it’s true.  [AS] And what was the first thing you did after you’d received the news and found out that it was true?  [SH] Ja, I read the paragraph that I wanted to read to the end [Laughs]. And then I called up my wife and tried to reach some of the people who are close to me.  [AS] But that’s marvellous, that’s true dedication, staying with the paper. I guess that’s what makes you successful. You defied conventional wisdom in thinking that you could break the diffraction barrier. What gave you the courage to try that?  [SH] I think it was insight. So, I had realised that, that was my view at least, that so much physics happened in the 20th century that it is impossible that there is no say phenomenon, or physical chemistry phenomenon, that would allow you to overcome the diffraction barrier that was coined in 1873 or so. So I felt that there must be something, a kind of phenomenon that leads you beyond the barrier. And so I got kind of convinced that there must be something, and so I tried to find something and eventually I found ways to overcome that limit.  [AS] Clearly you are deeply passionate about science. Do you consider science fun?  [SH] Yes, absolutely. So I love to be a scientist. I’ve always enjoyed being curious. I’ve always enjoyed doing challenging things and also challenging common wisdom. So, I think that’s something a scientist can do because a scientist works at a border, at the edge of science, at the edge of knowledge, and so there’s a lot of fun of reaching out and thinking about things that other people didn’t think about. And so it has a kind of exploratory notion, kind of adventurous part in it.  [AS] I think people often neglect that, that really you can be in the lab and be just as adventurous as people exploring the deep ocean.  [SH] Absolutely, and also creative. I mean, you can imagine that something works. I imagined there would be a way to crack the diffraction barrier. But of course I didn’t know exactly how it would work, but I had a gut feeling that there must be something and so I tried to think about it, to be creative. And that initial phase of the development, it was a creative act. In the end of course you have to prove that it’s not just imagination. It’s not just a theory or just a thought – it is true. And there is where the hard work comes in. And you have to really prove that the way you think about it is right. And that took, of course, some time and a lot of development.  [AS] Thank you very much indeed. That’s marvellous. I guess now that you’re going to be swamped by people like me asking you questions. How does that prospect …  [SH] Well, I locked myself in, and so I’m OK so far.  [AS] How very sensible of you. You sound like you’re well in control of this situation. So, I wish you a very enjoyable day. I hope the following hours are enormous fun. Thank you very much for speaking to us now.  [SH] Thank you very much for calling.  [AS] My pleasure. Thank you. Bye bye.  [SH] Bye. |
| **Interview** |  |
| Q4 | Could you describe your Nobel Prize-awarded work in simple terms? |
|  | Stefan Hell: I discovered that a light microscope can see sharper pictures that we believed in the 20th century, more than 100 years. This is important because light microscopy is the only way by which you can look into transparent things, important things such as cells, living cells or tissue. And the fluorescence light microscope that I invented allows you to see details that you couldn’t see before. But the basic discovery was that in the 20th century, before I made my work, people believed that you have to separate things if you looked into the microscope if you want to see them separately, if you want to see the details, by focusing the light very sharply. But what I discovered is that you can overcome this barrier by making the molecules, that we look at, distinct different. If the molecules are different you can see things separately and you can tear them apart. That was the discovery, that has led now to microscopes that are not limited by the focusing of light anymore, but you can see things at much greater detail because the separation of things is done by the molecules. |
| Q2 | At what point did you realize your work was a breakthrough? |
|  | Stefan Hell: There were many points, it wasn’t just a single point. First of all, you have to get the idea that you can do something rather like light microscope because people believe that this would not be possible, and it was fully accepted in the 20th century. So, I think the first point was when I had this kind of conviction evolving in me that there must be a way to do something about this diffraction barrier, as it is called. Then I was convinced continuing and then the second big event was when I had the first concrete idea. Actually, I had when I was a post-doc in Åbo in Finland, when I realised that you can separate fluorescence molecules that are closer together than this 200 nanometer barrier but turning them on and off, playing with the brightness of them. I discovered that you can use a phenomenon, but it is called stimulated emission and this phenomenon stimulated emission does nothing but keep molecules dark, shuts the molecules off. So, I used this phenomenon of stimulated emission to shut molecules off, turn them off to see that they break one. This was the second really important event in this journey.  The third important event was when I realised that this is doable, you can really do it in practice. This phenomenon of turning off really works the way I anticipated. The fourth event was when we got the first pictures that demonstrated – yes, you can see details in much much smaller scales because you can keep things dark and if you have two things that you cannot separate normally, because they hit at the same time with a big blob of light, you turned this one off to see this one and the you turn this one off to see that one. And that was, as it turned out, to be fundamental discovery and with that you can see now, in principal, down to the molecular scale and in practise now we are about 20 nano meters, 30 nano meters, but it is clear that the resolution will increase further and further if you perfect this state transition is a technical term of going for a brighter dark state or between two different states. |
| Q3 | What brought you to science? |
|  | Stefan Hell: It is fascination for what I am doing. It’s also … I am very much attracted to understanding things at a fundamental level. So, if I cannot break down things to very very simple phenomenon, so I can explain it to everyone, I feel that something is missing, I have not got the point. It is deeply rooted in my heart if this is true or not, for science in general, that is questionable, but that is my attitude. When I was a student, I spent hours over a certain phenomenon, sometimes days, just to understand at the really bottom, at the very basics and before I hadn’t grasped it, I didn’t stop. It is part of my personality and I have realised that my way of thinking about the problem with diffraction barrier is definitely correct. Of course, I had many people surrounding me at that time saying that this is not going to lead anywhere. But I had thought so much about the principles and also about protect the flaws, I always thought Could there be a flaw?, Could there be a flaw?  Could there be a flaw because I didn’t go out public saying – I thinking all the times of flaws, but that is what I did. I realised that I had ruled out flaws, conceptual flaws, and the only problem remaining was technical. It is very important to understand that you have separate or distinguish conceptual flaws and technical flaws. The conceptual flaws they probably are going to stay, you cannot overcome them. But technical problems you can overcome over time with development, technology progresses, there are better detectors, better lasers and so on. That is not a flaw, that is a technical shortcoming and this you can solve. I realised that my concept doesn’t have a conceptional flaw, so conceptually it is definitely working. I could easily stand up and say I am convinced that this I going to work because the problem that you are talking about are not conceptual, they are not for the metal they are technical so there will be metal detectors, will be better and so on. Eventually it will work and that kept me going. |
| Q5 | Who is your role model, and why? |
|  | Stefan Hell: I didn’t have explicitly a role model some say scientist that I wanted to be like that person. I think this is also part of the success story, because you have to find your own way. It is very important that you do something from the bottom of your own heart and you find yourself in what you do and the work. But of course, I admire scientists who had come up with fundamental and interesting ideas, with new ideas. Clearly to some extent, [Einstein](https://www.nobelprize.org/prizes/physics/1921/einstein/facts/) has always been a role model in a way of course, there is no comparison with him. He was unique. But seeing things differently, not caring about conventions, these are elements in his attitude of course that should be role models for all of us scientists and they are of course. But I also have great admiration for people like [Richard Feynman](https://www.nobelprize.org/prizes/physics/1965/feynman/facts/). I read his book and also his biographies and when I was a student, I found him very inspiring, his attitude. He explained quantum mechanics in his own way and that was really great because it gave you some insights and that led him to do it in a new way of coming up with new things, quantum electrodynamics. These are role models in a way, but of course I have to do my own thing and I have to do it very much in my own way. |
| Q14 | What are your future plans? |
|  | Stefan Hell: I definitely will continue because it is kind of part of my personality, if you like, so I am still attracted hearing discoveries, seeing things from a different angle, yes, I think it is kind of, how shall I put it, a kind of commitment saying no. But after I got the prize, I felt, maybe at some point I have to think about something else, open text books again and check out what else is there that people believe and has been repeated many times, many times, many times and everyone believes it. Maybe it is not the end of it or maybe something important has been missed out. I think it is very interesting to see how science works, this in retrospect, I didn’t expect it honestly. A lot of it is perception, I couldn’t have imagined that, so sometimes people and science perceive things in a wrong way and just taking a different angle and explaining things or sorting out things from a different angle – all of a sudden can open new aspects that were totally unanticipated and this is so important.  I think it is important to go back again and say okay now we have this phenomenon, we have this thing, but we have to take a different angle, maybe a different way of looking at it. Still, it has to be of valued one, no doubt, but taking a different angle is so important. I think, breaking the diffraction barrier is a fantastic example because, as I said, the the problem was that people saw, the scientists saw, you have to distinguish features, so to speak, by the focusing of light, the phenomenon of focusing of light and because they cannot focus light any better than a certain diameter you cannot do it. The breaking of the diffraction barrier happened because, I would back off and say oh, what do we have here, do we have to separate by the focusing of light or can we separate by the molecular states? Once we separated the molecular states, the focusing of light doesn’t matter or hardly matters. It is so important to understand, to just taking a different angle all of a sudden, make things look totally differently. |

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| **Chemistry\_2024-2000** | |
| **ID** | 0330 |
| **Biographical** | **Ancestry**  I was born on June 24, 1953 at Parks Air Force Base in Pleasanton, California, a city in the eastern region of the San Francisco Bay Area. Although this qualifies me as a California native, after only six weeks, my parents took me back to their home in San Antonio, Texas. From birth, my parents referred to me by my initials (“W. E.”) because my father and grandfather both had William as their first name, and my parents did not want me to be burdened with various diminutive nicknames such as “Little Billy,” “Billy Jr.,” etc. In their memory, I have continued to use initials for situations where a formal name is not required. Although initials are not uncommon in Texas, almost everywhere else in the world I have had to explain the use of initials, and most quickly adjust to this relatively strange nickname. As Johnny Cash stated in his classic song, “A Boy Named Sue,” it could have been worse: my parents could have named me “Sue.”  My mother, Bertha Frances Robinson Moerner, was born as an only child on August 23, 1924 in Winnsboro, Texas, to Elbert Esco Robinson and Callie Nannie Jane Harrison. Because my grandmother was one of the many Harrison siblings, half siblings, and step siblings, much of my early childhood years were spent with a variety of great aunts, great uncles, and numerous first and second cousins. Callie was a talented seamstress and a great cook, and often after school she took care of me and a couple of other cousins. My grandfather worked in a cottonseed mill in Winnsboro before the family moved to San Antonio in the mid-1940s. I remember him most as a hard-working carpenter who could build almost anything out of wood, and I owe part of my skill in building things to him.  My father, William Alfred Moerner, was born on July 21, 1922 in San Antonio, Texas, to William Emil Moerner and Florence Nightingale Lehmberg. My grandmother and grandfather spoke German as well as English, and she provided a loving home and great meals for my father and his brother and sister. Florence had a fine voice for singing, and my years singing with her and my father in the Woodlawn Methodist Church choir laid the foundation for my love of music to this day. My grandfather, a veteran of World War I, spent most of his career at the San Antonio City Public Service Board working up from ditch digger to office clerk and storekeeper, and in retirement he became an avid beekeeper. He was born in the Texas Hill Country, the son of Robert Hermann Moerner and Emma Hoting Moerner. My great-grandfather Robert was a well-known Methodist minister in Art, Texas, and he was the first Mörner (anglicized to Moerner) to emigrate to the United States from Schlanow in the Province of Brandenburg, Germany, in March 1885. Robert’s parents, Karl Ludwig Mörner and Augusta Wilelmina Gurkasky, were also from the Brandenburg area. Little is known about their ancestors, and any specific connection to the long line of Mörners in Germany and in Sweden is still waiting to be elucidated.  My parents (Fig. 1) fell in love during the years of World War II, something which greatly punctuated and influenced their lives and education. My mother studied English at the University of San Antonio and the University of Texas, and finished her studies at Trinity University in San Antonio. She subsequently spent many years as an English teacher at Fox Technical High School. My father went to college at Trinity University to study physics and mathematics, and I remember him telling me stories about launching rockets with the chemistry professor. His studies were interrupted by terms of service in the Air Force where he was trained as a bombardier and a navigator, but he did not see direct conflict. Mostly he and my mother traveled around to live at various military training locations such as Biloxi, Mississippi and Mobile, Alabama. They married on September 8, 1945, which makes me a member of the baby boomer generation. My father enlisted again during the Korean conflict, and this time additional training in electronics earned him an important but high stress position working on Special Weapons in New Mexico and Arizona. Unfortunately, he contracted scarlet fever and donated two units of blood at once, which led to medical problems that ended up being treated at Parks AFB in California; this explains why my parents were there in 1953 when I was born. After our return to San Antonio, my father joined the U.S. Civil Service at Kelly Air Force Base, where he was a professional/scientific photographer for many years. I clearly remember the photo lab there, which combined the optics of the cameras and enlargers with the vats of chemicals required to process silver halide emulsions into large photographs. **Early Childhood and Public School Education** I remember little from my earliest years, other than happy birthdays with all the cousins and some fun camping trips to the Texas Gulf Coast with my parents and the family of my cousin Randy Seaman. Randy’s mother, Emmy Lee Givens Seaman, was a first cousin to my mother and they were like sisters. My parents doted on me at every turn and taught me so much about the value of education and hard work – contributions to my development that were priceless. I profited from beginning school just after the launch of the Sputnik satellite in 1957 and the subsequent increase in public support for studying math and science.  I attended public schools in San Antonio for my education, beginning with Madison Elementary for the first grade in 1959. I do remember playing on the winning baseball team that year, even though I was not a stellar player. More importantly, my future interest in electronics began at this time when my parents gave me a diode or transistor radio kit in the first grade. Since my parents moved to the northwest side of San Antonio that year, the rest of the elementary years occurred at Maverick Elementary. It was an important realization made during the third grade that I was very near-sighted, and when I got glasses, a new world was opened to me. I remember the “New Math” in the fourth grade, which was based on worksheets with empty cells and it was necessary to figure out the function and to fill in the empty cells at the same time. My teacher asked me to help explain this new way of learning math to the class. These years were also filled with the Boy Scouts, a formative and important experience for me that taught me much about the outdoors, leadership, character, and accomplishment, and I have many great memories of camping and hiking. I received my Eagle Scout Award in 1967 from my father (the Scoutmaster of Troop 235) and my grandfather Moerner, both Eagle Scouts.  It was during the grades 7–9 at Longfellow Junior High School that additional key interests blossomed. I played clarinet and then bassoon in the orchestra, and I sang with a wonderful guitar/folk music group named the Acadians. I also served on the stage crew during assembly events to satisfy my desire to know how things were working behind the scenes. One course I remember vividly was Mrs. Gates’ 9th grade geometry class not only because I enjoyed all the material thoroughly, but also all the kids who also were good at math were in this class; this formed a critical nucleus for many close friends in high school later. These years also included me helping my father repair things, especially cars. I remember one time we were changing the oil in his car, and I dutifully removed the plug to drain the oil into a pan, put the oil away, and then carefully started pouring oil into the fill hole on the top of the engine without replacing the plug first! This kind of silly mistake was met with hilarious laughter from me and my father, the right way to deal with a simple error. How else does one really learn, without trying and making errors now and then? Learn from the mistake and move on! I also won the Grand Prize at the 8th grade science fair by measuring the viscosity of various motor oils using timed flow out of a calibrated pipette. This was a key early exposure to experimental science for me, involving many careful measurements and preparation to determine if multi-weight motor oils were truly different from single weight oils (Fig. 2). I am embarrassed to admit that I pipetted these oils with my mouth, a dangerous practice that has since been abandoned! Partly due to the influence from my father, I also furthered my interest in electronics by reading parts of my father’s book, *Elements of Radio*, by Abraham and William Marcus, which eventually led to various electronics projects. There were so many mysteries to understand! There were also mistakes to be made – I clearly remember when I got shocked working to repair the washing machine in my bare feet.  It was some time during the Junior High School years that my “Clubhouse” appeared in the back yard of our home. This was a steel box-like shed structure my father likely acquired from military surplus. It was too short to stand up in, so my grandfather Robinson, my father, and I built a wooden vertical extension with push-out windows for ventilation and greater height. This was the place for experiments from the chemistry sets my parents bought for me! Simple acid/ base reactions, burning metal powders, pH measurements, etc. were all great fun, mostly taken from *The Golden Book of Chemistry Experiments*, by Robert Brent. I also had a wonderful time picking up huge old discarded TV sets, and I proceeded to unsolder every single component and sort them into capacitors, resistors, diodes, coils, etc.  My subsequent three years at Thomas Jefferson High School (Jeff) produced a further explosion of activities and interests. My mother always said, “It is not enough just to be smart, but you also have to be well-rounded.” She also said “Idleness is the Devil’s workshop,” so I stayed busy. The grand campus of Jeff, with 980 plus students in each grade, was built in the classical Spanish Moorish design in 1932 just after the Depression, and today it is a Texas Historical Landmark. I was an outstanding student (one of five Valedictorians) who greatly enjoyed all the sciences: chemistry, biology, and physics, as well as many extracurricular clubs like BiPhyChem, the Math Club, and even the Russian Club. I was also involved in the debate team, and I played bass clarinet and bassoon in the band! All of these activities were great fun, such as playing and marching at the football games, serving as Editor of the literary magazine *Each Has Spoken*, or serving as the Captain of the “On the Spot” high school current events contest on the local TV station. My outside scientific interests in electronics grew even more with Heathkit shortwave radios, and my father and I (WN5ARM) got our amateur radio licenses in 1970 with the help of the Radio and Electronics Club at Jeff run by the physics teacher, Mr. Greenburg. Although I got distracted by other interests in college, amateur radio formed a foundation for my later work with lasers and it is still one of my favorite hobbies.  In the summer of 1970 between Junior and Senior years, a critical event occurred: I attended a National Science Foundation Student Science Training Program at Loyola University in New Orleans, Louisiana. This stimulating program covered Electronics, Chemical Kinetics, and Computer Science, setting the stage for my multidisciplinary interests later! We lived in the dorms, went to class, performed laboratory experiments, and had field trips to many nearby refineries and research centers. This experience set the stage for my future research interests and I loved every minute.  My most significant action during high school was the decision to follow the advice of a forward-thinking school counselor, Mrs. Blanche Rodriguez, who encouraged me to apply for a Langsdorf Engineering Fellowship to attend Washington University in St. Louis, Missouri. This fateful step was far out of the usual for my fairly provincial Texas-centered family, and it ultimately caused me to bypass the local Texas universities, thus broadening my perspective and world view. **Undergraduate Education** The summer before starting college I got a real job, as a statistical computer programmer for a biostatistician, Dr. Richard G. Domey, at the University of Texas Medical School in San Antonio. This was a useful way to expand my FORTRAN programming skills learned the summer before to write programs to analyze marine science data. My first publication was subsequently written with Dr. Domey and reported a factor analysis of the distributions of marine organisms in the Kuroshio Sea of Japan.  Heading off to Washington University as a Langsdorf Engineering Fellow was a watershed experience. “WashU” is one of the few universities with full tuition scholarships for top students (and I would not have been able to attend without the scholarship), plus the Langsdorf Program provided a nucleus of compatriots who were also friendly competitors at times. I joined a wonderful community of engineering students and truly relished every aspect of college, from the stimulating and challenging classes, to my many friends inside and outside engineering, to the further expansion of my interests in math and science. Even though it was tough on my parents for me to leave Texas, they were so supportive through it all, and not only paid room and board, but also sent me spending money every month. A further twist of fate during the WashU years occurred when I had to register for the draft. This was the last draft for the Vietnam War, and I was number 66 (!), but during the physical exam they learned that my eyes were so nearsighted that I received a “4F” – I could not be drafted and I could not enlist! Thus my path was clear for uninterrupted study.  I started out as an electrical engineering (EE) major, and the goal was to build on my interests in electronics and radio to pursue an engineering career. (I came in with Advanced Placement credits in Chemistry, so my love of this subject was postponed to later.) Many of the EE courses such as linear systems, microwaves, and communication theory were truly fun – the power of science combined with the need to make something with a purpose was thrilling. However, as an engineering major, I had to take many prerequisite courses in physics and mathematics. The introduction to physics course taught by Prof. James Burgess was so exciting to me, that I decided to add physics as a major. I still clearly remember taking quantum mechanics from a great physicist, Prof. Richard Norberg, another strong influence on me. My mathematics courses started out with a very difficult challenge, “Advanced Calculus,” which involved many proofs with epsilons and deltas. However, the subsequent mathematics courses, such as linear algebra, differential equations, complex variables, and group theory were quite enjoyable. Well, it turned out that at WashU, if a student satisfied all the requirements for a degree, then the student would graduate with that degree, even if some of the prerequisite courses were shared between more than one degree program! The many courses I took, combined with advanced placement coming in, made it possible for me to graduate in 1975 with three degrees: Bachelor of Science in Physics with top honors, a Bachelor of Science in Electrical Engineering with top honors; and an *Artium Baccalaurei* (A. B.) in Mathematics *summa cum laude*. I was proud to be recognized with the Ethan A. H. Shepley Award by the university.  On the fun side, one highlight was living in an engineering suite as a sophomore and spending some time helping Ed Snyder build a harpsichord. Another was meeting R. Burr Stewart while listening to Glenn Miller records during senior year; he became my lifelong best friend. We had many memorable experiences, even including flying with him as he piloted a small plane across the state of Missouri. Music continued to be another favorite hobby, and I returned to singing in church choirs at Second Presbyterian Church at the advice of another engineering friend, W. Wayne Ritchie, the Assistant Organist. It was very exciting to perform the Fauré Requiem and other great oratorios at Second Pres, because the choir gets to sing from a balcony just in front of a great pipe organ. During this time, I also received my second nickname, “Weo,” from a south St. Louis German-American father of a girlfriend, who just could not call me “W. E.”! He decided to call me “Weo” as this was the slogan of the A&P grocery stores at the time, which stood for “Where Economy Originates.” Well, at least this was printed on the grocery bags, so I got some free advertising! This moniker is still used by my family and closest friends.  I had the great pleasure to begin serious experimental research in college when I joined the group of Prof. James G. Miller in the Physics Department. His group has pioneered many advances in the area of ultrasound, from fundamental studies in solids to extensive applications of ultrasound to medicine, especially cardiology. In many ways, Jim Miller was a critically important mentor, and my experience in Jim’s lab set the stage for me to continue to excel and to pursue research in experimental solid state physics afterward. Not only did he teach me more about the scientific method, ferromagnetism, and ultrasound, but he also ran a group of graduate students and postdocs where the environment welcomed me as an undergraduate in every way. I spent many years working in the lab, as well as multiple summers and winter recesses, and proudly coauthored several papers. One particular topic gave me early exposure to the problem of extraction of specific physical quantities from experiments: The project involved determination of ultrasonic velocities from resonator frequency shifts, which I worked on under the tutelage of Harry Ringermacher, who was collaborating with Jim Miller while completing his PhD research under Dick Norberg. Knowing about ultrasonics was helpful to the single-molecule detection work in 1989, because one of the validations used ultrasonic strain waves to modulate the single-molecule absorption lines. Jim Miller was also a close personal friend, and he often patiently listened to me wax about the various personal situations that are common for an intense and precocious undergraduate, something I will never forget. **Graduate Studies** I applied to a number of graduate schools across the country to continue my studies in physics, and I was attracted to the Physics Department at Cornell University due to its particular excellence in solid state physics. Thus, in the fall of 1975, an engineering friend, Pat Jeffries, and I set out to share an apartment “Far above Cayuga’s waters” in Ithaca, New York. This began an intense six years of study, where I joined a cadre of outstanding graduate students herded by an excellent faculty. Outside the lab, Ithaca taught me a great deal about dealing with truly cold weather and snow, and I learned a bit about how to ski at the nearby Greek Peak; not a lot more than a hill, but just right for a beginner from Texas. I also enjoyed the strong seasons, the many opportunities for hiking and camping in the beautiful country nearby, and two years in a close relationship with Burr Stewart’s sister, Ann. Continuing my music interests, I played harpsichord with a pickup group of physics graduate students, sang in the Cornell Glee Club for one semester, spent a number of years singing with the local group Ithaca A Cappella, and even performed the role of Sir Joseph Porter with the Cornell Gilbert and Sullivan troupe! But these were all secondary to my focus on my graduate research.  At Cornell I was supported by a National Science Foundation Graduate Fellowship for the first few years, and I started out with my desk in the famous low temperature physics group headed by Prof. [Robert Richardson](https://www.nobelprize.org/nobel_prizes/physics/laureates/1996/richardson-facts.html), Prof. John Reppy, and Prof. [David Lee](https://www.nobelprize.org/nobel_prizes/physics/laureates/1996/lee-facts.html). Bob Richardson was eventually on my thesis committee, and I had the pleasure and honor to assist this inspiring scientist and educator in a special public evening lecture on low temperature physics in 1978. Years later, Bob always asked about my work when we met at meetings of the National Academy of Sciences. Even though the low temperature group was filled with exciting physics mostly about the fascinating properties of superfluid 3He (the area which would win the Nobel Prize in 1996 for Lee, [Doug Osheroff](https://www.nobelprize.org/nobel_prizes/physics/laureates/1996/osheroff-facts.html), and Richardson), in January 1976 I became attracted to the far-infrared spectroscopy group of Prof. Albert J. Sievers III.  Al Sievers’ lab was a truly exciting environment in which to study solid state physics. His work addressed almost any process that occurred in the far infrared (FIR) region of the spectrum, broadly defined, from 1 cm–1 to the edge of the visible. This huge range covered phonons, impurity modes in solids, superconductivity, internal vibrational modes of molecules, vibrational modes on surfaces, and many other physical effects. As such, the students and postdocs in Al’s lab worked on a wide range of projects, mostly using the tools of spectroscopy with lamellar and Michelson interferometers as well as lasers. His style of mentoring provided much flexibility for the students, as he believed that graduate students should find their own way in order to develop true independence, a key value that I use today with my own group. Al proposed a number of novel but risky small projects to get me started, on bismuth as a FIR source, on indium antimonide as a spin-flip Raman laser, etc. and most of these failed yet taught me a great deal, mostly through Al’s physical insight and the tutelage of the other Sievers’ group members like Rick Aurbach, Yves Chabal, Aland Chin, Eric Schiff, Don Trotter, and many others. One project involved the superconducting properties of palladium hydride created by ultrahigh pressure hydrogen gas. Because hydrogen can cause damage to hardened metals, I had to condense liquid hydrogen into a large hardened BeCu cell, and then vaporize the liquid by heating, which yielded hydrogen gas pressures in the range of 25,000 psi!  Eventually our interests turned to the infrared vibrational modes of molecular impurities in alkali halide crystals. I specialized in the perrhenate ion, ReO–4, which can substitute for the anion in a variety of alkali halide crystals, customgrown in the physics department facility. It turned out that particular CO2 laser lines were resonant with one vibrational mode of this molecule. I spent a very fruitful time studying the optical properties of this system with the methods of high resolution laser spectroscopy, starting out with optical saturation effects. This work was a continuation of work by a previous graduate student, Andrew Chraplyvy, who was a great colleague, mentor, friend, and collaborator. After his graduation from Al’s lab in 1978, Andy worked at General Motors Research Labs developing fully tunable infrared lasers, and he brought a bunch of these back to Cornell for some highly focused spectroscopy sessions with me on several occasions. These two week visits were very intense and truly great fun, and we accomplished a lot. We needed these tunable lasers, because we wanted to study the process termed “photophysical spectral hole-burning” that we had discovered in the low temperature inhomogeneously broadened absorption profile of ReO–4 in crystalline hosts like KI and RbI. Hole-burning here means that at the irradiation frequency, the absorption would reduce, producing a dip or “hole,” a relatively new spectroscopic effect which had been observed for electronic transitions in the visible around 1974 but was quite new for molecular vibrational modes (Fig. 3). Andy’s tunable lasers were put to good use, and I developed a dual CO2 laser approach as well, where one laser burns the hole, and a second one is tuned over a very small range on the order of 10 MHz to scan the shape of the hole.  A tough setback occurred for me in 1979 when my mother passed away from the breast cancer she had fought for some years. This left me very sad because she was so central to my earlier upbringing. Such events do affect an only child more than children with siblings, but I learned early on that it is best to pick up and move on in the face of events out of my control. I worked to help my father recover, and soon he chose to find a new wife, eventually marrying Maria Esther Soto Vertiz from Mexico in 1981, who ended up taking care of him for 30+ years, something for which I am very grateful. Back in Ithaca, I threw myself into my thesis research on ReO–4 in solids, and the writing of my massive 619 page dissertation was completed in the fall of 1981. I received the M.S. and Ph.D. degrees in physics from Cornell University in 1978 and 1982, respectively, formally in solid state physics, but the connection of this work to infrared vibrational modes in solids placed this research a bit closer to what is termed chemical physics.  It is clear that my experience with hole-burning in the infrared was instrumental to my next job along the way, which also concerned this process. **Independent Professional Career: IBM Research** I enjoyed research so much that after Cornell I decided to join one of the great corporate research labs which were churning out many advances at the time. I bypassed an offer from Bell Laboratories and instead joined the IBM Research Division in San Jose, California as a Research Staff Member. My experiences at Cornell motivated me to join an intense program there to develop spectral holeburning in the visible for frequency domain optical storage. Thus in the fall of 1981 I drove across the country to the San Francisco Bay Area where I have lived ever since (with the exception of three years in southern California described below). The physical science community at IBM Research was led by George Castro, Ed Engler, and Jerry Swalen, and am happy that these three took a chance on me. I had the opportunity to interact with several great laser spectroscopists, including Gary Bjorklund (who taught me laser FM spectroscopy, the ultrasensitive method used later to detect a single molecule), Marc Levenson, Roger Macfarlane, and Bob Shelby, and with top chemists such as Grant Willson, Robert Twieg, and many others, all set in the background of a company laboratory with a goal to be “famous for our science and technology.” This was a wonderfully stimulating interdisciplinary environment ideally matched to my broad background, because it was easy to change hats between being a physicist to being an engineer, and I had an opportunity to become a physical chemist as well. Because Roger and Bob covered inorganics for hole-burning, I decided to concentrate on hole-burning in organic materials, stepping into the role of Dietrich Haarer who had recently returned to Germany, and I took on the responsibility for learning about electronic transitions, photophysics, and photochemistry of organic molecules in solids. I benefited greatly from temporary visits from Dick Caldwell from the University of Texas at Dallas and Bryan Kohler from Wesleyan University, who both taught me much physical chemistry in the mold of the great book, *Modern Molecular Photochemistry*, by Nick Turro. Even though researchers at IBM had very small groups under their direct control, the research environment thrived in the 1980s due to the cross-fertilization and collaborative interactions between different scientists. I was fortunate that I was encouraged to publish much of my work, as this kept the door open to academia later.  A major life event occurred in 1982, when I decided to join the Gilbert and Sullivan Society of San Jose to pursue my musical interests, and to get out of the lab to meet people (women, to be more exact). After my partner in the operetta *Gondoliers* dropped out, the Director, Ruth Stein, paired me with her daughter, Sharon Stein, who had just graduated from Oberlin College and was working 72 hour shifts as a counselor at a facility for abused children. She was a perfect partner, friendly, talented, smart, and vivacious, with the long arms required to meet mine during the many dances, and we quickly fell in love! Sharon turned out to be the eldest of the “G&S” family of San Jose, in that her mother, and her father, Michel Stein, both physicians, directed and produced many, many shows as they helped found the group some years before. They welcomed me quickly into the family and we rented a house in San Jose. When Sharon got a letter to join a graduate program in psychology in Denver, it was time to propose to prevent her from leaving! We were married in her parents’ back yard on June 19, 1983 (Fig. 4). Sharon then pursued a Master’s in psychology at San Jose State University followed by a Ph.D. at the Pacific Graduate School of Psychology in Menlo Park, California. We lived in Fremont, California for some years before moving back to the Almaden Valley in San Jose in 1986, when the IBM lab moved from the San Jose disk drive plant site to its beautiful present home in the hills above the Almaden Valley.  The 1980s were a time of intense and exciting research at IBM as well as good times for me and Sharon with our friends and family. An earthquake in 1984 energized me to re-acquire my ham radio license to be able to communicate during emergencies, and Sharon later got her license, too. She used her excellent communication and organizational skills to become District Emergency Coordinator for the Santa Clara Valley Section, covering 13 cities. A close friend from IBM and ham radio, Dave Palmer, and his wife, Darcy, were common companions on radio and camping trips. After spending some years working on spectral hole-burning, in roughly 1987 I began the critical experiments (first with Tom Carter) which eventually led to the first optical detection and spectroscopy of a single molecule in a solid with Lothar Kador in 1989. This was mostly at the prescient urging of my IBM managers to “do the best science possible.” But 1989 was filled with other major events, too. Sharon and I traveled to Japan for a lovely vacation in September, but then the Loma Prieta Earthquake hit a few weeks later on October 17, interrupting all our activities. Sharon led the hams in the local response, and I worked to get the lab cleaned up. All this was stressful enough, but two weeks later I returned to Japan for a major business trip to give roughly five talks in five days. I learned my physical limits at this time!  The following year, with Sharon’s dissertation completed at last, it became time to grow our family, and early in 1991 she was “great with child” during her Ph.D. oral examination while I stood by with the car ready to rush her to the hospital! This was not necessary, and on a foggy and cold morning a month later I did drive her to the hospital where our son, Daniel Everett Moerner, was born on February 10, 1991. It has been a glorious and thrilling time to see Daniel grow from an incredibly bright boy to a brilliant and caring man.  Things did not go so well for IBM in the early 1990s, and after the major corporate loss of $8 billion in 1993, I began to consider alternate career paths. Although the research was highly stimulating, I felt a need to be able to expand my mind and my projects beyond my small lab at IBM Almaden. With the support of my managers, I took an 8 month sabbatical in 1993–1994 to become a Visiting Guest Professor in the lab of Prof. Dr. Urs P. Wild at ETH-Zürich, Switzerland. This was a time of more stimulating single-molecule research and was a mind-expanding experience which showed me that I could see a path for me other than being a lifelong IBMer, and that I should now tackle the challenge of making a career change after 13 years at IBM. Sharon and Daniel had a great time charging around Switzerland, albeit temporarily interrupting her career as a clinical psychologist. **Moving to Academia** With the quarterly profit fixation that was occurring at IBM plus the push to even pay the top scientists to leave, in 1994 I began interviewing for faculty positions in the western U.S. so that we could be close to Sharon’s family. I wanted to work for an organization centered on knowledge: the generation of new knowledge as well as the transfer of knowledge to young minds. I received offers from both physics and chemistry departments, but the best one came from the Department of Chemistry and Biochemistry at the University of California, San Diego. My family took the leap and moved south to La Jolla, California, in 1995, where I took a chaired position at UCSD as Distinguished Professor of Physical Chemistry. What followed was a key transformation, where I was able to broaden my research interests and applications of single molecules to include biological systems and biophysics, encouraged by the department chair Katja Lindenberg and key faculty mentors such as Kent Wilson. I enjoyed many professional interactions at UCSD, notably with Larry Goldstein on kinesin, with Bruno Zimm on polymer dynamics, with Jay Siegel on new molecules for photorefractivity, and with [Roger Tsien](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/2008/tsien-facts.html) on the study of variants of the green fluorescence protein for which he won the Nobel Prize in 2008. It was at UCSD, in Urey Hall, that the first imaging of single copies of yellow fluorescent protein was performed with Rob Dickson. We did live near the beach, but did not have a view of the spectacular ocean; in fact I was only able to find time to go to the beach a couple of times a year. But I still love the views of the ocean from the Torrey Pines State Reserve and the fact that it is possible to put your feet into the ocean on January 1 in La Jolla!  In 1997, having proved that I could teach and win additional grants to support my research, Harvard and Stanford decided to work to attract me away from UCSD. This was a very difficult decision to make, given that I had only recently arrived at UCSD. However, Sharon had been working with difficult patients and with her family still back in the Bay Area, we decided to move to Stanford in 1998. Sharon and Daniel moved first so that he could start second grade in Los Altos as quickly as possible, and I commuted back and forth from San Diego to Palo Alto for an entire year, designing and overseeing my new laboratory design and construction. I began as Professor in the Department of Chemistry at Stanford, then I became the Harry S. Mosher Professor of Chemistry in 2002, followed by Professor, by courtesy, of Applied Physics in 2005, and I then served as the Chair of the Chemistry Department (2011–2014). Throughout this time at both UCSD and Stanford, I have been blessed by wonderful graduate students, postdocs, and collaborations, and my work has focused on single-molecule imaging, spectroscopy, trapping, and related areas of biophysics, nanophotonics, and materials.  In every way, I have been extremely fortunate in my life in that I have been able to pursue my passions in science and in my personal life with general good health. For thirty-one years to the present, my wife has been my steadfast companion and rock of support, and I cannot thank her enough. My son, a deep thinker specializing in philosophy, has been a true joy and fellow music lover throughout, and I am very happy that he could experience Stockholm as well (Fig. 5). My parents and Sharon’s parents did not live to see my Nobel Prize, but their love and support were truly instrumental in this accomplishment. I look forward to continuing my career as a perpetual student, not willing to fit into any specific box and continuing to learn new areas of science. |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** | [WM]  [William Moerner] Hello  [Adam Smith] Hello, this is Adam Smith calling from Nobelprize.org, the website of the Nobel Prize in Stockholm.  [WM] Oh, hello.  [AS] Congratulations on the award of the Nobel Prize.  [WM] Thanks, thank you very much. I’m just totally thrilled.  [AS] Well, first of all, you’re in Brazil I gather?  [WM] That’s right, I’m at a conference.  [AS] How did you hear the news of the award?  [WM] I heard the news when my wife called me at about 7am this morning, Brazil time, because she’d been called by the Associated Press, and so that’s how I heard.  [AS] What was your first reaction on hearing from her that you’d been awarded the prize?  [WM] Ah, well I was just incredibly excited and thrilled, and of course your heart races, and you say “Oh, can this be? Can this be?” My life .. [unclear] .. has been recognised, I’m incredibly fortunate. And so I had that feeling of “Oh, what do I do now?” because you have to decide am I going to this meeting, do I have to get on a plane and fly to California. So there’s lots of things that all of sudden change when you get such exciting news and I’m incredibly happy about the recognition of the field, especially of all the workers and all the scientists at many places around the world who have contributed to the effort.  [AS] Are you going to change your programme for the day or are you just going to go to the conference as usual?  [WM] I can’t go to the meeting right now. It’s much better to talk to people like you and try to explain what’s so exciting about this development.  [AS] Really a great pleasure to speak to you, thank you very much.  [WM] Thank you.  [AS] Have a good day. Bye bye.  [WM] Bye. |
| **Interview** |  |
| Q4 | Can you explain your work in easy-to-understand terms. |
|  | The work that I did to receive the Nobel Prize, involved detecting single molecules, individual molecules. What you want to think about, is that a single molecule is incredibly tiny, just a few nanometers in size and those single molecules are now being used as light sources, which are used to make an image of a structure or an object inside a bacterium or a cell at extremely high resolution. Because they are so small, they can go beyond the diffraction limit of light, it is ultimate sort of limit, that has, until now, made microscopes be very fuzzy in pictures that they take. |
| Q2 | At what point did you realize your work was a breakthrough? |
|  | We realized that our work was going to be very important, when we started seeing amazing surprises from these individual molecules. You might think that “Oh, I look at an individual molecule at low temperatures and maybe they are all the same and so there is nothing really interesting”, but the molecules were behaving differently. One molecule would jump from one colour to another or wave links to another or they would turn on and off and blink in interesting ways. And it is because of the molecules do this, that they have an individual behaviour that we were very excited. Going beyond this previous limit of not being able to see single molecules, opened up a whole new arena of new science, new chemistry and new applications – such as the super resolution microscopy. |
| Q3 | What brought you to science? |
|  | When I was growing up, I became very interested in science, partly because of the influence of my parents who were encouraging me in science and mathematics in every way. I spent time taking apart old television sets, I learned how to do experiments in chemistry in the backyard. In terms of the sort of the stimulus from my parents and my father’s ability to repair things, I grew to love working and fixing things and figuring out how they work. So, those directed me towards science and the really important thing to think about is, how does this really work, how does everything in our world and nature, how does it behave and that’s kind of the sort of the passion for understanding. That really makes science exciting for me. |
| Q5 | Who is your role model, and why? |
|  | You know, when I think about role models, I can imagine many answers to that question. There is a lot of people that have been influenced me, my mentors in college and graduate school, but if I go back and think about the scientist that inspired me, I would have to say someone like Michael Faraday, who spent a great deal of time influencing multiple fields of science. That is contributing to chemistry and contributing to physics and contributing to materials and so forth and so that’s kind of guided me a lot, that idea of learning different areas of science and putting them together to push back some boundaries. It is kind of something that has been exciting me all along. |
| Q9 | What were you doing when you heard you had been awarded the Prize in Economic Sciences? |
|  | When that day occurred, I was at a conference in Brazil and I was getting ready go to the talks for this particular meeting on fundamentals of light matter interactions. So, what a wonderful conference to attend. I was not contacted directly by the Nobel Foundation because it was too difficult to reach me, so I received a phone call from my wife and I had just gotten dressed for the meeting but then I had to change clothes quickly to get ready for the interviews and so forth that occurred right after, so I was very surprised, excited and thrilled to hear about the prize. |

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| **Chemistry\_2024-2000** | |
| **ID** | 0331 |
| **Biographical** | **E****arly Years in Europe**  I was born in Vienna, Austria in 1930 [1]. Already before the Nazis entered Austria in 1938, our life had changed significantly, even from the viewpoint of an eight year old. Among our neighbors were two boys of ages comparable to my brother, Robert, and me. They were our “best friends,” and we played regularly with them. In the spring of 1937, they suddenly refused to have anything to do with us and began taunting us by calling us “dirty Jew boys” when we foolishly continued to try to interact with them.  On March 13, 1938, the German Nazi troops crossed the border into Austria and completed the *Anschluss*, the “joining” of Austria with Nazi Germany. A few days after the *Anschluss*, my mother, brother, and I left Austria by train for Switzerland on a “ski vacation.” My parents had been concerned about Hitler’s takeover of Austria for some time. For the previous three years, my Aunt Claire, who had studied in England, had been teaching English to me and my brother Bob. Well before March 13, train tickets had been purchased and a bed-and-breakfast “pension” had been reserved in Zurich.  The most traumatic aspect of our departure was that my father was not allowed to come with us and had to give himself up to be incarcerated in the Vienna city jail. In part, he was kept as a hostage so that any money we had would not be spirited out of the country. My mother reassured my brother and me, saying that nothing would happen to him, though of course she herself had no assurance that this was true.  At the end of the summer, the visas finally arrived, passage was booked, and the three of us were ready to leave for the United States. Although there had been no news from my father, he miraculously turned up at Le Havre a few days before our ship was scheduled to depart for New York. From my point of view, it was exactly what my mother had told me would happen: We would all go to America together. When my father joined us in Le Havre, Bob and I asked him what jail had been like. He told us that he had been treated well in jail and cheerfully described how he had passed the time teaching the guards to play chess. One aspect of my father’s personality, which strongly influenced both my brother and me, was to make something positive out of any experience. **A New Life in America** We arrived in New York Harbor early in the morning on October 8, 1938, and I stood on the deck watching the Statue of Liberty appear out of the mist. The symbolism associated with the Statue of Liberty may seem trite today (and somewhat deceptive given our present immigration policies), but in 1938 it was special for me. Most of the immigration formalities had been taken care of by Uncle Edu, so that a few hours after our arrival we boarded a train to Boston. During our initial weeks in the United States, we were lodged in a welcoming center in Brighton, where a large mansion had been transformed into an interim home for refugee families. We were taught about America (what it was like for foreigners to live in Boston), given lessons to improve our English, and aided in the steps required to be allowed to remain in the United States as refugees.  Soon we were ready to start a new life. My parents rented a small apartment in Brighton (part of Greater Boston), and Bob and I immediately entered the local public schools, as we had in Zurich. Motivated by their concern for our education, my parents then moved to Newton (a suburb of Boston), where the schools were recognized as superior to the Boston public schools. My parents bought a small house in a pleasant neighborhood in West Newton, and I attended the Levi F. Warren Junior High School.  My junior high teachers soon realized that I was bored with the regular curriculum, so they let me sit in the back of the classroom and study on my own. What made this experience particularly nice was that another student, a very pretty girl, was given the same privilege, and we worked together. The arrangement was that we could learn at our own pace without being responsible for the day-to-day material but had to take the important exams. Several dedicated teachers at Warren Junior High helped us when questions arose, particularly with science and mathematics. With this freedom, we explored whatever interested us and, of course, did much more work than we would have done if we were only concerned with passing the required subjects. **Beginning of Scientific Interests** When we moved to Newton, Bob was given a chemistry set, which he augmented with materials from the high school laboratory and drug stores. He spent many hours in the basement generating the usual bad smells and making explosives. I was fascinated by his experiments and wanted to participate, but he informed me that I was too young for such dangerous scientific research. My plea for a chemistry set of my own was vetoed by my parents because they felt that this might not be a good combination – two teenage boys generating explosives could be explosive! Instead, my father had the idea of giving me a Bausch and Lomb microscope. Initially I was disappointed – no noise, no bad smells, although I soon produced the latter with the infusions I cultured from marshes, sidewalk drains, and other sources of microscopic life. I came to treasure this microscope, and more than 60 years later it is still in my possession. One especially rewarding aspect of my working with the microscope was that my father, who was a thoughtful observer of nature, spent a lot of time with me and was always ready to come and look when I had discovered something. I had found an exciting new world and looked through my microscope whenever I was free. The first time I saw a group of rotifers I was so excited by the discovery that I refused to leave them, not even taking time out for meals. They were the most amazing creatures as they swam across the microscope field with their miniature rotary motors. (The rotifers come to mind today in relation to my research on the smallest biological rotatory motor, F1-ATPase.) My enthusiasm was sufficiently contagious that I even interested some of my friends. It was a special occasion when they came to my house and looked at the rotifers through the microscope.  This was the beginning of my interest in nature study, which was nurtured by my father and encouraged by my mother, even though it was still assumed that I would go to medical school and become a doctor. One day my closest friend, Alan MacAdam, saw an announcement of the Lowell Lecture Series (a Boston institution, originally supported by a Brahmin family – the Lowells), which organized evening courses on a wide range of subjects at the Boston Public Library that were free and open to the public. The series that had caught Alan’s eye was entitled “Birds and Their Identification in the Field,” to be given by Ludlow Griscom, the curator of ornithology at the Museum of Comparative Zoology at Harvard University. Alan and I occasionally walked in the green areas in Newton, particularly the Newton Cemetery, and looked for birds with my father’s old pair of binoculars. Together we attended the first lecture, which had a good-sized audience, although it was not clear whether most of the people came simply to have a nice warm place in winter rather than because of their interest in birds. I was enthralled by the lecture, which provided insights into bird behavior and described the large number of different species one could observe within a 50 mile radius of Boston. I was amazed that it was possible to identify a given species from “field marks” evident even from a glimpse of a bird, if one knew how and where to look. Alan did not attend the subsequent lectures, but I continued through the entire course. At the end of the fourth or fifth lecture, Griscom came up to me and asked me about myself. He then invited me to join his field trips, and a new passion was born. From that time on, my treasured microscope was relegated to a closet, and I devoted my free time to observing birds on my own, as well as with Griscom and his colleagues, with the Audubon Society, and other groups that organized field trips.  I entered Newton High School in the fall of 1944 but soon found that I did not have the same supportive environment as in elementary and junior high school. My brother, Bob, had graduated from Newton High School two years before and had done exceedingly well. My teachers presumed that I could not measure up to the standards set by my brother. Since I had always been striving to keep up with Bob and his friends, this just reinforced my feelings of inferiority. Particularly unpleasant were my interactions with the chemistry teacher. When my brother suggested I compete in the Westinghouse Science Talent Search, the chemistry teacher, who was in charge of organizing such applications, told me that it was a waste of time for me to enter and that it was really too bad that Bob had not tried instead. However, I talked to the high school principal and he gave me permission to go ahead with the application. I managed to obtain all the necessary papers without encouragement from anyone in the school. A test was given as part of the selection process, and I found a teacher who was willing to act as proctor. I did well enough to be invited as one of the 40 finalists to Washington, D.C. Each finalist had a science project for exhibition in the Statler Hotel, where we were staying. My project was on the lives of alcids, based in part on a trip to the Gaspé Peninsula and some of the field studies I had made during New England winters. The various judges spent considerable time talking with us, and the astronomer Harlow Shapley, who was the chief judge, charmed me with his apparent interest in my project. I was chosen as one of two co-winners. (At that time, there was one male and one female winner; Rada Demereck and I were co-winners.) The visit to Washington, D.C. was a formative experience. We met President Truman, who welcomed us as the future leaders of America. Moreover, winning the Westinghouse Talent Search made up for the discouraging interactions with some of my high school teachers. Their attitude contrasted with that of my fellow classmates, who voted me “most likely to succeed.” **College Years** I entered Harvard in the fall of 1947. There was never any question about my wanting to attend Harvard and I did not apply to any other school. In addition to the Westinghouse scholarship, I received a National Scholarship from Harvard to cover the cost of living on campus. Otherwise I would have had to live at home to save money. I would not have minded this, since I was not a rebellious teenager eager for independence and distance from my parents. However, as I soon discovered, much of the Harvard experience took place outside of classes at dinner and in evening discussions with friends.  At first I still intended to go to medical school but changed my mind during my freshman year. My teenage ornithological studies, fostered by Griscom and Donald Griffin, with whom I had gone on a field trip to Alaska, had already introduced me to the fascinating world of research, where one is trying to discover something new (something that no one has ever known). I began to think about doing research in biology, but concluded that to approach biology at a fundamental level (“to understand life”), a solid background in chemistry, physics, and mathematics was essential. I enrolled in the Program in Chemistry and Physics. This program, unique to Harvard at the time, exposed undergraduates to courses in both areas at a depth that they would not have had from either one alone. Although I shopped around for advanced science courses to meet the rather loose requirements, I also enrolled in Freshman Chemistry because it was taught by Leonard Nash. A relatively new member of the Harvard faculty, Nash had the deserved reputation of being a superb teacher. Elementary chemistry in Nash’s lectures was an exciting subject. A group of us (including DeWitt Goodman, Gary Felsenfeld, and John Kaplan – my “crazy” roommate, who became a law professor at Stanford) had the special privilege that Nash spent extra time discussing with us a wide range of chemical questions, far beyond those addressed in the course. The interactions in our group, though we were highly competitive at exam times, were also supportive. This freshman experience confirmed my interest in research and the decision not to go to medical school.  Harvard provided me with a highly stimulating environment as an undergraduate. I enrolled in a wide range of courses, chosen partly because of the subject matter and partly because of the outstanding reputation of the lecturers; these courses included one in *Democracy and Government* and another in *Abnormal Psychology*. More related to my long-term interests were George Wald’s *Molecular Basis of Life* and Kenneth Thimann’s class on plant physiology with its emphasis on the chemistry and physiology of growth hormones (auxins) in plants. Both professors were inspiring lecturers and imbued me with the excitement of the subject. These courses emphasized that biological phenomena (life itself) could be understood at a molecular level, which has been a leitmotif of my subsequent research career. Wald’s course also introduced me to the mechanism of vision, which led to my first paper on a theoretical approach to a biological problem [2].  Rather than taking the *Elementary Organic* course taught by Louis Fieser, I enrolled in Paul Bartlett’s Advanced Organic. It taught the physical basis of organic reactions. It was an excellent course, though difficult for me because one was supposed to know many organic reactions, which I had to learn as we went along. At one point, Bartlett suggested that we read [Linus Pauling](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1954/pauling-facts.html)‘s *Nature of the Chemical Bond*, which had been published in 1939 based on his Baker Lectures at Cornell. *The Nature of the Chemical Bond* presented chemistry for the first time as an integrated subject that could be understood, albeit not quite derived, from its quantum chemical basis. The many insights in this book were a critical element in orienting my subsequent research in chemistry.  At the end of three years at Harvard I needed only one more course to complete the requirements for a bachelor degree. During the previous year I had done research with Ruth Hubbard and her husband, [George Wald](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1967/wald-facts.html). (Although Hubbard was scientifically on par with Wald, she remained a Senior Research Associate, a nonprofessorial appointment, until very late in her career when she was finally “promoted” to Professor. This was not an uncommon fate for women in science.) I mostly worked with Hubbard on the chemistry of retinal, the visual chromophore. When I brought up my need to find a course for graduation, Wald suggested that I enroll in the physiology course at the Marine Biological Laboratory in Woods Hole, Massachusetts. This course was one of the few non-Harvard courses that was accepted for an undergraduate degree by the Faculty of Arts and Sciences. The physiology course was widely known as a stimulating course designed for postdoctoral fellows and junior faculty. The lectures in the course by scientists who were summering at Woods Hole, while doing some research and enjoying boating and swimming, offered students a state-of-the-art view of biology and biological chemistry.  In considering graduate school during my last year at Harvard, I had decided to go to the West Coast and had applied to chemistry at the University of California at Berkeley and to biology at the California Institute of Technology (Caltech). Accepted at both, I found it difficult to choose between them. Providentially, I visited my brother, Bob, who was working with J. R. Oppenheimer at the Institute of Advanced Studies in Princeton, New Jersey. Bob introduced me to Oppenheimer, and briefly to [Einstein](https://www.nobelprize.org/nobel_prizes/physics/laureates/1921/einstein-facts.html). When Oppenheimer asked me what I was doing, I told him of my dilemma in choosing between U.C. Berkeley and Caltech for graduate school in chemistry or biology. He had held simultaneous appointments at both institutions and strongly recommended Caltech, describing it as “a shining light in a sea of darkness.” His comment influenced me to choose Caltech, and I discovered that Oppenheimer’s characterization of the local environment was all too true. Pasadena itself held little attraction for a student at that time. However, camping trips in the nearby desert and mountains and the vicinity of Hollywood made up for what Pasadena lacked.  At Caltech, I joined the group of [Max Delbrück](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1969/delbruck-facts.html) in biology. He had started out as a physicist but, following the advice of [Niels Bohr](https://www.nobelprize.org/nobel_prizes/physics/laureates/1922/bohr-facts.html), had switched to biology. With [Salvador Luria](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1969/luria-facts.html) and others, he had been instrumental in transforming phage genetics into a quantitative discipline. His research fascinated me, and I thought that working with such a person would be a perfect entrée for me to do graduate work in biology.  After I had been in the Delbrück group for a couple of months, Delbrück proposed that I present a seminar on a possible area of research. I intended to discuss my ideas for a theory of vision (how the excitation of retinal by light could lead to a nerve impulse), which I had started to develop while doing undergraduate research with Hubbard and Wald. Among those who came to my talk was [Richard Feynman](https://www.nobelprize.org/nobel_prizes/physics/laureates/1965/feynman-facts.html); I had invited him to the seminar because I was taking his quantum mechanics course and knew he was interested in biology, as well as everything else. I began the seminar confidently by describing what was known about vision but was interrupted after a few minutes by Delbrück’s comment from the back of the room, “I do not understand this.” The implication of his remark, of course, was that I was not being clear, and this left me with no choice but to go over the material again. As this pattern repeated itself (Delbrück saying “I do not understand” and my trying to explain), after 30 minutes I had not even finished the 10-minute introduction and was getting nervous. When he intervened yet again, Feynman turned to him and whispered loud enough so that everyone could hear, “I can understand, Max; it is perfectly clear to me.” With that, Delbrück got red in the face and rushed out of the room, bringing the seminar to an abrupt end. Later that afternoon, Delbrück called me into his office to tell me that I had given the worst seminar he had ever heard. I was devastated by this and agreed that I could not continue to work with him. It was only years later that I learned from reading a book dedicated to him that what I had gone through was a standard rite of passage for his students – everyone gave the “worst seminar he had ever heard.”  After the devastating exchange with Delbrück, I spoke with [George Beadle](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1958/beadle-facts.html), the chairman of the Biology Department. He suggested that I find someone else in the department with whom to do graduate research. However, I felt that I wanted to go “home” to chemistry and asked him to help me make the transfer.  Once in the Chemistry Department, I joined the group of John Kirkwood, who was doing research on charge fluctuations in proteins, as well as on his primary concern with the fundamental aspects of statistical mechanics and its applications. I undertook work on proteins and the research started out well.  In the spring of 1951, as I was getting immersed in my research project, Kirkwood received an offer from Yale. Linus Pauling, who was no longer taking graduate students, asked each student who was working with Kirkwood whether he would like to stay at Caltech and work with him. I was the only one to accept and, in retrospect, I think it was a very good choice. Initially, I was rather overwhelmed by Pauling. Each day upon arriving at the lab, I found a hand-written note on a yellow piece of paper in my mailbox which always began with something like “It would be interesting to look at …” As a new student I took this as an order and tried to read all about the problem and work on it, only to receive another note the next day beginning in the same way. When I raised this concern with Alex Rich and other postdocs, they laughed, pointing out that everyone received such notes and that the best thing to do was to file them or throw them away. Pauling had so many ideas that he could not work on all of them. He would communicate them to one or another of his students, but he did not expect a response. After I got over that, my relation with Pauling developed into a constructive collaboration.  Given Pauling’s interest in hydrogen bonding in peptides and proteins, he proposed that I study the different contributions to hydrogen bonding interactions for a biologically relevant system, but I felt this would be too difficult to do in a rigorous way. Because quantum mechanical calculations still had to be done with calculating machines and tables of integrals (something difficult to imagine when even log tables have followed dinosaurs into oblivion), we had to find a system that was simple enough to be treated by quantum mechanical theory. I chose the bifluoride ion (FHF-) because the hydrogen bond was the strongest known, the system is symmetric, and only two heavy atoms are involved. (Today, such “strong” hydrogen bonds have become popular in analyses of enzyme catalysis, although there is no convincing evidence as to their role.)  The time at Cal Tech was very rewarding, all the more so because of the intellectual and social atmosphere of the Chemistry Department. The professors – like Pauling, Verner Schomaker, and Norman Davidson – treated the graduate students and postdoctoral fellows as equals. We participated in many joint activities that included trips into the desert, as well as frequent parties held at our Altadena house, where Feynman would occasionally come and play the drums. **Postdoctoral Sojourn in Oxford and Europe** One day in October 1953, Pauling came into the office I shared with several postdocs and announced that he was leaving in three weeks for a six-month trip and that “it would be nice” if I finished my thesis and had my exam before he left. This was eminently reasonable, since I had finished the calculations some months before and I had received a National Science Foundation (NSF) postdoctoral fellowship to go to England that fall. Pauling’s “request” provided just the push I needed, even though the introduction was all I had written thus far. With so much to get done, I literally wrote night and day, with my friends typing and correcting what I wrote. In this way, the thesis was finished within three weeks, and I had my final PhD exam and celebratory party before Pauling left. After a brief visit with my parents in Newton, I took an ocean liner for England and arrived shortly before Christmas 1953.  During my two years in Oxford as a postdoctoral fellow, I spent much of the time traveling throughout Europe and taking photographs; they are the basis of several exhibitions. Also, I spent more time thinking about chemical problems than actually solving them. My aim was to find areas where theory could make a contribution of general utility in chemistry. I did not want to do research whose results were of interest just to theoretical chemists. Reading the literature, listening to lectures, and talking to scientists like Don Hornig and the Oxford physicist H. M. C. Pryce, I realized that magnetic resonance was a vital new area. Chemical applications of magnetic resonance were in their infancy and it seemed to me that nuclear magnetic resonance (NMR), in particular, was a field where theory could make a contribution. I concluded that a quantum mechanical approach could aid in interpreting the available experimental results and propose new measurements. **Five Years at the University Of Illinois: NMR and Coupling Constants** As my postdoctoral fellowship in Oxford (1953–1955) neared its end, I was looking for a position to begin my academic career in the United States. With my growing interest in magnetic resonance, I focused on finding an institution that had active experimental programs in the area. One of the best schools from this point of view was the University of Illinois, where Charles Slichter in Physics and Herbert Gutowsky in Chemistry were doing pioneering work in applying NMR to chemical problems. The University of Illinois had a number of openings in Chemistry at that time because the department was undergoing a radical renovation; several professors, including the chairman Roger Adams, had retired. Pauling recommended me to the University of Illinois and the department offered me a job without an interview. I accepted the offer from Illinois without visiting the department, something unimaginable today with the extended courtships that have become an inherent part of the academic hiring process. The University of Illinois offered me an Instructorship at a salary of $5000 per year; the department offered nothing like the present-day start-up funds, and I did not think of asking for research support.  Having had such a good time as a postdoctoral fellow traveling in Europe, I was ready to get to work, and Urbana-Champaign seemed like a place where I could concentrate on science with few distractions. The presence of four new instructors – Rolf Herber, Aron Kupperman, Robert Ruben, and me – plus other young scientists on the faculty, such as Doug Applequist, Lynn Belford, and E. J. Corey, led to a very interactive and congenial atmosphere.  I focused a major part of my research on theoretical methods for relating nuclear and electron spin magnetic resonance parameters to the electronic structure of molecules. The first major problem I examined was concerned with proton-proton coupling constants, which were known to be dominated by the Fermi contact interaction. What made coupling constants of particular interest was that for protons that were not bonded to each other, the existence of a nonzero value indicated that there was an interaction beyond that expected from localized bonds. In the valence bond framework, which I used in part because of my training with Pauling, nonzero coupling constants provide a direct measure of the deviation from the perfect-pairing approximation. To translate this qualitative idea into a quantitative model, I chose to study the HCC’H’ fragment as a function of the HCC’H’ dihedral angle, a relatively simple system consisting of six electrons (with neglect of the inner shells). I believed that it could be described with sufficient accuracy for the problem at hand by including only five covalent valence-bond structures. To calculate the contributions of the various structures, I introduced semi-empirical values of the required molecular integrals. Although the HCC’H’ fragment is relatively simple, the calculations for a series of dihedral angles were time consuming and it seemed worthwhile to develop a computer program. This was not as obvious in 1958 as it is now. Fortunately, the ILLIAC, a “large” digital computer at that time, had recently been built at the University of Illinois. If I remember correctly, it had 1000 words of memory, which was enough to store my program. The actual program was written by punching holes in a paper tape. If you made a mistake, you filled in the incorrect holes with nail polish so that you could continue the program; the output appeared on spools of paper. Probably the most valuable aspect of having a program for this type of simple calculation, which could have been done on a desk calculator, was that once the program was known to be correct, a large number of calculations could be performed without having to worry about arithmetic mistakes.  Just as I finished the analysis of the vicinal coupling constants [3], I heard a lecture by R. V. Lemieux on the conformations of acetylated sugars. I do not remember why I went to the talk, because it was an organic chemistry lecture, and the chemistry department at Illinois was rigidly separated into divisions, which had a semiautonomous existence. Lemieux reported measurements of vicinal coupling constants and noted that there appeared to be a dihedral angle dependence, although the details of the behavior were not clear. The results were exciting to me because the experiments confirmed my theory, at least qualitatively, before it was even published.  As happens too often with the application of theoretical results in chemistry, most people who used the so-called *Karplus equation* had not read the original paper [3] and thus do not know the limitations of the theory. They assumed that because the equation had been used to estimate vicinal dihedral angles, the theory said that the coupling constant depends *only* on the dihedral angle. By 1963, having realized organic chemists tend to write and read Communications to the Journal of the American Chemical Society, I published such a Communication [4]. In it, I described various factors, other than the dihedral angle, that are expected to affect the value of the vicinal coupling constant; they include the electronegativity of substituents, the valence angles of the protons (HCC’ and CC’H’), and bond lengths. The main point of the paper was not to provide a more accurate equation but rather to make clear that caution had to be used in applying the equation to structural problems. My closing sentence, which has often been quoted, was the following: “Certainly with our present knowledge, the person who attempts to estimate dihedral angles to an accuracy of one or two degrees does so at his own peril.”  In spite of my concerns about the limitations of the model, the use of the equation has continued, and the original paper [3] is one of the *Current Contents* “most-cited papers in chemistry”; correspondingly, the 1963 paper was recently listed as one of the most-cited papers in the *Journal of the American Chemical Society* [5]. The vicinal coupling constant model, which was developed primarily to understand deviations from perfect pairing, has been much more useful than I would have guessed. “In many ways my feeling about the uses and refinements of the *Karplus equation* is that of a proud father. I am very pleased to see all the nice things that the equation can do, but it is clear that it has grown up and now is living its own life” [6].  At Illinois, my officemate was Aron Kuppermann. Our instructorship at Illinois was the first academic position for both of us, and we discussed science, as well as politics and culture, for hours on end. Aron and I decided that, although we were on the faculty, we wanted to continue to learn and would teach each other. I taught Aron about molecular electronic structure theory [we published two joint papers on molecular integrals] and Aron taught me about chemical kinetics, his primary area of research. Aron is officially an experimentalist, but he is also an excellent theoretician, as was demonstrated by his landmark quantum mechanical study of the H + H2 exchange reaction with George Schatz. This work was some years in the future (it was published in 1975), but in the late 1950s we both felt that it was time to go beyond descriptions of reactions in terms of the Arrhenius formulation based on the activation energy and pre-exponential factor. My research in this area had to wait until I moved to Columbia University, where I would have access to the required computer facilities. **Move to Columbia and Focus on Reaction Kinetics** During the summer of 1960 I participated in an NSF program at Tufts University with the purpose of exposing high school and small college science teachers to faculty actively engaged in research. Ben Dailey, one of the organizers of the program, asked me one day whether I would consider joining the chemistry faculty at Columbia University, where he was a professor. Because I had already been at Illinois for four of the five years I had planned to stay there, I responded positively. I heard from Columbia shortly thereafter and received an offer to join the IBM Watson Scientific Laboratory with an adjunct associate professorship at Columbia.  The Watson Scientific Laboratory was an unusual institution to be financed by a company like IBM. Although the laboratory played a role in the development of IBM computers, many of the scientists there were doing fundamental research. The Watson Laboratory had been founded in 1945 near the end of World War II to provide computing facilities needed by the Allies. It had a special attraction for me in that it had an IBM 650, an early digital computer, which was much more useful than the ILLIAC because of its greater speed, larger memory, and simpler (card) input. (No more nail polish!) I was to have access to considerable amounts of time on the IBM 650 and to receive support for postdocs, as well as other advantages over a regular Columbia faculty appointment. This was a seductive offer, but I hesitated about accepting a position that in any way depended on a company, even a large and stable one like IBM. This was based, in part, on my political outlook, but even more so on the fact that industry has as its primary objective making a profit, and all the rest is secondary. By contrast, my primary focus was on research and teaching, which are the essential aspects of a university, but not of industry. Consequently, I replied to Columbia and the Watson Lab that the offer was very appealing, but that I would consider it only if it included a tenured position in the chemistry department, even though I agreed initially to be at the Watson Lab as well. Columbia acceded to my request and after some further negotiation, I accepted the position for the fall of 1960.  The environment at the Watson Lab was indeed fruitful, both in terms of discussions with other staff members and the available facilities. I was able to do research there that would have been much more difficult at Columbia. However, not unexpectedly, the atmosphere gradually changed over the years, with increasing pressure from IBM to do something useful (i.e., profitable) for the company, such as visiting people at the much larger and more applied IBM laboratory in Yorktown Heights, essentially doing internal consulting. I decided in 1963 that the time had come to leave the Watson Lab, and moved to the fulltime professorial position that was waiting for me in Chemistry at Columbia. (IBM closed the Watson Lab in 1970.)  I continued research in the area of magnetic resonance after moving to New York. One reward of being at Columbia was the stimulation provided by interactions with new colleagues, such as George Fraenkel, Ben Dailey, Rich Bersohn, and Ron Breslow. Frequent discussions with them helped to broaden my view of chemistry. In particular, my interest in ESR was rekindled by George Fraenkel and we published several papers together, including a pioneering calculation of 13C hyperfine splittings [7]. Although the techniques we used were rather crude, the results provide insights concerning the electronic structure of the molecules considered and aided in understanding the measurements.  My interest in chemical reaction dynamics had deepened at Illinois through many discussions with Aron Kuppermann, as already mentioned, but I began to do research in the area only after moving to Columbia. There were several reasons for this. There is no point in undertaking a problem if the methodology and means for solving it are not available: It is important to feel that a problem is ripe for solution. (This has been a guiding rule for much of my research – there are many exciting and important problems, but only when one feels that they are ready to be solved should one invest the time to work on them. This rule has turned out to be even more important in the application of theory to biology, as we shall see later.) Given the availability of the IBM 650 at the Watson Lab, the very simple reaction, H + H2 → H2 + H, which involves an exchange of a hydrogen atom with a hydrogen molecule, could now be studied by theory at a relatively fundamental level. Moreover, early measurements made by Farkas & Farkas in 1935 of the rate of reaction over a wide temperature range provided important data for comparison with calculations. A second reason for focusing on chemical kinetics was that crossed molecular beam studies were beginning to provide much more detailed information about these reactions than had been available from gas phase or solution measurements. The pioneering experiments of Taylor & Datz opened up this new field in 1955. It made possible the study of individual collisions and the determination whether or not they were reactive. Thus, calculated reaction cross sections, rather than overall rate constants, could be compared directly with experimental data. To do a theoretical treatment of this or any other reaction (including the protein folding reaction), a knowledge of the potential energy of the system as a function of the atomic coordinates is required, as described in my [Nobel Lecture](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/2013/karplus-lecture.html).  Richard Porter, a graduate student with F. T. Wall at Illinois, had done collinear collision calculations for the H + H2 reaction. Much impressed by Porter, I invited him to join my group at Columbia as a postdoctoral fellow. At Columbia, we rapidly developed a semi-empirical extension of the original Heitler-London surface for the H + H2 reaction, based on the method of diatomics in molecules and calibrated the surface with *ab initio* quantum calculations and experimental data for the reaction [8]. This surface, which is known as the Porter-Karplus (PK) surface, has an accuracy and simplicity that led to its continued use in many reaction rate calculations by a variety of methods over the years.  Within the approximation that classical mechanics is accurate for describing the atomic motions involved in the H + H2 reaction and that the semi-empirical Porter-Karplus surface is valid, a set of trajectories makes it possible to determine any and all reaction attributes, e.g., the reaction cross section as a function of the collision energy. The ultimate level of detail that can be achieved is an inherent attribute of this type of approach, which I was to exploit 15 years later in studies of the dynamics of macromolecules.  Recently, I was pleased to learn that our paper was cited by George Schatz [9] as one of the key twentieth-century papers in theoretical chemistry. Schatz states, “The KPS paper stimulated research in several new directions and ultimately spawned new fields.” One of these as cited by Schatz was molecular dynamics simulations of biomolecules, as described in my Nobel Lecture. **Return to Harvard University and Biology** In 1965, it was time to move again. Columbia and New York City were stimulating places to live and work, but I felt that new colleagues in a different environment would help to keep my research productive. I had incorporated this idea into a “plan”: I would change schools every five years and when I changed schools I would also change my primary area of research. It was exciting for me to work on something new, where I had much to learn so as to stay mentally young and have new ideas. The initial qualitative insights obtained from relatively simple approaches to a new problem are often the most rewarding.  I received numerous offers and decided to “return” to Harvard. After I had been at Harvard for only a short time, I realized that if I was ever to again take up my long-standing interest in biology I had to make a break with what had been thus far a successful and very busy research program in theoretical chemistry.  A key, although accidental, element in my choice of a problem for study in biology was the publication of *Structural Chemistry and Molecular Biology*, a compendium of papers in a volume dedicated to Linus Pauling for his 65th birthday. I had contributed an article entitled, “Structural Implications of Reaction Kinetics,” which reviewed some of the work I have already described in the context of Pauling’s view that a knowledge of structure was the basis for understanding reactions. However, it is not my article that leads me to mention this volume, but rather an article by Ruth Hubbard and George Wald entitled “Pauling and Carotenoid Stereochemistry.”  On looking through the article, it was clear to me that the theory of the electronic absorption of retinal and its geometric changes on excitation, which play an essential role in vision, had not advanced significantly since my discussions with Hubbard and Wald during my undergraduate days at Harvard. I realized, in part from my time in Oxford with Coulson, that polyenes, such as retinal, were ideal systems for study by the available semi-empirical approaches; that is, if any biologically interesting system in which quantum effects are important could be treated adequately at that time, retinal was it. Barry Honig, who had received his PhD in theoretical chemistry working with Joshua Jortner, joined my research group at that time. He was the perfect candidate to work on the retinal problem. I will not elaborate on our studies here as they are outlined in my Nobel Lecture. **Hemoglobin: A Real Biological Problem** Another scientific question that appeared ready for a more fundamental investigation was the origin of hemoglobin cooperativity, the model system for allosteric control in biology. Although the phenomenological model of Monod, Wyman, and Changeux had provided many insights, it did not attempt to make contact with the detailed structure of the molecule. In 1971 [Max Perutz](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1962/perutz-facts.html) had just determined the X-ray structure of deoxy hemoglobin, which complemented his earlier results for oxy hemoglobin. By comparing the two structures, he was able to propose a qualitative molecular mechanism for the cooperativity. Alex Rich, now a professor at the Massachusetts Institute of Technology, had invited Perutz to present two lectures describing the X-ray data and his mechanism. After the second lecture, Alex suggested that I come to his office to have a discussion with Perutz. Perutz was sitting on a couch in Alex’s office and eating his customary banana. I asked him whether he had tried to formulate a quantitative thermodynamic mechanism based on his structural analysis. He said no and seemed very enthusiastic, although I was not sure whether he had understood what I meant. Having been taught by Pauling that until one expressed an idea in quantitative terms, it was not possible to test one’s results, I went away from our meeting thinking about the best way to proceed. Attila Szabo had recently joined my group as a graduate student, and the hemoglobin mechanism seemed like an ideal problem for his theoretical skills. The basic idea proposed by Perutz was that the hemoglobin molecule has two quaternary structures, R and T, in agreement with the ideas of Monod, Wyman, and Changeux; that there are two tertiary structures, liganded and unliganded for each of the subunits; and that the coupling between the two is introduced by certain salt bridges whose existence depended on both the tertiary and quaternary structures of the molecule. Moreover, some of the salt bridges depended on pH, which introduced the Bohr effect on the oxygen affinity of the subunits. These ideas were incorporated into the statistical mechanical model Szabo and I developed [10]. It was a direct consequence of the formulation that the cooperativity parameter *n* (i.e., the Hill coefficient) varied with pH. This was in disagreement with the hemoglobin dogma at the time and led a number of the experimentalists in the field to initially disregard our model, which was subsequently confirmed by experiments. **Protein Folding** In 1969 I was invited to spend a semester at the Weizmann Institute and I joined the group of Schneior Lifson. While there, [Chris Anfinsen](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1972/anfinsen-facts.html) visited and we had many discussions of his experiments on protein folding, which had led to the realization that proteins can refold in solution, independent of the ribosome and other aspects of the cellular environment. What most impressed me was Anfinsen’s film showing the folding of a protein with “flickering helices forming and dissolving and coming together to form stable substructures.” The film was a cartoon, but it led to my asking him, in the same vein as I had asked Perutz earlier about hemoglobin, whether he had thought of taking the ideas in the film and translating them into a quantitative model. Anfinsen said that he did not really know how he would do this, but to me it suggested an approach to the mechanism of protein folding. When David Weaver joined my group at Harvard, while on a sabbatical leave from Tufts, we developed what is now known as the diffusion-collision model for protein folding [11]. Although it is a simplified coarse-grained description of the folding process, it showed how the search problem for the native state could be solved by a divide-and-conquer approach. Moreover, the diffusion-collision model made possible the estimation of folding rates. The model was ahead of its time because data to test it were not available. Only relatively recently have experimental studies demonstrated that the diffusion-collision model describes the folding mechanism of many helical proteins [12], as well as some others.  When David Weaver and I developed the diffusion-collision model in 1975, protein folding was a rather esoteric subject of interest to a very small community of scientists. The field has been completely transformed in recent years because of its importance for understanding the large number of protein sequences available from genome projects and because of the realization that misfolding can lead to a wide range of human diseases; these diseases are found primarily in the older populations that form an ever-increasing portion of humanity. Over the past decade or so the mechanism of protein folding has been resolved, in principle. It is now understood that there are multiple pathways to the native state and that the bias on the free-energy surface, due to the greater stability of native-like versus nonnative contacts, is such that only a very small fraction of the total number of conformations is sampled in each folding trajectory [13]. This understanding was achieved by the work of many scientists, but a crucial element was the study of lattice models of protein folding. Such toy models, as I like to call them, are simple enough to permit many folding trajectories to be calculated to make possible an analysis of the folding process and free-energy surface sampled by the trajectories [14]. However, they are sufficiently complex so that they embody the Levinthal problem, i.e., there are many more configurations than could be visited during the calculated folding trajectory. The importance of such studies was in part psychological, in that even though the lattice model uses a simplified representation, “real” folding was demonstrated on a computer for the first time. An article based on a lecture at a meeting in Copenhagen [15] describes this change in attitude as a paradigm of scientific progress. **Origins Of The CHARMM Program** When I visited Lifson’s group in 1969 there was considerable interest in developing empirical potential energy functions for small molecules. The novel idea was to use a functional form that could serve not only for calculating vibrational frequencies, as did the expansions of the potential about a known or assumed minimum-energy structure, but also for determining that structure. The so-called consistent force field (CCF) of Lifson and his coworkers, particularly Arieh Warshel, included nonbonded interaction terms so that the minimum-energy structure could be found after the energy terms had been appropriately calibrated. The possibility of using such energy functions for larger systems struck me as potentially very important for understanding biological macromolecules like proteins, though I did not begin working on this immediately.  Once Attila Szabo had finished the statistical mechanical model of hemoglobin cooperativity, I realized that his work raised a number of questions that could be explored only with a method for calculating the energy of hemoglobin as a function of the atomic positions. No way of doing such a calculation existed. We decided the time was ripe to try to develop a program that would make it possible to take a given amino acid sequence (e.g., that of the hemoglobin alpha chain) and a set of coordinates (e.g., those obtained from the X-ray structure of deoxy hemoglobin) and to use this information to calculate the energy of the system and its derivatives as a function of the atomic positions. This could be used for perturbing the structure (e.g., by binding oxygen to the heme group) and finding a new structure by minimizing the energy. Developing the program a major task, but Gelin had the right combination of abilities to carry it out [16]. He would have faced almost insurmountable difficulties in developing the program (pre-*CHARMM*) if there had not been prior work by others on protein energy calculations. Although many persons have contributed to the development of empirical potentials, the two major inputs to our work came from Schneior Lifson’s group at the Weizmann Institute and Harold Scheraga’s group at Cornell University. The *CHARMM* program is now being developed by a wide group of contributors, most of whom were students or postdoctoral fellows in my group; the program is distributed worldwide in both academic and commercial settings.  Pre-*CHARMM*, while not trivial to use, was applied to a variety of problems. An early application of pre-*CHARMM*was Dave Case’s simulation of ligand escape after photodissociation from myoglobin; a study that was followed by the work of Ron Elber, which gave rise to the locally enhanced sampling (LES) and multiple copy simultaneous search (MCSS) methods now widely used for drug design. **The First Molecular Dynamics Simulation of a Biomolecule** Given that pre-*CHARMM*could calculate the forces on the atoms of a protein, the next step was to use these forces in Newton’s equation to calculate the dynamics. This fundamental development was introduced in the mid-1970s when Andy McCammon joined my group. A basic assumption in initiating such studies was that potential functions could be constructed which were sufficiently accurate to give meaningful results for systems as complex as proteins or nucleic acids. In addition, it was necessary to assume that for these inhomogeneous systems, in contrast to the homogeneous character of even complex liquids like water, classical dynamics simulations of an attainable timescale (10 to 100 ps) could provide a useful sample of the phase space in the neighborhood of the native structure. There was no compelling evidence for either assumption in the early 1970s. When I discussed my plans with chemistry colleagues, they thought such calculations were impossible, given the difficulty of treating few atom systems accurately; biology colleagues felt that even if we could do such calculations, they would be a waste of time.  The original simulation, published in 1977 [17], concerned the bovine pancreatic trypsin inhibitor (BPTI), which has served as the “hydrogen molecule” of protein dynamics because of its small size, high stability, and a relatively accurate X-ray structure; interestingly, the physiological function of BPTI remains unknown. This development, which played an essential role in the Nobel Prize, is described in my Nobel Lecture.  The conceptual changes resulting from the early studies make one marvel at how much of great interest could be learned with so little – such poor potentials, such small systems, so little computer time. This is, of course, one of the great benefits of taking the initial, somewhat faltering steps in a new field in which the questions are qualitative rather than quantitative and any insights, even if crude, are better than none at all. **Epilogue** As I read through what I have written, I see what a fragmentary picture it provides of my life, even my scientific life. Missing are innumerable interactions, most of which constructive but some not so, that have played significant roles in my career. The more than 250 graduate students and postdoctoral fellows who at one time or another have been members of the group are listed in my Nobel Lecture. Many have gone on to faculty positions and become leaders in their fields of research. They in turn are training students so I now have scientific children, grandchildren, and great-grandchildren all over the world. I treasure my contribution to their professional and personal careers, as much as the scientific advances we have made together.  Contributing to the education of so many people in their formative years is a cardinal aspect of university life. My philosophy in graduate and postgraduate education has been to provide an environment where young scientists, once they have proved their ability, can develop their own ideas, as refined in discussions with me and aided by other members of the group. This fostered independence has been, I believe, an important element in the fact that so many of my students are now themselves outstanding researchers and faculty members. My role has been to guide them when problems arose and to instill in them the necessity of doing things in the best possible way, not to say that I succeeded with all of them.  Discussing my scientific family makes me realize that another missing element is my personal family, an irreplaceable part of my life. Reba and Tammy, my two daughters whose mother, Susan, died in 1982, both became physicians (thereby fulfilling my destined role); Reba lives in Jerusalem, Israel, and Tammy lives Portland, Oregon. My wife, Marci, and our son, Mischa, who is an intern at the Harvard Kennedy School, complete my immediate family. As many people know, Marci also plays the pivotal role as the Laboratory Administrator, adding a spirit of continuity for the group and making possible our commuting between the Harvard and Strasbourg labs. Without my family, my life would have been an empty one, even with scientific success. **Postscript** The biography up to this point is based, as already mentioned, on an article published in 2006 [1]. Molecular dynamics simulations have continued their rapid growth as a result of methodological improvements, force field refinements, and the availability of faster computers. The citation of methods for the study of complex systems in this year’s Nobel Prize in Chemistry will have the important consequence of legitimizing simulations and make likely their greater acceptance by experimentalists. The introduction of simplified potential functions, the specific focus of the Nobel Prize, certainly played a role in making possible molecular dynamics simulations of macromolecules. However, I am convinced that the latter are the essential element.  I dedicated my Nobel Lecture to the 244 Karplusians who have worked in my “laboratory” in Illinois, Columbia, Harvard, Paris and Strasbourg. Without them, I would not have received the Nobel Prize in Chemistry. Over the last forty years, many of them have contributed to the methodology and applications of molecular dynamics simulations. I find it curious, as I state in the written version of my Nobel Lecture, that molecular dynamics simulations were not mentioned in the description of the “Scientific Background” of the Nobel Prize. The large community involved in molecular dynamics simulations, which includes all of this year’s Nobel Laureates in Chemistry, has transformed the field from an esoteric subject of interest to only a small group of specialists into a central element of modern chemistry and structural biology. Without molecular dynamics simulations and their explosive development, no Nobel Prize would have been awarded in this area.  There is perhaps a parallel here between the fact that molecular dynamics was not mentioned in the Nobel Prize citation and the citation for Einstein’s Nobel Prize in Physics (1921). He was awarded the Nobel Prize for the theory of the photoelectric effect and not for his most important work, the general theory of relativity, which had already been verified by experiment and was the origin of his worldwide fame as a scientist. Interestingly, when he gave his Nobel Lecture, it was on relativity, even though he knew that he was supposed to talk about the photoelectric effect. Correspondingly, I traced the history of molecular dynamics simulations and their development in my lecture and did not emphasize the development of potential functions for simulations, the focus of the Chemistry Nobel Prize citation. The complex deliberations of the Physics Committee in reaching its decision concerning Einstein’s Nobel Prize are now known because his prize was awarded more than fifty years ago. The public will again have to wait fifty years to find out what motivated the Chemistry Committee in awarding this year’s Nobel Prize. |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** |  |
| **Interview** |  |
| Q4 | Could you explain your Nobel Prize awarded work for young students? |
|  | Martin Karplus: Actually, I have a niece who is 13 years old who is with us here, and we talked a little about it. It turns out at least in the US children that age know a great deal about biology, they know what proteins are, they know what mitochondria are, so I am not sure it’s as difficult to explain as it seems to be implied by the question How do you explain it to a 13 year old? But one of the best things is to take an example of what we were able to do. One of the things that make cells work is that they have little transport systems, they have molecules that have basically two feet, and they walk along reels which are called microtubules and they transport things from one end of the cell to another.  In fact, the Nobel Prize in Physiology or Medicine was given for studying the vesicles, the things that these little engines carry from one part to another, but they just looked at the top part here and the vesicles that are carried. We figured out how a couple of molecules which are basically two globular domains like this, that are connected by a coiled-coil can actually walk and they walk the way we walk, in the sense that you put the left foot forward and the right foot forward, left foot forward and the right foot forward. That is one example of how, although people had studied them experimentally and had static pictures of what they looked like, they couldn’t figure out how they moved their feet, they sort of throw their feet forward and it’s that what is one application of the message that we developed, that it can teach us how molecular motors, as these are called, these are called kinesins, how they work. |
| Q3 | What brought you to science? |
|  | Martin Karplus: I have always enjoyed looking around, looking in nature, seeing things that are around me. When I was young, about nine years old or so, my brother received a chemistry set and so of course I also wanted a chemistry set, but my parents felt that having two chemistry sets in the family, making smells and exploding things was a little too much. So my parents gave me a microscope and what I did was to take sort of the run off on the sidewalk and such and I discovered, looking through the microscope, these little animals, they are called rotifers. They have little discs on the front of them and these discs rotate, and they sort of swim through the water. When I saw that I told my brother and then my father and then I had various of my school friends come and everybody thought that this was really great. That was sort of the beginning of my idea of going into science.  Actually, my family, we come from Austria, and they had left when Austria was taken over by the Germans. My family had always had a physician in there, so that each generation had been a physician because physicians were one of the things that you were allowed to be in Austria even though we were Jewish and since nobody else was interested in being a physician I somehow was designated and when I was little I used to go around and bandage chairs and such. But it was sort of, it wasn’t clear that I wasn’t going to go to med school and go into science even though I was very interested in understanding things and it was really only finally when I started college and got sort of more ideas, but I had a very good chemistry teacher and realized that if you wanted to understand biology you had to learn chemistry and physics and at that point is really when I gave up the idea of medical school and become a scientist. |
| Q9 | What were you doing when you got the message of being awarded the Nobel Prize? |
|  | Martin Karplus: Many people have asked me what was happening when we got the call, actually it was at 5 o’clock in the morning so we were asleep. The telephone is on my wife’s side of the bed so she picked it up and said: “Some call, maybe it’s for you, it wasn’t quite clear” and gave it to me and my first reaction was that when you get calls at 05.30 in the morning it’s usually bad news, maybe that our son was sick or our daughter in Israel, we hear that something has happened there. But little by little I discovered what it actually was, that it was a phone call from Sweden announcing the Nobel Prize and I was, you know, very pleased by that. To be quite honest many people have said that I should have had the Nobel Prize maybe 30 years ago, so actually for a while, until fairly recently, I used to sort of watch at the right time, usually whenever we spent half of our time in Europe and half of our time in the US. If you are in Europe of course the Nobel Prize is announced at a more decent time, you know around 11.30 or so and I used to watch, but the last few years I decided, well, I have sort of given up and so it was a pleasant surprise. |
| Q2 | What has been the most significant breakthrough in your career? |
|  | Martin Karplus: My early work was a breakthrough which is probably as famous as this, this was nuclear magnetic resonance and there is an equation named after me, it’s called the *Karplus equation*. So my life has been a combination of breakthroughs about every five years or so and maybe this will come up later again. I try to do something new and so I have had breakthroughs at various times during my life. And what was selected for the Nobel Prize is pretty arbitrary, so it’s a little hard to say what was the breakthrough. What they cite actually is something that I personally don’t think with a breakthrough but it’s sort of a little part of the important aspect of what I, and now many thousands of people who use the same methods, have done. |
| Q2 | How do you stay creative? |
|  | Martin Karplus: They had the idea that I should stay in a given university only five years and I stayed … I mean after being in Europe I went to Illinois and was there for five years and I went to Columbia and was there for five years, then I was at Harvard for five years, then I actually moved to Paris. My feeling was that it was very good to get a new environment, to start new problems, completely different problems like the first five years at the University of Illinois. I mentioned that I developed this equation and I was focused on nuclear magnetic resonance which was a new technique in chemistry, and I felt that the theoretical approaches could give insights that people didn’t have because it wasn’t sort of worked out. Then when I went to Columbia I started working on chemical reactions and I when I went to Harvard I started working on biological systems and I think that, as having a new environment and starting something new makes it most likely or more likely, maybe a fair answer, that you will really discover something. I would get invited to go to meetings that discuss what I had sort of stopped doing, and the people are doing interesting things, but for me, I had the feeling that yes, I know what is going on, and it doesn’t have the same excitement. Of course, being a professor having students you can still be working in the old area so you don’t suddenly stop publishing and people wonder what is going on while you are developing ideas as to what they are doing is new. I think it’s right if you want to continue to be creative you have to go into something that you don’t understand, otherwise, at least for me, it isn’t very exciting. |
| Q3 | Can you tell us about your passions? |
|  | Martin Karplus: In addition to being a scientist I have two other passions, one is photography and actually I had a exhibit of my photographs in Paris and they have nothing to do at all with the science, some of them were taken in Norway and the exhibit is in the 1950s and 60s. I traveled a lot and took Kodachrome pictures and for a while Emily took pictures of my family and thinking of maybe making up an exhibit from those photographs now that I am sort of better known as a photographer. The other thing is that when we do these calculations, we don’t really do any chemistry, the chemistry that I do do is actually cooking. For many years I used to work in a famous restaurant in France in such for two or three weeks every summer and work in the kitchen and replace the people who were taking their day off. That was the real chemistry that I lik to do and still at home now I do the cooking and my wife does the dishwashing and such. So, I think it is nice if being a scientist when you work, you really work full time. I think that’s one of the things you have realize that you have to work really very hard. You can be smart, but that’s not enough. But for me the very important part is okay. I work very hard when I am doing science, but then I do other things and I do them as well and I think that is a good way of living. It’s also better obviously for your family if you can sort of divide your time a little and we have a chalet in the Haute Savoie where we love to go walking and such. I think that’s … for me at least … somebody has written that actually it’s in the preface of a photobook that every scientist has a secret garden and that’s my secret garden. |

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| **Biographical** | **Family Background**  I was born in Pretoria, the executive capital of South Africa, on 9 May 1947. My mother, Gertrude, was also born in South Africa, in Johannesburg to parents who had emigrated from Czechoslovakia. My father was born in Plungė, Lithuania, and came to South Africa when he was 10 years old. My childhood memories are of having fun and playing with friends and of enjoying family vacations to the seaside in Durban, or to the Kruger National Game Reserve. School was enjoyable but not particularly challenging. I was good with my hands and remember building a model car from fiberglass, powered by a gasoline engine, most likely when I was younger than 13. I also remember hearing about computers for the first time in 1960 and being impressed that they could play chess. **Last Year in South Africa** My parents separated when I was nine years old and I became even closer to my mother. She was very upset one morning in December 1962 when I came home at 2 AM after staying out with friends. I had being playing snooker (a form of pool) with them and I had forgotten to call home. This triggered an event that changed the course of my life: we decided that I was bored with school and that I should try to finish the last two years of school over the summer vacation – in the southern Hemisphere, this is in January and is equivalent to July in Europe. This undertaking was difficult as I needed to pass the matriculation examinations in many subjects that I did not particularly like. Still my mother was paying a lot for the private tutoring and I took it seriously. In March, I passed the matriculation examinations and my mother arranged for me to attend Pretoria University a few months before I turned 16. There, I studied Applied Math, which was easy enough, although the lectures were in Afrikaans, a language I did not know very well. I had time for older friends and played a lot of Klaberjass (or Bela), a bridge-like card game, during lunch break. **London, 11/1963 to 10/1967** After passing my first year exams, I left Pretoria for London on 18 November 1963 to spend the summer vacation with my uncle, Max Sterne, who developed an effective, safe, and reproducible vaccine against anthrax, and my aunt, Tikvah Alper, the discoverer of the prion. This vacation trip may well have been a treat to compensate for how hard I had worked the previous summer vacation.  London was a shock as it seemed so cold and grey but I really enjoyed being close to my uncle and aunt who were established scientists. I also enjoyed a close friendship with a Swiss girl who was an Au Pair in their Earl’s Court home. I quickly decided not to return to South Africa but to continue studying in London, to which my mother agreed. This meant passing the A-level exams in three subjects, so within a month I was studying at Acton Technical College, where I made many new friends. This additional work was necessary even after a year’s study at Pretoria University, as the South African matriculation exam was at the same academic level as the O-levels in England. I needed to work hard but managed to get good marks in three A-level subjects: math, applied math and physics. This was enough to earn me a place at a good university where I would start in September 1964, less than two years after playing snooker and staying out too late.  Meanwhile, my mother came to England with my sister and my brother and our two dogs. This was a much harder transition for her, as she had had a life of privilege in South Africa and now had to earn money to support us. However, in the end the move was good for her children and for her too (my mother became a school teacher at the age of 50 but is still teaching almost 50 years later). For the first few months in London I spent a lot of time glued to my uncle and aunt’s TV set watching the 1964 Winter Olympics. There was no TV in South Africa and I had never seen snow. I also watched the BBC TV lecture series “The Thread of Life” by [John Kendrew](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1962/kendrew-facts.html), a newly minted British Nobel Laureate (Chemistry, 1962). This was a remarkable introduction to molecular biology made just a few years after it became clear that life was highly structured in space and time, just like a clock, but a billion times smaller and infinitely more complicated. I became enamored by the potential power of physics to be useful for life sciences, something that had seemed unimaginable.  This interest in the physics of living system led to my choosing to study at King’s College London, where the tradition of biophysics was strong and the glory of [Maurice Wilkins](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1962/wilkins-facts.html) sharing the 1962 Nobel Prize with [Crick](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1962/crick-facts.html) and [Watson](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1962/watson-facts.html) still fresh. Like school, university was mostly about friends and fun in what was becoming swinging London. I shared a flat in South Kensington with two classmates and spent the summers of 1964 and 1965 in Copenhagen washing dishes and having a wonderful time. College was easy as it was only physics and math and there was almost no classwork apart from exams. I passed the exams by borrowing the meticulous notes of a classmate and hand copying them. My mother sent me on a computer course at Elliott Computers in Borehamwood in North London, where I wrote my first program using paper tape. I had even greater exposure to computing in the summer of 1966 when my Aunt Tikvah, a radiation biologist at Hammersmith Hospital, helped me get a summer job at the Radiation Laboratory in Berkeley, California. There I wrote my first FORTRAN program using punched cards, a huge improvement over paper tape. I also had the most amazing and diverse experiences. It may have been the Swinging Sixties in London, but London was tame compared to Berkeley at the start of the Free Speech movement. **Getting Accepted by Cambridge** These distractions did not deter me from my ambition to do a PhD at the Laboratory of Molecular Biology, the fabled MRC lab in Cambridge where the four British Nobel Laureates had all worked. Thus, in the winter of 1967, I wrote to John Kendrew asking to be considered for entry after graduation (and a summer vacation), in September 1967. His reply was disappointing, saying that there was no space and they could not even consider me. At this point, my two classmates at King’s College, Ivan Bradbury and Peter Bostock, both destined to become very successful science entrepreneurs, convinced me to persist. In my reply to Kendrew, I asked if there was any possibility to join the lab a year later. This time he suggested I come for an interview, which went well, but led to another disappointment: I would be told in a year’s time whether I would be accepted.  This meant wasting a year, and again Ivan and Peter intervened and said I need to go to Cambridge to try to get an answer. Since I was shy by nature, this was really hard for me, but I put on my suit (from my Bar Mitzvah seven years earlier), and drove to the lab in my mother’s red Mini Estate. There I waited outside the offices of [Max Perutz](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1962/perutz-facts.html) and John Kendrew, joint heads of the Structural Studies Division. Max Perutz came towards his office and I bravely accosted him in the corridor saying that I needed to talk. He graciously, and perhaps also somewhat embarrassed, asked me to come into his office. There I said that the uncertainty about my future PhD was wreaking havoc on my ability to study for my final exams (an exaggeration but I needed to justify my rude intrusion). Max said that he needed to discuss the matter with Kendrew and that I should phone on the following Monday.  This did the trick and influenced my life beyond all expectations. When I called a few days later, they had decided to accept me in 1968 and Kendrew said that he would help me find something to do in the interval. Elated, I started to plan a grandiose year of travel that involved Paris, Boston and perhaps Tokyo. This was not to be: Kendrew said that I had to go to the Weizmann Institute to work with Shneior Lifson. Kendrew was on the Scientific Advisory Board of the Institute and had heard about Lifson’s consistent force field. I was not convinced, but then Kendrew sweetened the deal by getting me a Royal Society Exchange Fellowship that was meant for postdoctoral fellows and not fresh graduates such as I was (this was possible as the program was in its first year and there were no candidates). For me, the fellowship meant one thing: four times more money that I had had as an undergraduate. Before I left for Israel, Ivan and Peter helped me spend sixty percent of the money on tailor-made suits, hand-made shirts, silk ties, hand-knitted Lisle socks, a Brenell tape recorder, and top-of-the-line skin diving equipment. **Watershed Year in Rehovot, 10/1967 to 8/1968** I arrived in Israel by boat on Friday 13 October 1967, on the eve of Yom Kippur, and had to spend two nights in a hotel in Haifa so that I could release my trunks from Customs before proceeding to Rehovot. There, Shneior and Hannah Lifson accepted me as family and helped me in every possible way. I moved into the student residence and started to work with Arieh Warshel, who was already married but who also lived in Clore House. There is little doubt that the subsequent year was the real watershed in my life (perhaps because I had arrived on Friday the 13th?) with three momentous events: (1) I wrote the computer program with Arieh that enabled us to use the consistent Force Field to calculate properties of any molecule. (2) I met my wife, Rina, at a Christmas Party, 10 weeks after I arrived in Rehovot; (3) I applied Cartesian coordinate energy minimization to the two known protein x-ray structures. A vivid memory is checking the second derivative matrix of cyclohexane by printing out the 54-by-54 table of analytical and numerical derivatives and covering the floor with these computer printouts. I also remember building, with Yuval Eshdat, a model of lysozyme from brass Watson-Kendrew components. This was so tedious that putting the coordinates in the computer seemed obvious. Later that year, in August 1968, Rina and I married in Israel and together drove to London from Piraeus with my mother, sister Ruth Rettie and brother Jonathan Levitt, in the same red Mini. I was just 21 years old and had planted the seeds for a full family life as well as decades of future scientific research. **Phd and Children in Cambridge, 8/1968 to 9/1972** We arrived in Cambridge in September 1968, rented a small house in Derby St., Newnham (opposite the bakery that is still there) and I started to work at the Laboratory of Molecular Biology (LMB) under Dr. Robert Diamond, the supervisor assigned to me by Kendrew and Perutz. Diamond was a theoretician and computer expert focused on developing tools to improve modeling of protein structure from electron density. His masterwork was a program known as Real Space Refinement, which moved the atoms of a putative protein structure to better fit the electron density. Space was limited at LMB so I shared a 200 sq. ft. office with Tom Diamond, [Tom Steitz](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/2009/steitz-facts.html), a postdoc who would go on to solve the structure of the ribosome and share the 2010 Nobel Prize in Chemistry, and Lynn Ten Eyck, also a postdoc and a computer wizard. I looked so young then (Figure 1)!  Each year in September, there are annual lab talks at LMB that can only be attended by lab members. There, for the first time, I heard about tRNA and felt the excitement voiced by Francis Crick, [Sydney Brenner](https://www.nobelprize.org/nobel_prizes/medicine/laureates/2002/brenner-facts.html) and [Aaron Klug](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1982/klug-facts.html). As I reckoned that I could complete my PhD using the methods and program I had already developed in Israel, I focused on modeling tRNA working closely with Francis and Aaron. The resulting model was wrong in overall shape, but, right in many of the details and resulted in my second paper being a sole-author paper in *Nature*, submitted on my behalf by Crick; it was reviewed, accepted and published in 23 days!  Very soon after getting to Cambridge, we discovered that Rina was pregnant. I built models of tRNA at home in our upstairs work room. As a result I had to lower the space-filling (CPK) model of tRNA weighing some 60 lbs out of the window. Our first son, Daniel, was born in May 1969. When he was three months old, Rina, who has a degree in biology, went to work to support the family. My PhD studentship was definitely not sufficient. We did not want to leave Danny with a babysitter all day, so I decided to become a theoretician and work from home.  For the next two years, I cycled to work at LMB in the morning at 9 AM. and returned at 1 PM., so becoming a telecommuter well before the term was known. We did not have a telephone at home and certainly not a computer terminal. As a result, I would carefully plan the programs I needed to type in on punched cards, and spend the four hours at the lab furiously typing cards. Still, I did take a half-an-hour tea break, which was almost compulsory. Looking back, I am amazed that the senior scientists at LMB accepted this scheme, as regulations were quite strict and formal in Cambridge those days. Before Danny was born, I had thought of trying my hand at experimental work and spent a couple of months with Brian Clark (now at Aarhus) looking at tRNA chemical protection patterns so as to identify additional base pairs. I did not have the skills needs for experimentation, nor did I believe my own results.  My PhD thesis, defended at the end of 1971, was ambitious with 10 chapters that should have been published; only two of these ever became papers. Computational structural biology was a new field then and it was greeted with great skepticism. My attempt to publish chapters 3 and 4 of my thesis, which laid out the methodology of computing analytical first and second derivatives of any molecule with respect to Cartesian or torsion angle coordinates was ridiculed by a reviewer who said that had it been a term paper in an undergraduate course, it would have gotten an “F.” In retrospect, I suppose that I should have fought harder to get these papers published but they did not seem very interesting to me. I do remember that in August 1971 we had planned a camping vacation in Italy but my thesis work was progressing so erratically that I wanted to cancel the trip. Rina prevailed and to my amazement, a few days after we returned, feeling very relaxed, I was able to solve the problems that had been holding me up, so that I was able to finish up and start writing my thesis by December.  I stayed on as a staff member at LMB until September 1972 and then we went back to Israel so that I could work with Shneior Lifson at the Weizmann Institute. By now our second son, Reuven, had been born in June 1972. Rina had stopped working a year earlier as my MRC stipend had been replaced by a lucrative fellowship from Gonville and Caius College, Cambridge and we were able to buy our first home near the lab thanks to a college loan that covered the down payment. Knowing that I would be supported by a generous European Molecular Biology Organization (EMBO) fellowship in Israel, we bought a brand-new Citroen GS, free of import tax, for what was then almost a year’s salary and traveled in it to Israel. **First Post Doc with Shneior Lifson at Weizmann 9/1972 to 8/1974** Our first experience in Israel was the October 1973 war that occurred two months after we arrived. My Israeli colleagues, including Arieh Warshel, with whom I was collaborating again, were called up leaving me almost on my own with the computer. This was not an advantage and I started to be become very depressed. When Arieh returned from major tank battles on the Golan Heights, he was much more depressed than I and with much more reason. We spent hours each day talking about work as an escape from reality for us both. This was the start of a very fruitful collaboration. In a few short months it laid the basis for multiscale models in chemistry.  Our first collaboration was a coarse-grained model of a protein in which the 10 atoms in a typical residue are replaced by one of two interaction centers. How we dared to leave out 90% of the atoms is an interesting story. The early 1970s were the golden period of NASA’s space exploration, with six manned missions to the moon between 1969 and 1972. We were trying to tackle protein folding, and it seemed that it could be done by hand using the heavy plastic space-filling models, but gravity kept on weighing things down. Half joking, we speculated that this could best be done on a spacecraft with its zero gravity. Suddenly, we had the idea to simulate simplified molecular models as is they were in a spacecraft and drastically reduce the atomic structure of a polypeptide. This work went ahead quickly and by October 1974 we had submitted the paper that appeared in *Nature* in February 1975.  Our second collaboration occurred in a more systematic manner. Chapter 9 of my PhD thesis and one of the chapters that was published, albeit in conference proceedings, had shown that the enzyme lysozyme was too soft to mechanically deform the substrate as had been proposed by David Phillips. Instead I postulated that the strain would be electrostatic rather than steric (See [Nobel Lecture](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/2013/levitt-lecture.html)). As empirical force fields, both then and today, use fixed point charges on atoms, electrostatic strain cannot be modeled. Arieh and I discussed this at length and then he proposed combining quantum mechanics with classical mechanics. This was Arieh’s area of expertise but even then getting this to work took a long time and this paper was not submitted until September 1975 for publication in *J. Mol. Biol.* in February 1976. **Back to Cambridge, 8/1974 to 8/1977** In September 1974 we returned to Cambridge and shortly afterwards Arieh joined me there for a year. Sadly, he had been refused tenure by the Weizmann Institute and had to leave. In Cambridge we continued to work on the hybrid QM/MM force field and a breakthrough came when we realized how to represent the surrounding water as Langevin dipoles. At the end of his year with me, Arieh moved to the University of Southern California where he is to this day. I had a permanent position in Cambridge and started several diverse collaborations that included the first paper of a long collaboration with Cyrus Chothia (still at LMB) entitled “Structural Patterns in Globular Proteins,” a paper with Jonathan Greer, whom I had visited at Columbia University in New York for the summer of 1975, entitled “Automatic Identification of Secondary Structure in Globular Proteins,” and a paper with Tony Jack entitled “Refinement of Large Structures by Simultaneous Minimization of Energy and R Factor.” Tragically, Tony died on 14 July 1978 aged 30 and before his paper was published.  While all this paper writing was going on, our third son Adam was born in May 1976 (Figure 2). Although we owned our house, it was increasingly difficult to make ends meet. I remember that when our beloved Citroen GS was a total loss after a minor accident, in February 1976, I was thrilled as the insurance money made a huge difference to our finances for the next six months or so. Seeking a more permanent solution, we started to think about a second postdoc in the US. I first tried to get a postdoctoral position at Harvard with Martin Karplus, whom I had met in the summer of 1976 in Paris at the famous CECAM Summer School of protein dynamics [XX], but he showed no interest. Then I thought of going to work with Michael Rossmann in Purdue until we warned told about the Midwest climate. **Second Postdoc with Francis Crick at Salk, 8/1977 to 8/1979** Luck struck again when Leslie Orgel from the Salk Institute suggested I go there. He also told me that Francis Crick would be moving to the Salk Institute so I could work with them both. Leslie and his wife Alice were so kind to us and arranged a house on Coast Blvd. in Del Mar, north of the Salk Institute and a very short walk from a glorious beach. California was wonderful for us all. Rina started to draw and paint with Odile Crick, the children loved their schools and I generally worked from home, staying with Adam, a little toddler. The Salk Institute had no computer, so I first tried to use the large machines at the Health Science Center at UCLA in Los Angeles. This meant 4 hours driving and a night without sleep, so something needed to be done. I applied for two years of NSF support and got $110,000 that I spent to buy a VAX 11/780, Digital Equipment Corporation’s wonderful new computer with virtual memory. The Salk Institute did not want to house the machine, so it was kept and maintained at a local company with the understanding that I would be the sole user for the first year and then the machine would be theirs. The only terminal to the machine was a fast 120 character per second teleprinter connected to a very expensive 60 bytes/second leased line to our beachside home. I was ecstatically happy having such a powerful machine all to myself and developed a routine of working at home except for lunch time when I would drive to the Salk to join Francis Crick and Leslie Orgel. By this time, working anywhere except at home was becoming more and more difficult. **Weizmann Institute, 8/1979 to 7/1986** Towards the end of my stay at the Salk Institute, I applied for a permanent position at the Weizmann Institute. Leaving Cambridge would be hard as they had always treated me in the best imaginable manner but Rina wanted to be closer to her parents and I looked forward to the warm climate. I had hoped to be able to help Arieh Warshel to get tenure there so we could work together again. Francis Crick wrote a joint letter of recommendation for us comparing Levitt and Warshel to Crick and Watson. Unfortunately, the Weizmann Institute was not persuaded by it and we moved there without the Warshels in September 1979, again by car and boat but this time with a cheap and very practical Renault 4.  We settled in quickly and Rina became a full-time teacher for one year before deciding to pursue her art more seriously by studying for four years at Avni Art School in Tel Aviv. Punched card were now a thing of the past but terminals were too expensive to have at home so I actually worked at the Institute, coming home with the children in the early afternoon. Michael Sela, then president of the Institute, supported me tremendously. In 1980 he appointed me chair of the Department of Chemical Physics and at about the same time helped me get elected to EMBO so that I could serve on the Scientific Advisory Committee of the European Molecular Biology Laboratory (EMBL) in Heidelberg. The Weizmann Institute also bought me a Vax 11/780 computer, a color frame buffer display and a high-speed Vector General black & white display. With these wonderful conditions, I produced a series of nine sole-author papers in three years, something of which I remain proud. With Ruth Sharon, I focused on solving the very hard problem of simulating protein molecular dynamics in a large box of explicit water molecules. Computers were still slow and we had to truncate electrostatic interactions at short range while still conserving energy.  Each summer we traveled as a family to a destination where I was a paid visiting scientist, including Cambridge, Washington, San Francisco, London and Boston for the summers of 1980 to 1985). This last trip was for me alone and it was hard on Rina and all the family, as the summer in Israel was terribly hot. We did not have air conditioning and Rina did not think of buying additional fans. As a result, Rina wanted us to spend the next year on sabbatical in London. I was really happy to keep on working in Israel but could not refuse, especially since my mother, brother and sister all live in London. **Sabbatical in Cambridge, 7/1986–7/1987** Although, I was to work in Cambridge, we decided to live in Ealing, a suburb of London near my mother. This meant much better schools for the children and the pleasures of a big city for us all. It also meant I had to commute by bus, underground, train and bus, which took 2 to 3 hours each way but I only went to Cambridge three days a week. Laptop computers did not yet exist, so I did a lot of reading and perhaps thinking. In Cambridge, I mainly worked on getting the work on molecular dynamics in water ready for publication but also had a ‘quickie’ publication with my all-time hero, Max Perutz, entitled “Aromatic Rings Act as Hydrogen Bond Acceptors.” Otherwise, I enjoyed a rather quiet time with family and the cultural and artistic pleasures of London.  The ‘trouble’ started when our long-time friend Bill Eaton came to London for a day in November 1986. Bill had just been put in charge of NIH intramural grants directed towards treating the looming AIDS/HIV health crisis. Bill talked to Rina and said that I really needed to leave Israel and spend a few years at NIH. Until then, the idea of leaving Israel had never been considered but now we thought about it seriously. We were invited to an interview at NIH and on the next day I arranged an interview at MIT’s Whitehead Institute, where I had spent the summer of 1985. While I was in Cambridge (Boston), Steve Harrison, a long-time friend, hosted a cocktail party for us in his home. By pure chance our mutual friend [Roger Kornberg](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/2006/kornberg-facts.html) telephoned from Stanford and was surprised to hear I was thinking of leaving Israel. He immediately said that if I left, we had to come to Stanford.  Leaving the Weizmann Institute was actually very hard and we could not decide what to do until we were helped by preemptive action on the part of the some members of the Chemical Physics department to encourage me to leave. This made it so much easier to ask for three years leave of absence to move to Stanford. **Stanford from 7/1987** My dominant memory of coming to Stanford was how easy everything was. It seemed as if we had grown up on Jupiter and then moved to the Earth’s gravity. We were able to buy a beautiful house on the Stanford campus, our oldest son attended Berkeley and the other two sons attended exceptionally good local schools. Rina started making large monotypes under the direction of the wellknown Bay Area artist Nathan Oliveira. I decided to start a group of my own, something that I had shied away from until then, feeling I was not yet ready to direct others. I also liked – and still very much like – to do all aspects of the research myself. When I joined Stanford, I also became a consultant for Protein Design Labs and this helped in the development of current anti-cancer drugs (see Nobel Lecture). After a couple of years at Stanford, I decided to form my own small company, Molecular Applications Group, to sell molecular graphics software for the Mac II computer. I ran the company alone for two years and was then joined by my brother-in-law, Dor Hershberg. Venture capitalists soon invested and we had some exciting times until the market crashed in 2000. Our VCs were wonderful company and fun to talk to, but I wish they had been more keen to make money, a complaint that is very rare in the super-charged atmosphere of Sand Hill Road.  In June 1990, we decided to spend more time in Israel so that our two older sons could start their army training. We returned to the Weizmann Institute and the apartment that they had so kindly kept for us while I was away on leave of absence. At the start of Operation Desert Storm in January 1991, I had to return to Stanford to teach and it was terribly hard to leave my family while missiles were falling and we feared a nerve gas attack. It also became clear that I would need to arrange a proper joint appointment between Stanford and the Weizmann Institute. The then president of the Institute, Haim Harari, knew Stanford well, and he did his best to help me. Alas, the same people who had helped me leave four years before, raised objections that quickly made me realize that one academic affiliation is enough.  We bought and renovated an apartment in Rehovot and left the protective cocoon of the Institute to enter Israel proper. This was surprisingly difficult but we now know how to be good neighbors. It took about six years for all three boys to finish their army service, and during this time Rina was mainly in Israel and I was mainly in the air between Israel and Stanford. After completing their service, our sons moved back to Stanford and our center of gravity moved there too. I was chair of the department in Stanford from 1992 to 2004, a task that I found very easy indeed. **Last Decade from 1/2003** Rather surprisingly, the last ten years have been the most enjoyable in my life. In 2003 I won a Blaise Pascal Sabbatical Chair in Paris and we had a wonderful year there in 2003 and 2004 (Figure 4). Our first grandchild, Barak, was born on March 2003 (Figure 3) and when he moved back to Israel with his parents in 2004, Rina decided that she wanted to move back too. She said it was a shorter trip from Paris to Israel than to Stanford. Initially it was hard for me to balance the requirements of my fairly large Stanford group, travel and doing my own science, but I became better at it with time. When I turned 60 in 2007, things seemed to get even better. I started to hike with a Bay Area group and have done some amazing trips, the hardest of which was in Patagonia last year (130 km in 13 days carrying 17 kg). I generally became much more excited by physical activity including a risky, but magical, solo sea kayak trip in the Swedish archipelago in 2011 (see Nobel Lecture). After a break of 15 years, I again started writing solo-author papers that are not reviews, with one in 2007 and another in 2009. A couple of years ago, I started going to a personal trainer two or three times a week and have never felt fitter. Meanwhile, both of our two younger sons have also married and has each given us a grandchild, a boy and a girl.  Life was wonderful and just when I thought things could not get any better, I was woken at 2:16 AM on the morning of 9 October. The transition from being mere mortal to a Nobel Prize winner is a great surprise (in fact, I have taken to saying “No one should expect the Nobel Prize” to myself over and over again). Still, so far it has been a magical journey. Nobel Day in Washington was perfect training for the harder Nobel Week in Stockholm and one cannot fail to be impressed and honored by the grace and hospitality shown to us. It felt like a fairy tale and we relied on our Nobel Attaché, Maria Velasco, and our Driver, Estelle Savalle, to keep us from floating away buoyed up by our swollen heads. The banquet (Figure 5) and after-party Nobel Nightcap was so perfectly balanced by our Royal Palace dinner the next night, both wonderful but in such different ways. We had planned to go hiking in Patagonia on 11 December (as I wrote before, “No one should expect the Nobel Prize”) but went instead three weeks later in January. This helped us to get our feet back on the ground, although the attention, especially in Israel, seems to never end. For me, the best antidote is to work by myself, being creative by analyzing data, making figures, writing computer programs and even writing this biography.  It is not easy when people start listening to all the nonsense you talk. Suddenly, there are many more opportunities and enticements than one can ever manage. I have decided to be selective but in a random way, so that I get a taste of everything. I have also adopted a pet project, namely to try to ensure that the young scientists today get all the opportunities afforded to us baby boomers. Failure to do this will dry up the well of innovation that is so important for all aspects of a modern society. |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** |  |
| **Interview** |  |
| Q4 | Could you explain your Nobel Prize awarded work for young students? |
|  | Michael Levitt: Firstly we have been helped very much by the Nobel Committee because they really helped to define a certain part of work and I would say that the work that we did was develop models for the big molecules in chemistry and biology that would enable one to do calculations on these models. One needs to remember that computers were really really slow back then, something like a hundred million times slower than today and basically the key thing was to simplify things, and as [Einstein](https://www.nobelprize.org/prizes/physics/1921/einstein/facts/) once said something , at least it’s attributed to Einstein, although the wikiquote said it wasn’t really him, and that was that you should make everything as simple as you can but no simpler. So we had to make things as simple as we could so that the computer could do the calculation and not so simple that the results would be meaningless. We were lucky, I think we got the right level of simplicity. We were then able to put them in to the computer and do calculations on large molecules simulations. It’s a bit like simulating the weather, which I guess in Sweden doesn’t work very well, but in some countries like California it really works well, because tomorrow will be like today will be like yesterday and so on. But in calculations you can do the same thing for biological molecules and then you can sort of calculate the date in between experiments so it becomes a tool that can be used with experiments and I think there is going to be many things in the future where computers are going to be so important. |
| Q3 | What brought you to science? |
|  | Michael Levitt: One answer is that when I was fifteen, I used to like to play pool, snooker, and one night I came back really late and my mother was really upset and worried, I was in South Africa and it wasn’t that safe. She said: “If you have so much time to go and play with your friends you should work harder at school”. She made me skip two years of school and go to university two years earlier, but I had an uncle and an aunt who were scientists in England and it was also an television programme on the television in England in 1964 and it was given by a very famous British Nobel Laureate, [John Kendrew](https://www.nobelprize.org/prizes/chemistry/1962/kendrew/facts/), who got the Nobel Prize in -62. This was a television programme called *The thread of life* and it really had a big influence. I remember in South Africa there would be no televisions, for me television was really a big deal and the television I had was probably a really expensive black and white television about this big, in fact it was black and yellow. On the BBC they had this programme *The thread of life* as well as the Winter Olympics in -64 and I think I liked *The thread of life* more, so that’s what made me into that area. It was a lot of different kind of lucky things happening. I am very pleased, even without the Nobel Prize I am very pleased to be a scientist, it’s a great carrier. |
| Q9 | What were you doing when you got the message of being awarded the Nobel Prize? |
|  | Michael Levitt: I was very surprised, somewhat very tired because I got to sleep one hour before, so I was just getting into sleep. I think initially with feeling of chock, disbelief, but then the committee was very clever, they ask you questions that only they would know, people said to me: “You had to send that review four years ago and you never did it, where is it?” Somebody else said “Remember how we got drunk in Italy in the summertime” and the other person said: “When you go to the archipelago you’d better come with me, don’t go by yourself”, so this made me realise … I actually talked to the Chairman of the committee today and he said somebody last year had been called the night before on a joke call and when they called him he was really upset so they decided from now on they would have this verification scheme. Very quickly, it’s a real chock, I was like, I describe it as five double espressos maybe it was seven, but it was really an adrenalin burst, that’s amazing, kind of a nice drug. |
| Q2 | Have you had a eureka moment? |
|  | Michael Levitt: I think when we did the work, and this was work that was done, I was between the ages of 20 and 25, I was very young. I think we thought the work was exciting, but I think a scientist always thinks their work is exciting, and there is a big difference. Even if you think your work is exciting and having an impact, to get a Nobel Prize it’s got to be a certain area and I think I have always worked in many different areas. I think it was quite hard for them to find one area that went right back to the beginning so I was certainly surprised. I think that in science you hardly ever have a eureka moment, you have lots of little eureka moments, like I have just found an error in a programme or where did I leave my keys or whatever, but I think that it’s much more. Science is a mixture of ideas and lots of hard work and being very persistent. I think you have to not give up, you have to believe in yourself, you have to realize that if it’s a new idea, people are not going to like it and if people like it then it’s not a good idea. |

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| **Chemistry\_2024-2000** | |
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| **Biographical** | I was born on November 20, 1940 in Kibbutz Sde Nahum in the Beit She’an Valley, in what was back then the pre-independent Israel. I grew up in a relatively happy environment at the so-called “kids house,” where the kids from the same class slept together. The idea was for kids to have quality time with their parents for about two hours a day, while spending the rest in each other’s company. It was years later that I came across some books lamenting the alleged trauma that this type of arrangement may cause, although I actually found it to be a very reasonable as well as enjoyable way of growing up in a kibbutz.  I vividly recall how I and the other kids would run every Saturday morning for one kilometer from the kibbutz fence to the old tracks of the Damascus-Haifa railway. I was frequently found at the end of the group in this Saturday ritual, but I mostly managed to be the first to hit the finish line. This gave me some early hints about the role of perseverance. In fact, even in recent years, I keep maintaining the feeling that if I continue working sufficiently long on a scientific problem, I will probably find solutions to the most challenging question. Another related recollection was the fact that as a kid, I liked to play football mainly as an attacking midfielder, who supports the offense and connects it to the back flank. This idea of the importance of connecting different parts stayed with me in my scientific life.  In the kibbutz school we were subjected to rather unregimented studies, where most kids did not try too hard to study for exams, since the only consequence of failing was not being allowed to see the next movie (which was always shown outdoors). However, I was actually prepared for the exams. (Moreover, noticing learning outcomes of others who were not being forced to study for the exam shaped my future opinions on utopian ideas of learning well only because you had a good teacher. This led me years later to the opinion that without examinations and grades, it would be very hard to advance in sciences).  At any rate, although we did not have many studies of scientific subjects, I liked to experiment in building handguns and primitive voice recorders as well as other objects that had no clear relationship to chemistry. During the school year we used to work for two hours a day, whereas in the summer we worked six hours a day. Our jobs were quite diverse and mine ranged between working in the fish ponds, working at the dining room, working in gardening and being an apprentice to an electrician.  In 1957 (the last year of our high school) our small class moved to study at a neighboring Kibbutz (Ein Harod, Meuhad) with a collection of students from several kibbutzim. This was termed the “unified class” and being in this class was a great experience. That year, 1957 to 1958, was one of the happiest years in my life. As before, we did not study for any particular “useful” direction and there was no emphasis on material that could be included in the matriculation. Thus, for example, we studied very opposing opinions on communism and socialism, analyzed the famous “short course of the communist revolution” of Joseph Stalin along with much deeper thinkers like Otto Bauer and Rosa Lichtenstein.  I started my army service in August 1958, first as a communication specialist (Morse transmission, etc.) in the headquarters of the famous Golani infantry brigade and then, as a communication officer in a special radio surveillance unit. After two and a half years, I finished my regular service but my commander tried to keep me in the army and told me that I could sign on for permanent service under almost any condition that I would ask for. At this time I was determined to go to a university, but I did not have a matriculation, since the left-leaning kibbutzim of that time were not interested in the option that people would go to universities instead of working in the fields. Thus, I asked and accepted a position in the IDF Chief of Staff headquarters, where my night shifts would leave me time to study for the matriculation. In fact, I was already prepared since I carried in my army kitbag physics and mathematics books during my entire service. I probably trained mice in physics with this habit since during my time at Golani the mice ate pages from my Sears and Zemansky physics book. After passing the external matriculation, I found out that my grades were not good enough to be accepted to the Hebrew University. Thus I took and passed the dreaded entrance examination of the Technion (Israel Institute of Technology). Several years later, I asked my classmates at the Technion how it is possible that their grades are always lower than mine while their matriculation grades were so high. They told me the secret: the teachers in the city schools would leak to the students the matriculation materials, whereas I and others who took the external examinations had to study, for example, the entire Bible for any possible random question.  After being accepted to the Technion, I rather randomly chose to study chemistry and started my studies in 1962. Eventually, during my third year, I became interested in understanding how enzymes can accelerate chemical reactions – sometimes by up to twenty orders of magnitude. I started an experimental project that resulted in perhaps the first NMR measurement of the fast step in the catalytic reaction of chymotrypsin, but I did not see any reasonable clues pointing towards the origin of the catalytic effect. In fact, I did suspect electrostatic effects, but my experiments showed that changing the ionic strength does not influence catalysis in a major way. At that time I took a very intimidating class in quantum mechanics at the Physics Department, learning about the so-called ‘impact parameter’. The class was much above the level of what we learned in chemistry, and the only part that I could fully comprehend was the implication that asymptotic quantum mechanical wave functions (i.e. functions that describe the nature of the system at its initial and final states) can always solve many complex problems in physics. Thus, I told one of my classmates that in the distant future I was going to develop an asymptotic wave function for enzymes to understand how they work. Of course, I did not have any clue what enzymes look like and how a wave function would explain the action of enzymes – eventually it was the EVB approach (which will be considered below) that captured the asymptotic features of enzymatic reactions.  I had to support myself with summer jobs, and at the end of the third year I got a summer project in the department of soil engineering. This involved working, with professors Rephael Mokadi and Benjamin Zur, on optimizing diffusion devices for dripping irrigation and related applications. I took clay plates, covered them with different types of cellulose layers and measured the rate of diffusion of water under high pressure. The results were converted to countless values of speed and other parameters. Then, I typically spent eight hours of calculation in order to convert tables of numbers to diffusion constant. I told about this tedious computational work to a friend, who had already seen the action of a digital computer (which was using a paper tape). He mentioned that what I was doing with a manual calculator could be done much more efficiently with a computer. I was very impressed, but unfortunately this discussion occurred too close to the end of my summer job. However, this new direction influenced my thoughts on how one can use computers to replace manual computations.  My studies at the Technion progressed quite well and I received the “best third year student” certificate from the then Israeli Prime Minister Levi Eshkol. However, when considering continuing my M.Sc. studies at the Technion, I learned that I would be obliged to take two to three courses in different languages. I decided to look for another place.  Thus, I made an appointment with Professor Shneior Lifson, who was the scientific director of the Weizmann Institute. I was attracted to him because of a news article that said that Lifson was from a kibbutz (Nir David), which is located very near to my kibbutz. Interestingly, both Kibbutzim were at 1936 and 1937, respectively, the first in the new form of settlement called Stockade and Tower (Homa and Migadal), which were enough to establish the legality of the settlement in the British Mandate period. I also learned that Shneior was moving from statistical mechanics of helix coil transitions to modeling molecules with digital computers, which was still extremely far from my interest in enzyme wave functions. I and my then girlfriend Tamar (who became my wife in August 1966) went to see Shneior at his imposing director’s office. Although he told me that he was determined not to accept any students, I successfully convinced him with the help of my grades to join his non-existent group. I moved to the Weizmann Institute in fall 1966 and started to develop what became known as the consistent force field (CFF), where the general direction was to represent molecules as balls and springs (this became known as molecular mechanics or “force field” approach) to reproduce energies, structures and perhaps vibrations of small molecules.  As a start I attempted to model cyclic amides, on the way to parameterizing amino acids’ potential functions, by an extension of the internal coordinate approach of Mordechai Bixon, who was a former student of Lifson. However, this approach involved derivatives of complex interdependent transformation matrices and after spending enormous efforts in debugging my program, I finally realized that obtaining general analytical derivatives (especially for ring molecules) is basically impossible. Out of desperation, I tried to abandon the common description of molecules in terms of bond lengths and bond angles and to move to a Cartesian coordinates description, where, suddenly, all the problems with analytical derivatives seemed to disappear. Most remarkably, obtaining vibrational modes now required only the use of one simple equation in terms of the Cartesian second derivatives. At this stage, Shneior told me that this was unlikely to be correct (a situation that continued throughout my career), but fortunately the Weizmann Institute had a specialized computer called the Golem (named after the ‘robot’ from Jewish legend that helps the famous rabbi from Prague) that had a remarkable double precision. Thus, I was able to obtain very accurate first and second numerical derivatives and to prove that I was on the right track in obtaining exact minima and molecular vibrations in a general molecule. Encouragingly, Shneior was always gracious enough to agree with me, and eventually he started telling others “don’t argue with Arieh, he will always turn out to be right.”  At that point I started to write a program with Cartesian analytical derivatives and a least squares force field refinement (using the numerical derivative in pinpointing errors). My progress with Cartesian coordinates convinced Lifson to let me finish my M.Sc. degree in less than a year and to basically jump to the Ph.D. project, considering the potential for fast progress in the general CFF direction. To reach this stage I wrote the a short master summary and a Ph.D. proposal to reach this stage, but then was called to the Army reserve force for a three week nerve-wracking “waiting period” before the Six-Day War. During the first days of the war my wife was running up and down to the shelter during the air raid alarms with a plastic bag that some assumed contained her non-existent jewelry. However, it actually included my Ph.D. proposal.  During the Six-Day War, I fought as the communication officer of a reserve tank battalion that together with another battalion took the Golan Heights. After some additional reserve service, I returned to the Weizmann Institute. Around this time Michael Levitt appeared, and following Shneior’s suggestion, we developed together the general CFF Cartesian force field programs that allowed one to use molecular mechanics (MM) and to find exact local minima and vibrations of any general molecule. The CFF parameter refinement turned out to be quite a demanding job, including inventing automatic frequency assignments, developing a general way of refining parameters that would reproduce known unit cell dimensions of molecular crystals, finding ways to evaluate crystal free energies from their calculated crystal vibrations and much more. Each of my developments further convinced me that with computers you could address almost any problem.  Incidentally, in contrast to today’s easy access to computers, my work at the computer center involved the use of punch cards, where the best turn-around time involved at most two runs a day. This meant that I would lose a day with two errors and it also meant that I had to come late every evening to try to manage to get an additional submission of my job. Thus, every time I returned with my wife from a show or other event we went to the computer center before going to sleep.  During 1968, a year that turned out to be eventually significant, I also started experimenting with combining my newly developed CFF MM method (with the spring-like description of bonds with localized electrons) and a valence bond (VB) quantum approach in a QM(VB)+MM model.  After a relatively fast completion of my Ph.D. (1967–1969), I accepted a postdoctoral position at Harvard with Martin Karplus (who visited the Weizmann Institute in the second half of 1969). Arriving in Harvard at the beginning of 1970, I discussed with Martin what would be the best project for me and we agreed that a promising direction would be to make the QM+MM CFF more general. Here the development of a QM+MM approach with a molecular orbitals (MO) description for electrons seemed to be a way to quantify the studies conducted by Karplus and his postdoc Barry Honig, who were working at that time on retinal (the chromophore of the visual pigment). The development of the QM(MO)+MM method, which I eventually called QCFF/PI, was a major project that resulted in an extremely powerful way of studying conjugated molecules but still could not describe real chemical reactions, which involve bond breaking and bond making. Overall, I enjoyed the time at Harvard, where my wife Tami and I and our first daughter, Merav, made sure to travel every weekend to different places like the New Hampshire Mountain and ski resorts. We also enjoyed the postdocs’ housing at the Botanic Garden, although Tami had the hard task once in a while (in a rotation) of taking care of Merav and the kids of other postdocs, which included undoing the winter compact snowsuit whenever a kid wanted to go to the bathroom.  Upon returning to the Weizmann Institute in 1972, I started to develop a very effective hybrid orbitals quantum program (QCFF/ALL) that represented all the atoms in a relatively small part of a molecule quantum mechanically, while representing the rest classically. I felt that this should allow me to finally make progress on my old dream of studying enzymes. At that time Mike returned from his Ph.D. work at the Medical Research Council (MRC) to the Weizmann Institute and I started to explore the possibility of combining my quantum mechanical model with his MM calculations on lysozyme. I was also advancing my π-electron calculations, trying to develop general models for chemical reactions in molecular crystals and developing approaches for resonance Raman calculations of large molecules.  The 1973 Yom Kippur War (where I fought in the Golan Heights again) was quite traumatic for me, and perhaps the major motivation to move faster to biology. Thus, I became involved in the protein folding project with Mike, where I was greatly encouraged by the remarkable success of the simplified protein model. This coarse grained (CG) model converged to reasonably folded structures of the small protein Bovine pancreatic trypsin inhibitor (BPTI), without spending infinite computer time to sample in the theoretically assumed enormous available configurational space. Incidentally, our approach was strongly criticized, implying that simpler amino acid chains would also fold similarly to our BPTI, i.e. with a glycine in the right position. Of course, the glycine was placed in the proper place in the chain of BPTI by evolution and not arbitrarily by us. More importantly, our point was that we resolved the Levinthal paradox and showed that the folding process did not require infinite sampling of the phase space. Thus, the fact that simpler systems fold like BPTI has only been a proof to our point. In fact, our accomplishment was not so much about predicting the folded structure but about simulating a folding process. The progress on the folding problem helped me to obtain an EMBO fellowship, allowing me to collaborate with Mike when he moved back to the MRC.  I arrived in the fall of 1974 at the MRC, with Tami, Merav and our second daughter, Yael, and started to focus on my efforts on modeling enzymatic reactions. My trial and error attempts led to the realization that the only way to progress is to introduce the explicit effect of the charges and dipoles of the environment into the quantum mechanical Hamiltonian. This led to the breakthrough development of the QM/MM approach, where the QM and MM where consistently coupled in contrast to the previous QM+MM attempts. Our advances also included the development of the first consistent models for electrostatic effects in proteins. This model, that was later called the protein dipoles langevin dipoles (PDLD) model, represented explicitly (although in a simplified way) all the electrostatic elements of the protein plus the surrounding water system and thus evaded all the traps that eluded the subsequent macroscopic electrostatic models.  At any rate, the use of our QM/MM approach in modeling the catalytic reaction of lysozyme paved the way for the current direction in modeling enzyme action and has become a major direction in theoretical chemistry and biophysics.  While working on the QM/MM project, I also decided to peruse my realization that semi-classical trajectory approach can be used to study photisomerization reactions, and to simulate the first step in the vision process. Here, in the absence of structural information I had the ‘brilliant’ idea of binding retinal to chymotrypsin, obtaining crystals and measuring the quantum yield. However, when I suggested this project to Richard Henderson, who was working at the MRC on the electron microscopy structure of bacteriorhodopsin, he declined, telling me that in his early work with chymotrypsin he developed an allergy to this protein and could no longer touch it. At this point I decided to model the protein effect by a steric cavity plus an assumed internal counter ion, and used the semiclassical surface hopping approach with a Schiff base of retinal constrained to be in the starting 11-cis conformation. My molecular dynamics (MD) simulations predicted correctly that the primary process takes about 100 femtoseconds, with an enormous probability of jumping to the ground state due to the very large non-adiabatic coupling. Being surprised by the unexpected large jumping probability, I discussed the issue of modeling interference semiclassically with William Miller from Berkeley (who was an Overseas Fellow at Cambridge and happened to be the world expert on this issue). Basically, I felt that with such a multidimensional system it does not matter if the crossing occurs in one point or if we allow interference between trajectories from many crossings. However, Miller confessed that he was not sure about it and I assumed that my treatment was valid (an assumption that turned out eventually to be justified). At any rate, in subsequent years, I sometimes regretted not adding some trivial (and somewhat meaningless) calculation of the isomerization in the active site of some arbitrary protein, which would also establish that I have done the first MD simulation of a protein. However, performing the first MD simulation of a biological process, addressing a real functional problem and after all obtaining the correct unknown results was quite gratifying.  I was involved in several other projects at the MRC and it was in some respects the most productive time for Mike and me. It was also the period where suddenly I started to understand what are the problems in different biological systems. It is not clear if this maturity in thinking was induced by the MRC afternoon tea breaks, or by other factors, but it was clearly a crucial change in my thinking.  In February 1976 I moved from Cambridge to the University of Southern California (USC) and started my job there. Although the teaching load was significant, I continued with a very aggressive research program.  Around 1978, I started to formulate the question of enzyme catalysis in a clear and coherent way, realizing that this issue must be addressed by comparing enzymatic reactions and the corresponding reactions in solutions. This realization forced me to extend the QM/MM to chemical reactions in solution. Thus, I had to invent a CG model for water solution, where the water molecules were represented as dipoles embedded in soft spheres and calibrated to reproduce solvation effects and other properties. This completely reasonable model was rejected by three journals with entirely illogical referees’ comments, (a phenomenon that has continued even until the present day). Had I known that my model was basically an extension of the so-called Stockmyer model (with my realization that the calibration of the model is the key to its performance) I would perhaps have saved myself major aggravation, since the referees would hopefully be less aggressive. Nevertheless, my ability to compare reactions in enzymes and in solution led to the realization that the corresponding difference can be best quantified by a Valence Bond formulation (in what became later the EVB model). This realization led in 1978 to what I believe has been the solution to the puzzle of enzymatic reactions. That is, I realized that enzyme catalysis is due to a large free energy penalty for the reorganization of the solvent in the reaction *without* the enzyme (the work of rotating the water molecules towards the transition state charges). The reorganization energy increases the activation barrier in solution, whereas the enzyme polar groups that stabilize the transition state do not have to rotate significantly, since they are already folded with correctly polarized dipoles. In subsequent years, I was also able to prove that the change in the electrostatic reorganization energy accounts for almost the entire catalytic power of enzymes.  My ideas of electrostatic stabilization were in line with Max Perutz’ intuitive feeling but the details appear to be fundamentally different, as Perutz and other assumed that enzymes stabilize charges by a non-polar low dielectric environment, while I pointed out to Max that enzymes actually work by having relatively fixed permanent dipoles in very polar environment. Significantly, the majority of the biochemical community did not believe in electrostatic catalysis, in part driven by the finding that the electrostatic effects on model compounds in solution are very small, and the fact that changing the ionic strength does not change catalysis in a significant way (see above my Technion days). Interestingly, when the late Jeremy Knowles visited USC in the 80s, he told me that the longer the scientific community would not believe in my electrostatic ideas the better it will be for me, since it would be harder to say that my ideas are trivial and well known.  My electrostatic ideas gave me and my coworkers a major advantage over competitive approaches, where the PDLD model allowed us to obtain realistic energetics for charges in proteins long before the continuum models with their original unrealistic dielectric constant and their initial neglect of the protein permanent polarization started to modify their assumptions and started to give reasonable results.  In 1981, I felt that I must move to fully microscopic models, since computer power started to allow such simulations and since it was clear that my advances with simple electrostatic models would be ignored once microscopic models would start to give reasonable results. This move was helped by an anonymous supporter who put me on the list of the speakers of the 1981 theoretical chemistry conference in Boulder and assigned to me a talk on all atom MD simulations of reactions in water. Although I still felt that it was too early to ask serious functional questions with full atomistic models, I decided to accept the challenge and develop a simple all atom polarizable water model and, much more importantly, used this model to introduced the microscopic equivalent of Marcus electron transfer theory, as well as to introduce free energy perturbation calculations of solvation effects. The same model has been then incorporated in microscopic free energy calculations using the EVB approach. In fact, in 1982–1983 I already introduced the same treatment in studies of enzymatic reactions.  The advantage of working and developing multiscale computational tools for studies of biological functions (rather that looking in a less focused way on technological issues such as keeping constant temperature) has allowed me and my coworkers to move very effectively. One of the best examples was the elucidation of the nature of the primary event in photosynthesis. Here, following studies of model systems with my long time collaborator Bill Parson and other coworkers, we waited four years until we could put our hands on the coordinates of the photosynthetic reaction center, and then having all the computer programs ready and tested for a long time, it took us only two weeks at the end of 1987 to convert the structure of the RC to a detailed functional mechanism. Our study combined all the different methods needed to solve this problem, ranging from surface hopping, microscopic Marcus type parabolas and free energy calculations, and actually predicted the correct sequential hoping mechanism in contrast to the super-exchange mechanism assumed by most workers at that time..  During the period 1978–1980, I started to realize that the QM (MO)/MM calculations are unlikely to tell me in a quantitative way how enzymes really work. I eventually realized that the question could be formulated in terms of the changes in energy of ionic and covalent valence bond states in moving from water to the protein active site. This led to the development of the empirical valence bond (EVB) method that became an extremely powerful way of modeling reactions in solutions and proteins.  I must admit that in the years between 1978 and 1990 I was still not sure how reproducible my results for enzyme catalysis were. The initial stable results were obtained with the electrostatic PDLD model, including series of EVB/ PDLD calculations. In 1983, I already formulated the EVB in a fully consistent microscopic way (including capturing the so called non-equilibrium solvation effects). The EVB approach worked well in reactions in solutions but I was not sure about its convergence in enzyme studies. The problem was the fact that the computers of that time allowed me to run about 5 free energy perturbation mappings of 10 picosecond. This was frequently sufficient to capture electrostatic effects that converge quite rapidly, in particular with our specialized spherical surface constraint boundary conditions, but once in a while we would lose the calculated catalytic effect. Eventually, it was Johan Aqvsit (a postdoctoral associate with me from 1988 to 1990) who started to get stable results by his persistence and by running significantly longer equilibration runs.  The gradual acceptance of my work has not been a simple ride, my key idea and results were originally considered to be incorrect and then termed as trivial ideas that were persistently attributed to others. The referee reports were almost always very hostile and my fight with referees became legendary and some people assumed that I actually enjoyed those fights. In actual fact, I look at the refereeing system as a clear mark of the problem with the scientific idea of peer review, but this should be left to another essay.  In more recent years, I became increasingly interested in the functions of large molecular machines. Here we recruited back the CG idea of the protein folding but undertook a major modification focusing on the representation of electrostatic effects. The resulting CG models appeared to provide what is arguably the best current tool for moving from structure to function of molecular machines allowing us to use our CG model in simulations of molecular machines and other complex biological systems. Instructive examples are the simulations of the vectorial action of F1-ATPase (which is the best-studied biological motor), the conversion of proton gradient to work in F0-ATPase, the action of voltage-activated ion channels and the function of other molecular machines.  Today there is no doubt that computers are assuming larger and larger roles in modeling complex systems and that their role will only increase even further in the future. In this respect, the contribution of my colleagues and myself in pushing the field forward has been just the first step in what is going to be a long lasting merger of experiments and computations.  In concluding this biographical essay, I would like acknowledge the help of my students postdoctoral associates and coworkers. In particular I would like to give special thanks to my wife, Tami, who followed me along my scientific life, and helped me to both endure difficulties and enjoy successes. |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** | [AW]  [SN] Are you there Professor Warshel?  [AW] Yes.  [SN] Congratulations, so how do you feel at this very early morning time for you?  [AW] Extremely, extremely well.  [SN] (Laughs) That’s good to hear. I’m sitting here in the session hall of the Royal Swedish Academy of Sciences. And in front of me …  [AW] I see you.  [SN] Oh, you see as well. Well we have a lot of persons from the media all over the world. And are you willing to take some questions from them?  [AW] Very glad to.  [SN] Do we have a question?  [AW] Yes.  [MGA] Yes, hello Professor Warshel, my name is Maria Gunther Axelsson and I’m writing for the Swedish newspaper Dagens Nyheter. First, congratulations to the prize.  [SN] Thank you very much.  [MGA] Yes, and we just had a presentation here on what you have done. Could you just say something that have been easier to understand now that you couldn’t understand before you had this …  [AW] Usually I say it in a more complex way, but what we done, from what I was able to see from the presentation by Gunnar, is to develop methods that allow *[line cracks]* how proteins actually work. Because x-ray structure … exists for some time and it’s like seeing a watch and wondering how actually it works. So in short what we developed is a way which requires a computer to look, to take the structure of a protein and then to eventually understand how exactly it does what it does. Like if you have enzymes that digest food, and the structure exists, you want to understand how this is happening, and then you can use it for example to design drugs or just, like in my case, to satisfy your curiosity.  [SN] Ok, thank you. You had a question?  [JR] Hello, my name is Joanna Rose, I am writing for a Swedish popular science magazine Forskning och Framsteg. Congratulations to the prize. I’m curious about what is the work that you are doing now? Presently?  [AW] I am now using the, I saw it in the presentation … On one hand I continue to this combined quantum molecular mechanics to understand how proteins that are responsible to transfer signals in the cells, how they exactly work. So this is like thirty percent of what I’m doing, and I also use this simpler representation to understand how molecules, how molecular motors work. To understand how very complex molecules are working. So all the time, its how the things are working, and every time it is for a more complex question.  [SN] Ok, thank you very much, I see any more questions here? I don’t think so, so thank you once again Professor Warshel and congratulations. We are looking forward all to see you here in Stockholm in December for the Nobel Prize Ceremony. Bye.  [AW] Thank you, thank you very much, and looking forward. |
| **Interview** |  |
| Q4 | Could you please explain your Nobel Prize awarded work for 13-14 year olds? |
|  | Arieh Warshel: To explain to 13-14 year olds … I essentially try to give my lecture to my granddaughter who is maybe 14 and then I found out that I have to change a lot. There are several things to explain. First of all the idea which is very simple to any age that if you have a very very complex system, the best is to focus on the main part and not to, like if it is a picture, not to look on all the parts in the same details. For example in my lecture we try to, I am still working on it, but we have a cart in the forest and we try to focus on the cart and to have the forest with much less pixels, so this is the general idea of what one call multiscaling. When it comes to biology you have a complex protein and you want to understand how it works.  First of all you have to assume that you could deal with it, not to listen to people who say that it is too complex. Then you say: I want to understand how it works, like if you have a watch and the watch is already there and you want to understand how it works. You are first to think about it, which I think that a 13 year old boy or girl could understand, then you look on parts of it and try to figure out how they work when all the rest is not moving and then you try, after you understand this, to let the rest of it move and then you get a picture how it works. So it’s basically understanding how biological molecule works and to explain more you have to take given system like proteins that chop molecules and you want to understand why it works so fast. The main point is that it is very hard to do it without a computer so young people understand what is computer, but this is not to send text message but to actually model how things are working and when you model it you kind of understand it, it’s like simulator for flight training so you are going inside the protein and see how it works. |
| Q3 | What brought you to science? |
|  | Arieh Warshel: I grew up in kibbutz and even going to university was considered quite different, because in the kibbutz at that time they want you to – and I don’t blame them – they want you first to return your share to work in the kibbutz so they did not encourage you to do what is called matriculation or anything else and I felt at some stage that I want to go to university, but it was mainly for the accomplishment without any clear pattern of what it would be. I read books, I read about [Marie Curie](https://www.nobelprize.org/prizes/physics/1903/marie-curie/facts/) and other, but there was no connection so after the army when I was accepted to the Technion I met a friend in the Technion yard and asked him what direction I should take and he says that I have a good eyesight and therefore I should go to chemistry. For me it was really studying and getting the highest grades, but I felt that eventually I would figure out which direction to go, so its not that I dreamt of solving some problems. |
| Q9 | What were you doing when you got the message of being awarded the Nobel Prize? |
|  | Arieh Warshel: I was of course sleeping, It was two o’clock and my wife pick the phone and I said “It is too early, so it must be something else”, because I felt that the news conference should be at 12 and this was ten o’clock. Then I picked up the phone and I was very happy to hear the Swedish accent and then I heard in the background people that I know so I was very happy, though it takes very long time to internalize this so I didn’t to anything. I think that my wife did something like [waving with his arms[, but for me it took a while. |
| Q5 | Who is your role model, and why? |
|  | Arieh Warshel: The question about having a role model, so again I just say it’s not going from young age, but there are a few people that I admire in science, very few and one of them is Ludwig Boltzmann that I hold in very high regards, regardless of the fact that he commited suicide at the end. He is the guy who kind of invented statistical mechanics, he is the guy who figureed out what is entropy while everybody else got it from the work of heat engines. He figured out how it works on molecular level and he had a lot of detract also, who claims that he is wrong. He did not necessarily influence his career, I don’t know if he got Nobel or not, but he was a very important professor and a very original thinker so I think I put him at the highest. He is in some respect a role model, like many times when I give seminars and I try to explain how enzyme work and how they do not work, I put his photo as example of at which direction you have to look. He is buried in Trieste and essentially I heard that is good. When I teach chemistry, I force the students to draw his picture for one point, so I have a role model. |
| Q2 | At what point did you realize your work was a breakthrough? |
|  | Arieh Warshel: One time was when the work on protein folding. The question is how protein could fold to one structure instead of many structures. When this worked, it was something that was declared as a major problem, though to me it was not such a big deal or puzzle, but it was clearly something impressive. The other part which I consider more important, like understanding how enzymes works, figuring out how to model enzymes. I felt this is breakthrough when it was done, but it was not necessarily shared by the referees or the community, so there is this gap between me thinking that’s something important to asking whether it will make impression. I had quite many problems that I was extremely happy to solve, then of course unhappy from the response of the referees, but overall there were several major accomplishments that I felt this is nice. |
| Q9 | How do you find being a Nobel Laureate? |
|  | Arieh Warshel: Obviously, I am very happy. I was told by other Laureates that this should be the nicest week in my life, at present it does not look like this because of too much stress from interviews, not yours. I am sure that it happens to others, but it must eventually well out and you’re left only with the nice memories, so I am really looking forward for the rest of the week. I have many friends here so we will be very happy to see them. |

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| **Biographical** | According to an article in *The Times of Israel* (issue of Dec. 9, 2012) by Mark Schulte, Dr. [Alvin Roth](https://www.nobelprize.org/nobel_prizes/economic-sciences/laureates/2012/roth-facts.html) (co-recipient of this year’s Nobel Prize in Economic Sciences) and I share two attributes with thirty-three other Nobel Laureates. We are Jewish and we were educated in New York City public high schools. This article further highlights the fact that “the overwhelming majority” of this group descended from “Eastern European Jews who came to America between 1881 and 1924, during the great migration.” In my case this was true of all four of my grandparents. My paternal grandparents, Mariam (Mary) Kremsdorf and Louis Lefkowitz, were from two nearby towns in southeast Poland, Czestochowa and Zoloshin. They were already married with one child when they immigrated to the United States in 1903, initially settling on the Lower East Side of Manhattan. They would live their entire lives in New York City, primarily in the Bronx and raise seven children, the second oldest of whom was my father, Max, (b. 1905). My grandfather was a cap maker and my grandmother, a homemaker.  My mother’s parents, Bernard and Rivka Levine, were from Russia and also immigrated to New York City. My mother, Rose, was the elder of their two daughters. My maternal grandmother’s family included several scholars and professionals. Her brother, Shlomo (Solomon) Polachek, was a famed rabbi and Talmudic scholar. Born in a small Russian village, he was known as a child prodigy at a young age and ultimately immigrated to the United States to become head of the Theological Seminary of Yeshiva University in New York City. One of his sons, Harry, was an ordained Rabbi and a prominent mathematician. The latter led him to become Technical Director of the Naval Applied Mathematics Lab, where he was an expert in early commercially available computers.  CHILDHOOD I was born in 1943 and raised in the Bronx, in a high rise apartment complex known as Parkchester, the only child of Max, an accountant who worked in the garment district in Manhattan and Rose, an elementary school teacher. My mother was a high-strung perfectionist. She would check my homework for the slightest imperfection and demand that it be redone if she detected any flaws, which she invariably did. My father, in contrast, was easy going and affable and delighted in helping me with any project. He had a remarkable ability with numbers and could perform complex calculations in his head more rapidly than I could with pencil and paper. He would teach me many arithmetic manipulations and tricks several years before I would encounter them in school. When my absence of athletic ability manifested itself in an initial failure to meet required school standards for rope climbing and tumbling maneuvers, he insisted on setting up makeshift props at home and coaching me to ultimate success. As an adult, I can easily discern elements of both my parents’ personalities in myself.  As an only child lacking siblings and playmates, I was alone a great deal of the time. Much of this was spent reading virtually anything I could get my hands on. I began with my parents’ rather modest collection of volumes but then quickly discovered the local public library, from which I would regularly cart home the maximum allowable number of books (6 as I recall). I was rather precocious in this regard. I recall joining book clubs by sending in coupons I clipped from the newspapers which entitled me to claim a free set of books on the condition that an agreed upon number of additional volumes would be purchased over the next year. In this way I acquired, for example, Winston Churchill’s six-volume history, *The Second World War*, and Carl Sandberg’s six-volume biography of Abraham Lincoln. By the time I was about thirteen I had completed both sets. My parents, initially unaware of the contracts to which I had obligated them, were left to buy the remaining volumes, further adding to the family library. Increased time for reading these books was, on occasion, gained by faking illnesses such as abdominal cramps so that I could stay home from school and read all day.  My reading at this early stage also included numerous fiction and nonfiction titles related to medicine such as [Sinclair Lewis](https://www.nobelprize.org/nobel_prizes/literature/laureates/1930/lewis-facts.html)‘ *Arrowsmith*and Paul de Kruif’s *Microbe Hunters*. My interest in these was sparked by my family physician, Dr. Joseph Feibush. By the third or fourth grade of elementary school I had decided that he was my occupational role model. I was enthralled by what he did, which included making routine house calls, performing physical exams, especially with a stethoscope, and writing illegible prescriptions. From then on I never wavered from my goal of studying medicine and becoming a physician.  Nonetheless, there were some early signs of interest in chemistry and biology as well. Among my favorite “toys” was my 1950s era chemistry set. Together with a friend we would follow the instructions in the manual, producing solutions of various colors or precipitates. We would copy out the experimental protocols from the guidebook into a notebook and make our own comments about what we saw. We told ourselves that we were creating a “chemistry textbook.” A “lab notebook” would have been a better description. A toy microscope of relatively low magnification was another favorite. Through it I viewed human hairs, insect parts of all sorts and a variety of prepared slides that came with the microscope set.  Lest I present myself as a totally bookish nerd at this stage (partial would be a better description), I hasten to point out that I enjoyed a wide range of activities typical of kids growing up in New York City during the 40s and 50s. These included stick ball, punch ball, trading baseball picture cards and riding bicycles. I was also an ardent fan of the New York Yankees major league baseball team (“the Bronx Bombers”) and can still repeat the batting order and uniform numbers of the teams from the early 1950s. I was active in the Boy Scouts and for many years took piano lessons, demonstrating relatively little talent. I played the drums, to the dismay of those living in neighboring apartments who would beat on the heating pipes to alert me that I was too loud. I was a member of the first generation of children to watch television, the earliest tiny sets arriving in some of my friends’ apartments when I was about five and in our home several years later. However, I can still remember listening to my favorite radio shows sitting on the floor in front of a large console radio.  One other influence which shaped me as a youngster was my participation in a family society called the Associated Kremsdorf Descendants (AKD’s). This family circle, consisting of the extended family of my paternal grandmother, would meet once a month for a meal, fellowship, entertainment and a formal business meeting. Complete with elected officers, committee reports and following strict rules of parliamentary procedure, these gatherings attracted dozens of family members from multiple generations. Such organizations were quite common among Eastern European immigrant Jewish families living in the northeast in the mid-20th century (as depicted in the movie “Avalon”). From these gatherings, which I greatly enjoyed, I gained a sense of the importance of family and a respect for, and appreciation of, the older members of the extended family who had all come from Europe.  EDUCATION The Bronx High School of Science After attending public elementary and junior high schools I entered The Bronx High School of Science (10th grade) in the autumn of 1956, graduating at age 16 in 1959. “Bronx Science” is one of several public high schools in New York City which admits students on the basis of a competitive examination. The student body, representing approximately the top 5% based on the exam, are gifted and interested in science and math. The accomplishments of graduates of this high school are quite remarkable. For example, I am the 8th Nobel Laureate to have graduated from this school, the 7 previous ones having received their prizes in Physics. For me, attending this school was a formative experience. Whereas in elementary and junior high school I was not greatly challenged, here I was among a group of remarkably bright, interesting and stimulating classmates. The curriculum featured many advanced classes at the college level. I was particularly drawn to chemistry and, as a result of taking these college level classes, I was able to receive full credit for two years of chemistry when I entered Columbia College in 1959. Thus I began as a college freshman with organic chemistry, a course generally taken by juniors.  The level of scholarship maintained by the student body was such that even with an average of about 94% my final class rank was about 100th out of 800. A classmate and friend at the time and at present, the famous geneticist David Botstein, had an almost identical average, a fact we tease each other about to this day.  College Along with dozens of classmates, I moved on to Columbia University where I enrolled as a pre-medical student majoring in chemistry. The two year core curriculum in “Contemporary Civilization” was required of all students. With an emphasis on reading classic texts in history, philosophy, sociology and the political sciences and discussing these in small seminars, it was for me an opening to a whole new world. In addition, I took courses with and was exposed to, such intellectual giants as the literary critic Lionel Trilling, the cultural historian Jacques Barzun and the sociologist Daniel Bell, among others. I have very fond memories from this period of spending many hours in the public reading room at the 42nd Street New York Public Library, researching papers for those classes.  I also studied advanced Organic Chemistry with Cheves Walling and Physical Chemistry in a department which was strongly influenced by the then recently retired prominent physical organic chemist, Louis Hammett. However, the chemistry professor who had the most profound influence on me was actually a young Assistant Professor of Chemistry, Ronald Breslow. As a college senior I took an advanced seminar in biochemistry which he taught single handedly. This introduction to the chemistry of processes in living organisms really excited me in part, I suspect, because of his very lively teaching style. None of this, however, in any way diverted me from my goal of studying to become a practicing physician. In fact, by midway through my second year at Columbia it had become clear to me that, as a consequence of the credits I had received for college level courses taken in high school, I would be eligible for graduation after only three years. I needed only a couple of courses in summer school, graduating in 1962 at the age of 19, and moving uptown to the Columbia University College of Physicians and Surgeons.  Medical school I greatly enjoyed my four years in medical school. I had dreamed about becoming a physician since grade school and now I was finally doing it. As a freshman immersed in the basic medical sciences I was able to deepen my interest in, and fascination with, biochemistry. Our biochemistry professors included a remarkable array of scholars (not that any of us appreciated that at the time). We heard lectures on metabolism from David Rittenberg, Chair of the Department; from David Shemin on porphyrins; from Erwin Chargaff on nucleic acids; and from David Nachmansohn on cholinergic neurotransmission. As stimulating as these subjects were to me, it was the clinical work that I was really pointing toward. Much as I enjoyed learning about biochemistry, at this stage the idea of actually doing research never entered my mind. In fact, although short blocks of time were available for research electives, I always chose clinical ones instead.  One young professor left a lasting impression on me. Paul Marks was then a young academic hematologist who taught the Introduction to Clinical Medicine course in which we studied clinical problems for the first time, examined case histories, and looked at blood specimens. Not only was he a good clinician but he assigned readings from the basic science literature that were relevant in a very meaningful way to the cases we studied. This showed me how scientific information could be brought to bear on clinical problems. Among my classmates and friends in medical school was [Harold Varmus](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1989/varmus-facts.html), who was the co-recipient of the 1989 Nobel Prize for the discovery of oncogenes.  At the end of my first year of medical school, I married Arna Gornstein and our first two children, David and Larry, were born in 1964 and 1965.  House staff Upon graduation in 1966, I remained at Columbia for two years of house staff training in internal medicine at the Columbia Presbyterian Medical Center. This experience was intense, exhausting as well as exhilarating. I was doing what I had longed to do and I loved it, but I was not sleeping very much. As interns we followed a two week on call cycle in which one week was five nights on duty and two off, and the second was two nights on call and five off. “On call” meant that one slept in the hospital, though it was rare indeed to get more than a very few uninterrupted hours. It was not rare, however, to go two successive nights and intervening days with absolutely no sleep. This consistent sleep deprivation taught us what the limits of our endurance were and fostered a remarkable work ethic. However, it simultaneously degraded our performance at work and our ability to enjoy family time when at home, since the need to sleep overwhelmed all else. Needless to say, this schedule left precious little time for keeping up with the scientific or medical literature. Regulations now prevent working anything like these hours for house staff physicians.  At this time the Vietnam War was raging and there was general conscription with a separate “doctor draft” for physicians. Regardless of which branch of the service you joined, the only certainty was that you would spend a year in Vietnam. One way around directly participating in this very unpopular war, which was of particular interest to budding academic physicians, was to join the commissioned corps of officers in the United States Public Health Service and to be assigned for two years to clinical and laboratory duties at the National Institutes of Health in Bethesda, Maryland. Obtaining one of these commissions was extremely competitive at the time but, because of my strong academic record and recommendations, I was successful.  NIH On July 1, 1968 I moved my family (now including the recently born Cheryl) to Rockville, Maryland to begin my research career at the NIH in nearby Bethesda, Maryland. I had been assigned, through a matching program, to work with Drs. Jesse Roth and Ira Pastan in the Clinical Endocrinology Branch of the National Institute of Arthritis and Metabolic Diseases (NIAMD), now known as NIDDK, the National Institute of Diabetes and Digestive and Kidney Diseases. I was a Clinical Associate, meaning that in addition to doing full time research ten months out of the year, for two months I also supervised a clinical endocrinology in-patient service. Because of this, I gained a remarkable exposure to unusual endocrine diseases which were under study at the time. An example of this was acromegaly.  It was the heyday of interest in second messenger signaling after the discovery of cAMP by [Earl Sutherland](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1971/sutherland-facts.html). He would receive the Nobel Prize in Medicine and Physiology for this in 1971. One hormone after another was being shown to stimulate the enzyme adenylate cyclase thus increasing intracellular levels of cAMP. The idea that these different hormones might work through distinct receptors was talked about but was controversial. Moreover, at the time there were no direct methods for studying the receptors. I was assigned the challenging task of developing a radioligand binding method to study the putative receptors for adrenocorticotropic hormone (ACTH) in plasma membranes derived from an ACTH responsive adrenocortical carcinoma passaged in nude mice. Lacking any prior meaningful laboratory experience, I spent my first year failing at virtually everything I tried and not handling this very well.  Toward the end of 1968 I traveled with my family to New York City to spend the Thanksgiving holiday with family. I discussed my great frustration, unhappiness and lack of progress with my father. He counseled me to just “hang in there” while making plans to continue my clinical training in medicine and cardiology after the completion of my two year stint at the NIH. We agreed that I obviously was not cut out to be a scientist and besides I had always dreamed of being a physician anyway. This plan made good sense to me. Our conversation, however, turned out to be the last time I spoke with my father, who died several weeks later after suffering his fourth myocardial infarction at age 63. His death affected me deeply and I felt, in some odd way, a responsibility to fulfill the plan of my future career that he and I had devised together during our last conversation. His death, combined with my repeated failures in the laboratory during 1968–69, made this one of the most difficult years of my life.  Accordingly, over the next few months I made plans to move to the Massachusetts General Hospital (MGH), one of the Harvard teaching hospitals, in July 1970 for an additional year of medical residency followed by two years of cardiology fellowship. Then, during the summer of 1969, my experiments began to bear some fruit. I was successful in developing the binding assay for ACTH and over the next year wrote my first scientific papers and presented my findings at meetings for the first time. It was exhilarating and fun. For the first time I began to consider the possibility of a career that included a research component. These musings were moot, however, since by now I was committed to moving on to full-time clinical training in Boston.  Recently, two Nobel Laureates, [Mike Brown](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1985/goldstein-facts.html) and [Joe Goldstein](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1985/goldstein-facts.html), published a brief essay discussing the remarkable number of Nobel Laureates (9 so far) who have in common the fact that they came to the NIH as physicians during the brief space between 1964–1972 for postdoctoral research training. (1)  They dissect the unique convergence of circumstances which may have been responsible for this extraordinary result, including the quality of basic science mentors on the full time NIH staff, the competitiveness of “the best and the brightest” to obtain these positions during the Vietnam War years, and the now bygone emphasis on teaching of basic sciences in medical schools in the 1960s.  I was particularly fortunate to have access to two physician scientists as mentors, individuals with very different styles and personalities. Jesse Roth was highly imaginative, creative and burned with an infectious enthusiasm for almost any experimental result. Ira Pastan, no less creative, was much more staid, methodical and critical of every result. He could always spot a crucial control I had left out of my experiment, thereby rendering the result essentially uninterpretable. In addition to guiding me through these early days of my scientific career, they provided ongoing support during the period of repeated failure. I owe to these two men my introduction to research in general and to receptor biology in particular. As with my parents, I can readily perceive aspects of both of their approaches in my own scientific investigation and mentoring.  Lineages among Nobel Laureates are often commented upon. In my case, Jesse Roth had trained with Solomon Berson and [Rosalyn Yalow](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1977/yalow-facts.html) whose development of radioimmunoassay led to the Nobel Prize in Medicine and Physiology to Yalow (1977) after Berson’s untimely death in 1972. Moreover, training in Ira Pastan’s laboratory contemporaneously with me was my medical school and house staff classmate and future Nobel Laureate, Harold Varmus. Ira had himself trained in the lab of another NIH career scientist, Earl Stadtman, who also trained a future Nobel Laureate, Mike Brown.  Massachusetts General Hospital A defining experience occurred during my first six months back in clinical service as a Senior Resident at MGH. I gradually became aware of the fact that I missed being in the lab. Deprived of my daily “fix” of data, I felt somehow unsatisfied. This, despite the fact that I was again enjoying the hectic pace of the clinical work. Upon completion of the first six months of my residency year I was entitled to choose clinical electives for the next six months. Instead, and in clear violation of hospital rules for resident physicians, I elected to start back in the laboratory. Dr. Edgar Haber, the Chief of Cardiology and a prominent immunochemist, allowed me to begin working in his lab. I was fascinated by receptors and what I saw as their potential to form the basis for a whole new field of research just waiting to be explored. I spent a great deal of time analyzing which receptor I should attempt to study. As an aspiring academic cardiologist I wanted to work on something related to the cardiovascular system. I also wanted a receptor known to be coupled to adenylate cyclase. I initially focused on two models, the cardiac glucagon and *β*-adrenergic receptors. However, my attention quickly became focused on the latter, for very practical reasons. Unlike the case for peptide hormones such as glucagon or ACTH, literally dozens, if not hundreds of analogs of adrenaline and noradrenaline, as well as their antagonists were available which could be chemically modified to develop the types of new tools which would need to be developed to study the receptors. These would include radioligands, photoaffinity probes, affinity chromatography matrices and the like. Moreover, the first *β*-adrenergic receptor blocker (“*β*-blocker”) had recently been approved for clinical use in the United States, adding further to the attractiveness of this target to me.  So in the early months of 1971 I began the quest to prove the existence of *β*-adrenergic receptors, to study their properties, to learn about their chemical nature, how they were regulated and how they functioned. This work has consumed me for the past forty years. Over the next several years in Boston, working mostly with membrane fractions derived from canine myocardium, I sought to develop radioligand binding approaches to tag the *β*-adrenergic receptors. I focused initially on the use of [3H]labeled catecholamines such as norepinephrine, which are agonists for the receptor. Specific saturable binding could be demonstrated, and I thought initially that we had developed a valid approach to label the receptors. However, it became increasingly clear over the next few years that the sites being labeled lacked many of the properties that would be expected for true physiological receptor binding sites. Coming to this realization was difficult.  During this time I also published some of the very first studies demonstrating GTP regulation of *β*-adrenergic receptor stimulated adenylate cyclase following after the work of [Martin Rodbell](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1994/rodbell-facts.html) on GTP regulation of glucagon sensitive adenylate cyclase. I was now a cardiology fellow. As at the NIH, nights on call were often spent in the lab doing experiments while hoping that my on call beeper would remain quiet. During these years, I had many stimulating and profitable discussions with Geoffrey Sharpe, a faculty member in the Nephrology Division with an interest in cell signaling and adenylate cyclase.  The period in Boston from 1970–1973 was one of the busiest in my life. In addition to my “day job” as a Medical Resident and Cardiology Fellow, I also worked several “moonlighting jobs” to help support my growing family (my fourth child, Mara, arrived in 1971). I worked in various emergency rooms, did physical exams for insurance companies, and even served as team physician for a high school football team for two seasons (they never won a game during this time).  In the summer of 1972, I was recruited by Duke University Medical Center to join their faculty to develop a program in “molecular cardiology.”This was to begin upon the completion of my fellowship at MGH in 1973. The overtures came from the Department of Medicine (Chair, Dr. James B. Wyngaarden), the Cardiology Division (Chief, Dr. Andrew Wallace) and the Department of Biochemistry (Chair, Dr. Robert Hill). I initially declined their offer but, when they subsequently raised the ante including an Associate Professor rank in Medicine, it seemed like an offer “I couldn’t refuse.” Now, my course was set to move to Duke in Durham, North Carolina, to begin my faculty career on July 1, 1973.  Duke Arriving at Duke on July 1, 1973, with my wife and 4 children (ages 2–9), I proceeded to set up my lab in a brand new building, the Sands Bldg., on Research Drive. I would occupy this space for fifteen years before moving to the new CARL building. It was clear that we still needed to develop a radioligand binding assay for the *β*-adenergic receptors in order to be able to study them. This would ultimately take us close to another year. However, in work with postdoc Marc Caron in the spring of 1974, we succeeded in developing [3H]dihydroalprenolol. Contemporaneously, Gerald Aurbach at the NIH, and Alex Levitzki at the Hebrew University in Jerusalem also developed similar approaches using different radioligands. This was a watershed event because it finally opened the door to direct study of the receptors. Together with M.D./Ph.D. student Rusty Williams we developed comparable assays for the α-adrenergic receptors shortly thereafter. Over the next several years we developed a variety of tools such as photoaffinity probes and affinity chromatography matrices for the various adrenergic receptor subtypes as well as computer based analytical approaches for analyzing ligand binding data. These approaches greatly facilitated the discovery of new receptor subtypes and led to new ways of conceptualizing receptor G protein interactions (for example the ternary complex model).  During my first five years at Duke I juggled clinical and laboratory responsibilities, attending Cardiology clinic each week as well as making teaching rounds on the Medical Service. As the years passed I gradually reduced these clinical activities, but I continued to make teaching rounds until 2003. For the past 10 years I have not engaged in clinical work.  For the first 20 of my 40 year career at Duke, I focused on three essential questions about G protein coupled receptors: what is their chemical nature; how do they signal; how is their function regulated? This period included the isolation of all four of the then known adrenergic receptor subtypes; cloning of their cDNAs revealing the homology with rhodopsin and the existence of the much wider gene family of seven transmembrane G protein coupled receptors; the discovery of the arrestin and G protein coupled receptor kinase gene families, the products of which desensitize the receptors; and the discovery of constitutively active mutant receptors, now known to be the cause of a growing number of inherited and acquired diseases. Our early work with the adrenergic receptors provided a template upon which many labs were able to build, using the first sequences of these receptors and homology cloning techniques to rapidly build out the family of GPCRs to its current huge size of ~1,000 genes in humans. The sheer size of this family, including hundreds of olfactory receptors, was not anticipated.  The next 20 years, until the present, have been focused more on the *β*-arrestin proteins. Originally discovered in the context of their role in desensitizing receptors, we have found that they are also key molecules involved in receptor signaling and endocytosis. I have been particularly interested in the phenomenon of “biased agonism”at GPCRs. This term refers to the unexpected ability of some receptor ligands to stimulate some receptor-promoted responses while blocking others. Working initially with the angiotensin AngII1A receptor we found peptide ligands that could stimulate *β*-arrestin mediated signaling while serving as antagonists for G protein mediated responses (“*β*-arrestin-biased”). The existence of such biased ligands has important implications for both basic and clinical research. For example, it strongly implies that there must be multiple active conformations of the receptor which have now become the object of biophysical and structural studies. Moreover, this discovery suggests that such biased GPCR ligands might represent an entirely new class of drugs which might display more specific actions with fewer side effects. To try to develop such agents, about five years ago, I co-founded a company called Trevena with my Duke colleague Howard Rockman. Details of many of the discoveries mentioned above are provided in my Nobel Lecture.  Throughout my scientific career there have been a number of sources of special satisfaction. One has been the trainees whom I have mentored, more than 200 at this point. Many of these have gone on to distinguished careers in academia, biotechnology and the pharmaceutical industry. My co-recipient of the 2012 Nobel Prize in Chemistry, Brian Kobilka, joined my lab as a cardiology fellow in 1984 and left for Stanford in 1989. He played a major role in our cloning of the adrenergic receptors. Even during those early years in training he demonstrated an appetite for risk and the talent for developing bold, original technical approaches to difficult scientific problems which have characterized his independent career ever since. In a gratifying turn of events over the past several years, Brian and I have been collaborating again on several projects of mutual interest.  There is no way that I can acknowledge here the many other individuals whose work, in aggregate, was recognized by my Nobel Prize. However, during the 70s and 80s, Marc Caron was a long term partner and deserves special mention.  A second major source of satisfaction has been the rapid translation of many of our findings and techniques into practical consequences in drug development. GPCRs are one of the commonest targets of therapeutic drugs. Thus, the development of radioligand binding methods and associated computer based analytic techniques fundamentally altered the way in which drug candidates were screened and developed, as well as how receptor subtypes were discovered. The cloning of the receptors led to discovery (by others) of many new “orphan” receptor drug targets. More recently our discovery of so called “biased” ligands which can preferentially activate G protein or *β*-arrestin signaling has suggested an approach to development of more specific drugs with potentially fewer side effects. A special aspect of my career has been my relationship with the Howard Hughes Medical Institute. I became an HHMI Investigator 37 years ago in 1976, at a time when there were only about 50 Investigators. Today there are well over 300 and I am one of the two longest serving Investigators (the other being Richard Palmiter). The Institute’s “Investigator” based support, rather than the “project” based support of conventional grant funding agencies has given me great freedom over the years to pursue my research goals in an unfettered and very privileged way. My research has also been supported throughout my career with grants from the NIH.  Along the way to receipt of the Nobel Prize I have been fortunate to receive a number of other awards for my research. Among others, these include: The Gairdner Foundation International Award (1988); Bristol-Myers Squibb Award for Distinguished Achievement in Cardiovascular Research (1992); Fred Conrad Koch Award – The Endocrine Society (2001); Jessie Stevenson Kovalenko Medal of the USA National Academy of Sciences (2001); Institut de France – Fondation Lefoulon-Delalande Grand Prix for Science (2003); The National Medal of Science (2007); The Shaw Prize in Life Science and Medicine (2007); The Albany Medical Center Prize in Medicine and Biomedical Research (2007); Research Achievement Award, American Heart Association (2009); BBVA Foundation Frontiers of Knowledge Award (2010).  I have been elected to membership in the National Academy of Sciences, the Institute of Medicine of the National Academy of Sciences, the American Academy of Arts and Sciences, The American Society of Clinical Investigation and The Association of American Physicians.  PERSONAL LIFE I have a strong family history of coronary artery disease, my father having died at age 63 of a myocardial infarction and my mother having suffered a myocardial infarction at age 57. Perhaps not surprisingly, I developed angina at age 50 and had quadruple bypass surgery in 1994. I have tried to minimize my risk factors as aggressively as I can with daily physical exercise, a vegetarian diet and appropriate medications.  I have five children with my first wife, Arna: David (b. 1964); Larry (now Noah Jordan)(b. 1965); Cheryl (b. 1968); Mara (b. 1971) and Joshua (b. 1977). At the time of this writing I have five grandchildren: (Maya, Jonah, Madeleine, Samantha and Ethan). I have been married to the former Lynn Tilley of Durham, North Carolina, since 1991.  My family has always been a great source of pride, love and support for me throughout my career. While there can be little doubt that my obsessive focus on my science somewhat limited the time I could spend with each of my children as they were growing up, I like to believe that my work ethic, passion and enthusiasm for my life’s work provided a valuable role model for them. I started my family when I was quite young. My eldest child, David, was born when I was only 21 and my youngest, Joshua, was born when I was 34. In consequence, I have had the pleasure and privilege of relating to them for many years as adults. Having all of them, their spouses and significant others, two of my grandchildren and my wife Lynn with me during the festivities of Nobel Week was a joyous experience which we will always remember (Fig. 1). |
| **Autobiographical** |  |
| **Podcast** | No scripts |
| **Telephone**  **interview** | [RL]  [Robert Lefkowitz] Hello.  [Adam Smith] Hello there, this is Adam Smith from Nobelprize.org  [RL] Yes  [AS] So, we have a tradition of interviewing new Laureates very briefly for the website. Could we talk for just a very few minutes?  [RL] Sure. It’ll be my pleasure.  [AS] Thank you very much, indeed. First of all, sincere congratulations on the award.  [RL] Well, thank you, it’s a very exciting day, needless to say.  [AS] It must be, in fact, in fact I’ve been talking since the announcement with my old friend Richard Bond from Houston, who’s been …  [RL] Oh yes! I love Richard, he’s an old buddy of mine.  [AS] Indeed, and he’s been describing that he’s been hearing about the scenes of jubilation that are going on in your lab and it’s crammed with people.  [RL] Absolutely, and it’s, when I got in this morning, it was a bit late as I’ve been doing phone interviews from home, and they had balloons up, they greeted me outside. It’s just such a boost, you know, for the people in the lab. You know, they work so hard everyday and to see recognition for what we’ve been doing over the years, even if, you know, it was done by the apprentices, is a huge source of pride and excitement for all of them.  [AS] It must be absolutely wonderful. I guess it must played havoc with the plans for the day, but that’s another story.  [RL] Oh absolutely. In fact, I was supposed to get a haircut at one o’clock today, which I badly need. If you had video, I’m sure you’d agree. But instead, I have a news conference to do. So the haircut will have to wait a day or two. But in addition to the people in the lab, everybody, you know, people are just walking in here, colleagues who have known me for years. I sense an immense sense of institutional pride. We’ve not had a Nobel Prize at Duke. We’re a relatively young institution at 75 years, which pales by comparison with things like Harvard or Princeton, this kind of thing. So, I think, for everybody at the institution, I think everybody is sort of feeling real good about it.  [AS] And, indeed, there seems to be a worldwide celebration, because your lab, of course, has been working on GPCRs for four decades. It has spawned an awful lot of people who have gone out to other places and the whole field seems to be happy there’s an award now.  [RL] I think so, and I think, as you will probably know better than many, the Nobel Prizes are often seen as, of course, awards to individuals. But beyond that they are recognition often of a field. So everybody in the field feels good about it. Especially, if they feel good about the particular people from the field who are getting the award. And I really do think that, you know, the kind of contributions that Brian and I have made over the years are generally regarded, you know, very positively and as being important in the field, you know, everybody in field really feels good about it.  [AS] Those four decades have really been a golden era for the discovery of neurotransmitter receptors.  [RL] Absolutely, the whole idea that there might such receptors goes back a century but interestingly, when I started doing my work, forty years ago, there was still huge scepticism as to whether things like receptors really existed. Even from some of the people who were central in pharmacology. And in the very early years of the work there was a lot of push back in terms of, whether you can really do this, you’re isolating receptors, how do we know they are receptors? And now, of course, to my students and fellows, they are surprised to hear there was ever such scepticism.  [AS] [Laughs] Yes, because your isolation and then the sequencing the beta-2-adrenoceptor, really, well it was the first isolation and it sort gave the Rosetta Stone through which everybody else was able decode the dozens of others receptors.  [RL] I think this is exactly right. And, you know, like so many contributions in science, it took years. It took us a decade to get these receptors isolated. And then another number of years, to get them cloned. So you’re talking fifteen years to get to that point. And similarly with Kobilka’s recent crystal structures, you can throw in another 10, 15 years there. So I mean, it’s tough. It really is.  [Both laugh]  [AS] It takes time, it takes perseverance.  [RL] Exactly.  [AS] Now, it was during the sequencing of the beta-2-adrenoceptor project that Brian Kobilka joined your lab.  [RL] Yes, exactly, he was a fellow working in my laboratory. We were collaborating with a lab in Edmurk. And we had already purified the receptor, and together with them we had quite these little stretches of protein sequence, which was truly the Rosetta Stone which allowed the cloning. The whole key to the whole thing was that decade of work to get those receptors purified. And so Kobilka, in my lab, was the fellow leading the cloning work, not the original biochemistry. Then we were collaborating with a group at Edmurk. That was sort of his baptism of fire, so to speak. And so he was very active in that research. He was in my lab for, really, about five year all together, and had a very productive time. It was clear to me then that he was a very, very special guy.  [AS] Well it’s funny, because he’s disarmingly quiet. He’s such a self-effacing chap.  [RL] Oh my goodness, I think he’s painfully shy. I think that’s why he’s very self-effacing and that’s just his personality. I hope he can really enjoy this today and the next month or two, because this is not his comfort zone, I would say.  [AS] Yes, exactly, in fact we spoke to him earlier and he was expressing the fact that he thought he probably wouldn’t enjoy what about to come.  [RL] Yes, I think that’s correct.  [AS] But hopefully he’ll enjoy the trip to Stockholm.  [RL] Well I’m sure he will.  [AS] But in the meantime, we should leave you to enjoy your celebrations. And unlike Brian Kobilka you sound like the kind of person who will enjoy the next few days.  [RL] Indeed, I intend to enjoy this day to the fullest.  [AS] [Laughs] I’ll let you get on with it then. Thank you very much for speaking to us.  [RL] Okay, thank you. Bye bye.  [AS] Bye bye. |
| **Interview** |  |
| Q9 | I know you have been looking forward to this. This trip, this prize – how has it been so far? |
|  | Robert Lefkowitz: Very very hectic. In a way we almost don’t get a chance to look forward to it too much, because we are so busy with interviews and preparations and just doing things for the press etcetera. Now finally we are here and it’s happening and it is just remarkable. |
| Q5 | You’re known to be a person that makes other people glow – a great mentor – how do you manage? What’s your recipe? |
|  | Robert Lefkowitz: This is a very good question. I think that for most things of this nature, there probably isn’t a recipe. I try to teach my fellows that we are all born with certain gifts and with certain deficiencies. You have to play … The key to be successful I think is to emphasize your strengths and try to stay away from your deficiencies. One of my gifts, I guess, is that I have a great level of enthusiasm for what I am doing and that seems to be infectious. If I am enthusiastic about something everybody around me seems to get enthusiastic about it. I once looked up the derevation of the word enthusiasm. It comes from the Greek and apparently literal derevation means “a God within” this enthusiasm. I think enthusiasm is just something bubbling up from inside you and I think it’s a wonderful thing to bring to your work, because if you bring that kind of enthusiasm to your work, it feels like play. |
| Q17 | You are a quite focused person, very dedicated. Were you dedicated to your piano playing? |
|  | Robert Lefkowitz: No, I was terrible at the piano. My mother insisted that I’d take piano lessons and I hated … The low point of my week – I had weekly lessons – the low point of my week was when I would walk into the studio and have to perform for my teacher and he would say, “You’re not doing very well” and I’d say, “I know” and he’d say, “Did you miss any days this week, of practice?” – I was supposed to practice an hour a day – and I’d say, “Well, I guess I did” and he’d say, “How many did you miss?” and I would have to say, “Well, six”, so not very much practice. |
| Q10 | Have you started a club, like secret one with a secret code? |
|  | Robert Lefkowitz: Not really a secret club, but it is remarkable. There was a little essay published in a very prominent journal called Science just last week written by two of my closest friends and colleagues [Mike Brown](https://www.nobelprize.org/prizes/medicine/1985/brown/facts/) and [Joe Goldstein](https://www.nobelprize.org/prizes/medicine/1985/goldstein/facts/) from Dallas Southwestern university, he is a prior laureate. They were sitting behind me – which I had no idea that would be the case – they were directly behind me on the stage, there was a row of former laureates. It turned out that they wrote an essay, the impetus to which was my being awarded the Nobel Prize. The theme of the essay was that there were nine of us now – who had won the Nobel Prize – who trained at the National Institute of Health, physician scientists in an eight-year period between the mid–1960s and the early 1970s. It’s a remarkable record. |

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| **Biographical** | I was the second of two children born to Betty (Elisabeth) and Franklyn Kobilka on May 30, 1955 in Little Falls, Minnesota, a town of approximately 7,000 inhabitants along the Mississippi River. While small by most standards, Little Falls was the largest town in Morrison County and was known as the boyhood home of the pioneering aviator Charles Lindbergh. My sister Pam was three years older (Figure 1). My father owned and operated a bakery in Little Falls.  My father’s bakery was relatively large for a small town, with 6–8 full time employees and several part time high-school students performing various jobs after school. My sister and I worked part time in the bakery from the age of 13. My first job was slicing and packaging bread for sale at local supermarkets. Working at the bakery gave me the opportunity to see my father in action. The bakery was operated by my grandfather and great uncle before World War II. When my father returned from service in the army he took over the management and started to expand the bakery from a simple storefront business to one that supplied fresh baked goods to local supermarkets, restaurants and schools. The bakery was a relatively complex small business that prospered by producing a large variety of excellent baked good including breads, pastries, cakes and candy. To make all of this work, my father had to be able do every job in the bakery, because when someone called in sick he had to be able to fill in: bake bread, pastries and donuts, decorate cakes, drive the delivery truck. He also did all of the purchasing, planned the production and managed accounting, payroll and advertising. I believe his success was due to his versatility, work ethic, good humor and ability to motivate people to do their best. While I have a very different occupation, I believe that I learned a lot from my father that has helped me manage a research group.  I attended St. Mary’s elementary school through the eighth grade then moved onto Little Falls High School. I was not a particularly good student in grade school. I remember having some problems learning to read. However, by the time I entered high school I had overcome these problems and was doing well academically.  My interest in science probably grew out of my interest in becoming a physician. I was very impressed by the respect given to local physicians and I particularly admired my pediatrician, who lived in my neighborhood. Whenever I was sick, I would be taken to his office or his home for treatment. My favorite classes in high school were math, physics, chemistry and biology. I found the subject matter most interesting and the teachers were engaging. I struggled more with languages, literature and writing, but fortunately I had a teacher who insisted that we learn to express ourselves in writing.  While I wasn’t a gifted athlete, I enjoyed running (cross country and track) and bicycling. I was introduced to bicycle touring and racing by an older friend, Tim Hansen, the son of my pediatrician. When Tim graduated from high school (he was 17 and I was 14) he convinced my parents to let me go with him on a bicycle tour to Yellowstone National Park and back – approximately 1,400 miles. As you can see in the picture we were small, skinny and weighed only slightly more than our bicycles and gear (Figure 2).  At the end of each day riding an average of 100 miles, we would look for some place to spend the night for free. We slept in schools, churches, private homes, and on two occasions in jail cells. It was an amazing experience and I still remember struggling up a mountain pass, looking up from my front wheel and seeing a massive male moose eating grass by the side of the road. I was hooked on cycling and during the next few years would spend summers riding across the U.S., touring England as well as doing some racing. I continue to enjoy cycling and in 2005 I had the pleasure of riding in the Pyrenees with my son Jason during the Tour de France (Figure 3). **Undergraduate Years** In 1973 I entered the University of Minnesota, Duluth with the intention of studying biology in preparation for medical school. During my first term I met two people who would have a lasting effect on my life and career. The first and most important encounter occurred in biology lab. Students worked together in groups of four. On the first day of class my group consisted of three freshmen and an irate sophomore. The sophomore (Tong Sun Thian), who was upset at having to defer to freshmen for choice of lab, would become my wife in 1978 (more about Tong Sun later).  The second important encounter was with Professor Conrad Firling, the biology professor who taught both the course and my lab section. Professor Firling delivered lectures in basic biology with enthusiasm and passion. I learned that he was willing to take undergraduates into his lab to work on projects in developmental biology. The first technique I learned was the proper way to wash glassware, and I washed a lot of glassware. I eventually progressed to bench work and helped Professor Firling develop an organ culture medium for *Chironomous tentans*, a model system for developmental biology. Tong Sun also joined the Firling lab and worked with me on this project.  As an undergraduate, I majored in biology and chemistry and benefited from excellent teachers and small classes. In addition to my work with Professor Firling, I worked on a summer project with Professor Robert Carlsen, an organic chemist. In spite of my growing interest in basic research, I applied to ten medical schools as well as a few graduate programs. I still envisioned a career in medicine and the graduate programs were a back-up option if I didn’t get into medical school. Of the medical schools to which I applied, Yale was by far the long shot. I was very surprised when I received the acceptance letter. **Yale University Medical School** My move to New Haven was a culture shock because of the inner city location and the academic environment. The medical school was located in a neighborhood troubled by crime and poverty. In school, I was intimidated by my classmates, many of whom came from Ivy League schools, some having had successful careers outside of medicine.  At Yale, all medical students were required to write a thesis based on original research, which we were to fit into our normal class schedule and vacations. My first research project involved dengue fever and allowed me to spend a summer working in a lab in Malaysia experiencing tropical epidemiological research. This gave me the opportunity to observe field research first hand, as well as perform bench work under more primitive conditions than I was used to at Yale. While this project was not successful, it was a great experience and led me to briefly consider tropical medicine as a career. For my thesis project I worked with Professor Denis Knudsen, a virologist in the department of epidemiology, studying the genetic diversity of rotavirus, a common cause of gastroenteritis in children.  Tong Sun and I married in 1978, after my first year in medical school. At Yale she worked in the Lab of Professor Caroline Slayman and obtained a masters degree in East Asian Studies in her spare time. **Clinical Training At Barnes Hospital** My career path following medical school was dictated early on by financial constraints. My medical school tuition was covered by a Public Health Service Corps scholarship that obligated me to work in a medically underserved community for three years following my residency training. As such, a career in research was not an immediate option. I decided on a residency in internal medicine and was assigned by the match program to a position at Barnes Hospital, which is affiliated with Washington University School of Medicine in St. Louis, Missouri. My career options changed during my final year at Barnes. Due to budget cuts, many of the Public Health Service programs lost funding. As a result, I was allowed to pay back my medical school scholarship by working in an academic hospital for three years, giving me the opportunity to explore basic research.  During my clinical training at Barnes Hospital, I became particularly interested in intensive care medicine. Patients admitted to one of the three intensive care units (medical, pulmonary and cardiac) were typically very unstable, requiring urgent intervention, often with medications acting on G protein coupled receptors (GPCRs) including adrenergic and muscarinic receptors to regulate their heart rate and blood pressure, as well as opioid receptors to control pain. My interest in intensive care medicine led me to apply for cardiology fellowships. I was particularly interested in the program at Duke University, which allowed fellows to work for several years in a basic research lab. Moreover, the laboratory of Robert Lefkowitz at Duke was doing pioneering research on adrenergic receptors, giving me the opportunity to explore basic research in an area relevant to cardiovascular and intensive care medicine. I was fortunate to be accepted into the fellowship program and the Lefkowitz lab. **Fellowship Training At Duke University** While in St. Louis, Tong Sun and I started our family. Our son Jason was born June 7, 1981, one week before I started my internship. Our daughter Megan was born November 28, 1983 during the last year of my residency. My only regret is that my training and call schedule prevented me from spending more time with my young family during this time. In June 1984 we packed up our belongings into a U-Haul trailer and I drove east to Durham, North Carolina with the family following by plane (Figure 4). We moved into a spacious but drafty two-story apartment a few miles from the University and I would often run to work, leaving the car for Tong Sun and the children. I had started running back and forth to work in St. Louis as my only way of getting exercise. The trip was approximately 5 miles one way, or 8 if I was working at the Veterans Hospital. I would carry my clothes in a backpack and shower at the hospital. My running commute at Duke was shorter, so I would often supplement that with a 5 mile run on the Duke track before going to the lab. During the first few years in the lab I was in the best physical shape of my life. Tong Sun had taken up running regularly in St. Louis, and in Durham we would often take the children to a local high school track and take turns running while Megan and Jason played in the long-jump sand pit or jumped on the cushions for the pole vault.  Duke University gave cardiology fellows the option of starting in a research lab before completing their 18 months of clinical rotations. This was perfect for me because I was tired of being on call every 2 to 4 nights and wanted to spend more time with my family. My first few weeks in the Lefkowitz lab were a bit awkward. As a senior resident in medicine at Barnes, I was in charge of a team of junior residents and medical students that cared for 20–30 patients. On joining the Lefkowitz lab I became the least experienced person in a group of very talented young scientists consisting of predominantly postdoctoral fellows and a few graduate students. I was not familiar with any of the techniques being used and had yet to familiarize myself with the literature leading up to work being done in the Lefkowitz lab at that time. My colleagues were very friendly, but also very busy with their own projects and I really didn’t know where to begin.  During the first months in the Lefkowitz lab, while learning basic techniques such as ligand binding and adenylyl cyclase assays, I became aware of the effort to obtain a cDNA clone of the *β*2 adrenergic receptor (*β*2AR). This was a collaborative project between the Lefkowitz group and Merck. Jeff Benovic, then a graduate student, had succeeded in purifying enough *β*2AR from hamster lung tissue to obtain several peptide sequences. These were being used to make degenerate and ‘guessed’ oligonucleotide probes to isolated clones from cDNA libraries. Richard Dixon, an experienced molecular biologist at Merck, was doing the cloning work. This was exactly the type of research project I hoped to be involved in, so I asked if I could contribute. At this stage of the project, almost all of the work was being done at Merck, Bob Lefkowitz decided that I could try to generate antibodies to purified *β*2AR, which could then be used to identify cDNA clones using expression cloning methods. The project was relatively simple. I would purify protein from hamster lung tissue and immunize rabbits. This kept me busy part time for several months and in my spare time I started testing various cell lines in an effort to find one that expressed high levels of *β*2AR for use in making cDNA libraries. I screened approximately 10 cell lines and found that many appeared to express relatively large amounts of *β*2AR. For a brief period of time I felt I was making a real contribution to the effort. Unfortunately, careful scrutiny of my data and methods by one of my experienced colleagues revealed that most of what I was detecting as *β*2AR was in fact non-specific binding of radioligands to membrane lipids. To this day I remember the feeling of disappointment and stupidity associated with these botched experiments. My antibody work was going a bit better and I was able to obtain antibodies that could recognize the receptor, but the polyclonal serum reacted with a number of other proteins on western blots and was not specific enough to be useful for cloning purposes.  In brief, my first five months in the lab were far from successful. Surprisingly, Bob allowed me to continue. Despite my having made no meaningful contribution to the cloning effort using the biochemical and pharmacological expertise in the Lefkowitz lab, Bob allowed me to spend time at Merck learning molecular biology from Richard Dixon. Over the next few months, I made several one-week trips to Richard’s lab at the King of Prussia site of Merck just north of Philadelphia. This amounted to intensive training sessions where I learned how to prepare and screen cDNA libraries. When I returned to Duke, Bob gave me his approval to set up a molecular biology lab within the Lefkowitz lab. Tong Sun, who had a masters degree in microbiology, was hired part time to help with our fledgling molecular biology effort and over the coming months I would be joined by a few other new postdoctoral fellows and a graduate student. Our initial goal was to screen libraries prepared by Richard Dixon. During this time I had experience with non-specific binding of another sort. Many of our initial “hits” turned out to be non-specific interactions with our probes. This led to many cycles of exhilaration and disappointment common to many research efforts.  After about a year of failure, we came to the conclusion that *β*2ARs were expressed at such low levels in most cells that we might not be able to isolate a clone from a cDNA library. Additionally, we had concerns about the degenerate and ‘guessed’ DNA probes we were using. Using degenerate probes meant that we had the correct sequence, but also many incorrect probes that could contribute to non-specific false positives. To avoid this, we took advantage of codon bias information to make a best guess of the coding sequence for several peptides. This would limit non-specific interactions; however, if we made too many errors in guessing the coding sequence, we had no chance of pulling out the clone. We realized that we might stand a better chance of pulling out a DNA fragment from a genomic library. Even if the genomic clone was incomplete and interrupted by introns, we reasoned that it would provide a larger, more specific probe that would allow us to make enriched cDNA libraries or identify rare clones in existing libraries. I made a genomic library from hamster lung DNA and sent an aliquot to Richard at Merck. The library was initially screened with a few long guessed probes at Merck and Duke, and both groups isolated a clone that surprisingly contained the full coding sequence with no introns. After almost two years of frustration, we had an amazing stroke of good fortune.  Cloning of the *β*2AR led to cloning of several other adrenergic receptor genes as well as an orphan receptor that turned out to be a member of the serotonin receptor family. The initial G protein coupled receptor (GPCR) clones revealed a common seven transmembrane architecture shared with rhodopsin, a GPCR specialized for the detection of light. It was subsequently determined that there were nine genes encoding distinct adrenergic receptor subtypes.  After having a few adrenergic receptor clones in hand, I began exploring approaches to understand receptor structure. I first took advantage of having closely related receptors that responded to adrenaline, but activated different signaling proteins and bound to specific synthetic agonists and antagonists. Chimeric receptors generated from the alpha and beta adrenergic receptors provided the first clues to the role of specific domains of the receptor in ligand binding and G protein coupling. However, these studies did not tell us how the receptor worked in molecular detail, and I started to think about obtaining a crystal structure. Several years earlier Deisenhofer and Huber had obtained the first crystal structure of a membrane protein, proving that membrane proteins could be crystallized and demonstrating the value of protein structure in understanding mechanisms. However, the photosynthetic reaction center was a naturally abundant protein that could be obtained from bacteria. In contrast, even in lung tissue, where the *β*2AR was most abundant, it represented a very small fraction of membrane proteins. **Stanford University** Early in 1989 I began considering career options. I was offered a junior faculty position at Duke, and interviewed for similar positions at Washington University in St. Louis, the University of California San Francisco and Stanford University. At Stanford, Professor Richard (Dick) Tsien, who had just moved from Yale, was building a new Department of Molecular and Cellular Physiology in a new building called the Beckman Center. I remembered Dick from his medical school lectures at Yale; he was one of our favorite teachers. I was impressed by his enthusiasm and vision for the new department at Stanford. Most of the faculty would be junior recruits and new to Stanford. I accepted a position and moved to Stanford shortly after the Loma Prieta earthquake in 1989.  The move to Stanford brought many challenges and opportunities. The greatest challenges were financial. We would be moving from one of the most affordable housing markets to one of the most expensive. While I would be earning more at Stanford, our mortgage would triple and we would have only one income, as Tong Sun had started medical school. To accommodate the larger mortgage and medical school tuition, I took a 48 hour shift as an emergency room physician at a nearby hospital once or twice a month. During the six years at Stanford, with Tong Sun a full time medical student, I had the opportunity to spend more time with Jason and Megan as their primary care giver, making up for some of the time I missed during my residency training.  In the lab I focused on two questions: understanding the structure and mechanism of activation of the *β*2AR, and determining the physiologic role of specific adrenergic receptor subtypes. Cloning and pharmacological studies had identified 9 adrenergic receptor subtypes coded by 9 different genes: three *β*ARs, three *α*1ARs, and three *α*2ARs. The drugs available at that time were not sufficiently selective to allow assignment of specific functions to each receptor subtype. To address this problem we used recently developed methods to disrupt genes in mice. In collaboration with my Stanford colleague Greg Barsh, we created strains of knockout mice for 5 of the 9 adrenergic receptor genes (*β*1AR, *β*2AR, *α*2AAR, *α*2BAR and *α*2CAR) and were able to assign their roles in cardiovascular function and behavior.  At the same time we were laying the foundation for future biophysical and crystallography studies. We continued to use mutagenesis and chimeric receptors to provide a more detailed map of the functional domains of adrenergic receptors. We were also investigating receptor biosynthesis and exploring protein engineering techniques that would enable expression and purification of sufficient quantities of receptor for crystallography. My own efforts in the lab focused on comparing different expression systems (mammalian cells, insect cells, bacteria and yeast), and establishing an efficient purification protocol. By 1993 we were able to express and purify sufficient quantities of functional *β*2AR in insect cells to begin using fluorescence spectroscopy, one of the most sensitive biophysical techniques, to investigate receptor structure. We labeled purified *β*2AR with small, environmentally sensitive fluorescent probes, most often attaching them to a single reactive cysteine introduced into a specific domain. Using this approach we were able to observe ligand-induced conformational changes in real time. These relatively simple fluorescence experiments provided important insights into the dynamic character of the *β*2AR that would ultimately guide our strategies for crystallizing the *β*2AR and the *β*2AR-Gs complex.  With incremental improvements in expression and purification strategies we were able to produce enough *β*2AR to start crystallography trials. My Stanford colleague Bill Weis taught me the basics of setting up crystallography trials and would continue to be my crystallography mentor. These initial trials introduced me to the many types non-protein crystals (salts, detergent, lipids) that one encounters trying to crystallize membrane proteins. Each cycle of failed trials led to a reassessment of the approach followed by modifications to the strategy and a new round of trials. The increasing number of prokaryotic membrane protein structures being published during this time provided a constant source of inspiration. But it wasn’t until 2004 that we obtained the first crystals of the *β*2AR. These crystals were very small (β2AR crystals to the ESRF. Using a high intensity 5 micron beam we were able to see diffraction compatible with a protein crystal at a resolution of approximately 20Å. While we were disappointed in the poor quality of the diffraction, we were encouraged by the fact that we were able to form crystals of the *β*2AR. This was an important milestone in the effort and suggested that a crystal structure of the *β*2AR was not an impossible goal. With this milestone, I felt I could begin to involve postdoctoral fellows in the effort.  In 2005 Dan Rosenbaum and Søren Rasmussen, two very talented and intrepid postdoctoral fellows, joined the lab with the goal of crystallizing the *β*2AR. Søren and Dan took two different approaches to generate better quality crystals of the *β*2AR. Søren identified antibodies that bound to a particularly flexible region of the receptor and Dan used protein engineering to replace the same region of the *β*2AR with T4 lysozyme (T4L), a highly crystallizable soluble protein. Both approaches were designed to minimize conformational flexibility and increase the amount of polar surface area for forming crystal lattice contacts. During 2006 we obtained crystals using both approaches combined with a newly developed lipid-based media known as bicelles consisting of a mixture of lipid and detergent. Initial crystals of the *β*2AR-Fab and the *β*2AR-T4L fusion protein complex both diffracted to below 4 Å. We subsequently obtained a 3.4Å structure of the *β*2AR-Fab complex grown in bicelles. This was our first look at the three dimensional structure of the *β*2AR, but a higher resolution structure would soon follow.  In the fall of 2006 we sent purified *β*2AR-T4L complex to Vadim Cherezov in the lab of Raymond Stevens at Scripps. Vadim had trained with Martin Caffrey at the Ohio State University. Martin’s lab had recently developed miniaturized, high-throughput methods for lipidic cubic phase (LCP) crystallography. We previously explored the use of LCP methods to crystallize the *β*2AR in 1999 in collaboration with Peter Nollert; however, at that time the methods were very labor intensive and used relatively large amounts of protein to screen very few conditions. The methods developed in Martin’s lab together with the robot built by his team enabled screening of thousands of conditions with a few milligrams of protein. Vadim had recently joined the Stevens lab, bringing with him a LCP robot on loan from Martin Caffrey. This collaboration led to a 2.4 Å structure of the *β*2AR-T4L complex. The fusion protein strategy developed for the *β*2AR has since been successfully applied to a growing number of other GPCRs.  These first *β*2AR structures represented inactive states; however, our goal had been to understand the mechanism by which agonist binding leads to G protein activation. At a Gordon Conference in 2005, I met Roger Sunahara, a kindred spirit who had crystallized the G protein Gs during his postdoctoral fellowship in the lab of Al Gilman. Roger and I soon became friends and started a very enjoyable and fruitful collaboration. During the next 5 years our labs would use a variety of methods to study activation of the Gs by the *β*2AR and together with an incredible network of colleagues (outlined in my [Nobel Lecture](https://www.nobelprize.org/prizes/chemistry/2012/kobilka/lecture/)) we would accumulate the reagents and expertise to stabilize and crystallize the *β*2AR-Gs complex. The *β*2AR-Gs crystal structure was published in 2011 together with two companion studies using single particle electron microscopy and deuterium exchange mass spectrometry to characterize the dynamic aspects of this complex. These combined studies provided unprecedented insights into GPCR signaling at a molecular level.  As noted above, I have benefited from mentorship, advice and collaborations with colleagues from a broad spectrum of disciplines. I have been particularly privileged that my wife Tong Sun Kobilka has worked with me in the lab on and off for more than 30 years providing emotional, intellectual and technical support. It has been great to share the joy of scientific discovery with her and to have her encouragement when research wasn’t going well or funding was tight. My career in basic research has been very rewarding from several perspectives: discovering new knowledge, working with many brilliant and often intimidating students and postdoctoral fellows, developing friendships with scientists throughout the world, and having the flexibility to spend time with my family. I am very grateful to be honored with a Nobel Prize in Chemistry for my work on G protein coupled receptor, and for the recognition it brings to my colleagues in the field. |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** | [BK]  [Brian Kobilka] Hello.  [Adam Smith] Oh hello, may I speak to Brian Kobilka please?  [BK] Speaking.  [AS] Oh hello, this is Adam Smith, calling from Nobelprize.org, the website of the Nobel Prize. We have a tradition of recording extremely short interviews with new Laureates. Could we speak for just a very few minutes?  [BK] Sure.  [AS] [Laughs] Thank you. I know it’s the middle of the night there. First of all, sincere congratulations on the award.  [BK] Thank you.  [AS] I imagine the household was asleep when the call came?  [BK] Yes it was.  [Both laugh]  [AS] Who took the call? Did you get it?  [BK] Well, the first call I think, didn’t get answered. [Laughs] And the second one I did.  [AS] So they keep trying.  [Both laugh]  [AS] And what are one’s initial thoughts on getting that call?  [BK] I thought it was some friends, initially. But I don’t have friends that have a really good Swedish accent, so then I started believing it.  [AS] [Laughs] Do you feel that this is an utter surprise?  [BK] Ah, yes.  [Both laugh]  [AS] How nice, how nice.  [BK] It’s very nice.  [AS] So you’ve been awarded the Prize for your studies on G-protein-coupled receptors, and since the eighties when you joined the Lefkowitz lab, you’ve been trying to disentangle the structure of those receptors. For those who’ve never seen one, could you describe what they look like? Their beauty?  [BK] Oh, that’s really tough. I’m trying to think of something in nature that I could use as an example, but there really isn’t anything you encounter in the day that you could say is a good model for it. But to be able to see it for the first time is really amazing, in three-dimensions. So that was probably, there were times when you see some of the structures that we’ve got, and particularly the one last year where you see everything together and how it works together. It was really, really very satisfying.  [AS] So this is the entire complex together, with the G-protein attached and the ligand in place?  [BK] Yes.  [AS] That’s an amazing feat. It took so many years to get to that point. And many, I think, felt that it was an almost impossible task. What kept you going?  [BK] I don’t know. It was just something that I really wanted to see and I had a great group of colleagues working on it, and we were all excited about doing it. And, we just kept making incremental improvements in what we were doing and finally we succeeded. As I said, it was really a group effort. A lot of people involved and it was a very exciting project.  [AS] And it’s strange as these receptors are normally said to mediate the actions of about half the medicines we take, and yet, nobody really knows about them. It’s amazing. We’re full of them and they are so important but they’re rather unknown.  [BK] Yes, and we don’t really know how to control them very well yet. So the medicines still aren’t perfect. They have side-effects. Some of these are because targeting for one receptor, they are still kind of promiscuous and they’ll bind to another type of GPCR, so we still have quite a way to go before we can really take advantage of what we know about them in terms of therapeutics.  [AS] Now, you are a notoriously self-effacing person and quite a quiet person, I gather. How do you feel about the prospect of the deluge of press attention that’s about to arrive?  [BK] I’m not really looking forward to that.  [AS] You tend to avoid the limelight, as far as I know.  [BK] Yes, and as I said, I am not looking forward to that at all.  [Both laugh]  [AS] Maybe you can minimise the impact. You’ve been awarded with Bob Lefkowitz, with whom as I say, you worked in the eighties. And in a way, you’re very different characters. How did the two of you mesh together?  [BK] Oh, we mesh together very well. In fact, we still speak on a regular basis. And, in fact, we are just starting to put together a paper that our groups have been collaborating on a project for a couple of years, and we’ve gotten, made some progress. So, yeah, he’s a fantastic mentor. We are quite different, but I think, sometimes that works out well.  [AS] Yes. It’s a marriage of opposites.  [BK] And I couldn’t be happier for him.  [AS] It’s a lovely pairing. Really, really nice. Just one last thought. The field of structure solving in GPCRs is quite a competitive one, with people racing to get to the first structures. Again, how does one deal with the competition element of it?  [BK] I don’t know how much it affects you. When you have a goal, you obviously want to be the first there. Scientists are sometimes as competitive as professional athletes, maybe. But you can’t worry about it too much, or it will distract you from your goal. So I’m not sure what else to say about that. But if you really want something bad enough, if you’re really interested in something enough, you know, you just keep working on it.  [AS] Thank you. That’s a lovely answer. Just personally I just want to say that once when I was the editor of *Nature Reviews Drug Discovery*, you contributed beautifully to some GPCR features we were doing so it’s a particular pleasure for me, individually, to be speaking to you now.  [BK] Oh, well thank you. Was that the collection of comments?  [AS] That’s right, that’s right. It was the state of GPCR research, back in 2004.  [BK] I think at that time I said someone would get a GPCR structure soon.  [AS] Exactly.  [BK] Yes, I remember making some comment to that effect. [Laughs] I think that was quite a bit before we got the structure.  [AS] So when you said someone, did you have yourself in mind? Or were you not that certain.  [BK] Well, I hoped it would be me [Laughs]. I wasn’t very confident at the time we would get it.  [AS] There’s a difference between, yes, certainty I suppose and confidence. Because you seem to have remained confident in the ability to get somewhere, even though you weren’t certain you’d make it.  [BK] That’s true, I think I was somewhat confident. I think I had worked on it long enough. I think I knew the protein really well. So somehow, I mean, you’ve got to believe you can do it, otherwise … [Laughs]. I mean, it’s sort of a struggle because you have to get funding and keep the lab going. You have to believe in yourself to some extent.  [AS] Well it’s been a great pleasure to speak to you and I can picture the scene. Presumably all of the family is now up as well?  [BK] My wife and I are up, and kids have heard about it. And I have to tell that I have one of those rare marriages where my wife and I have been working together in the lab, ever since I was in the Lefkowitz lab, and we still work together. So it’s particular satisfying because she shares a lot of the credit for my success in the field and so I feel like I’m sharing it with her as well.  [AS] That’s lovely, that’s really nice. I suppose the Nobel Prize is always a family prize but this makes it even more so.  [BK] Yes.  [AS] Lovely, the kids are aware, but are they going to go back to sleep or what do they do?  [BK] Well my kids are kind of old.  [Both laugh]  [BK] My daughter is going to turn 29 soon and my son is 31. So they are not here in the house with us. But we texted them, and they woke up and they called us.  [AS] So there are sleepless people all over the States now.  [BK] Yeah, yeah.  [AS] When you come to Stockholm in December, we have a chance to interview you at a greater length and I very much look forward to that.  [BK] OK, thank you.  [AS] Lovely, best of luck with the day. Thank you.  [BK] Bye.  [AS] Bye bye. |
| **Interview** |  |
| Q9 | You are here for Nobel Week, the culmination of two months of fairly frenzied activity I imagine since the calls came. How have those last two months been? How have you found it? |
|  | Brian Kobilka: A bit overwhelming. It would have been a busy two months had this not happened, but it has been an extraordinarily busy time. |
| Q9 | I suppose not. And you had the added ownness of being the first Nobel Laureate from Duke University? |
|  | Robert J. Lefkowitz: Yes, indeed. This caused quite a bit of ruckus, that it was the first, and they likened it to when we won our first NCAA basketball championship under the very famous coach K, coach Krzyzewski. I think one of the most exciting things that happened to me, during this period of time was that I was honoured at Cameron Indoor Stadium, which is the basketball stadium, by coach K and the basketball team that presented me with a jersey with a number one on it and my name. Which seemed to impress my children perhaps even a bit more than the Nobel Prize itself. |
| Q3 | So why did you choose that field for your own research when you started research? |
|  | Robert J. Lefkowitz: I had been at the NIH for a fellowship in 1968 to 1970 and this was the golden age of second messenger signalling. [Earl Sutherland](https://www.nobelprize.org/prizes/medicine/1971/sutherland/facts/) had recently won the Nobel Prize for his discovery of cyclic AMP which is a molecule generated on the inner surface of the cell membrane when what we now know GPCRs are activated. My mentors there Jesse Roth and Ira Pastan thought it might be possible to label the receptors because they felt they existed. They were what would be called molecular endocrinologists and they thought it would be possible to label them with radioactively labelled materials. I was assigned the project of trying to label a receptor for ACTH, Adrenocorticotropic hormone, which works through a G-protein couple receptor and I spent my two years there radioactively labelling ACTH and showing that I could bind it to some sites on the plasma membrane of a tumour which was responsive to ACTH, so it was an ACTH responsive cancer that I passed in nude mice. We were successful in doing that. The work did not really go any further than just developing these radioligands, but really, the idea caught fire in my imagination! |
| Q2 | But you started out with the intention of becoming a medical doctor? And then you transitioned to research. I was going to ask you both, what sort of flipped you away from medicine onto the bench? |
|  | Brian Kobilka: I think I had the intention of, at the time I was in training in internal medicine in St Louis, of being an academic physician. Which meant that I would continue seeing patients and I would find some line of research. At the time I was really very interested in intensive care medicine and I believe there were not intensive care medicine fellowships at the time. It was either cardiology or pneumology and so I decided to go into cardiology. I learned that … I was also really interested in research, although I cannot at the time say I was really interested in adrenergic receptors. I was interested in the concept of using adrenaline in other compounds like that in intensive care unit. And Duke hade a fantastic research program for cardiology fellows. You could go to Duke, you could spend at least a year and a half doing research and you could do it up front, which was really attractive to me after spending three years taking care of patients and really wanting to try out research. I do not know how many places I applied to, but I was very happy to be accepted into Duke and very happy that Bob chose to let me in his lab. |
| Q6 | We will come to your lab environment soon. When was the last time you saw a patient? |
|  | Brian Kobilka: Actually, I continued to see patients while I was a fellow, primarily moonlighting and weekends, and I am not sure, but I think I can say this now since the statute of limitations is up, but when I moved to Stanford my wife Tong Sun started medical school, so our children were old enough to go to school. She started in medical school in Stanford, so we had a very large mortgage in tuition, and I continued to moonlight for quite a few years in emergency rooms. |
| Q2 | Maybe you are still moonlighting, maybe we should not talk about this … How about you, Bob, you had wanted to be a doctor? |
|  | Robert J. Lefkowitz: I very much wanted to be a physician, and had harboured that goal, I would say from the time I was eight or ten years old. Like Brian, I learned last week, a very similar experience, I was inspired by my family physician, who made house calls, and I decided that is it, that’s what I want to do, and I thought about nothing else in terms of a goal, right through grade school, high school and college. I would say that Brian, for what I know, who actually showed an interest in research earlier than I, because as I understand Brian had a mentor experience in college, and I think even won an award for his research thesis at Yale, if I am not mistaken. I had absolutely no research experience until I went to the NIH in 1968. In fact, in medical school we had a couple of opportunities to do two month’s electives in research – I never took one – I had no interest in it, I wanted only the clinical electives, so called sub-internships.  But in the late 60s, the Vietnam war was raging and many of us were opposed to that war on multiple grounds, there was a drift, physicians were drifted. You had to go in after two years of training which many of us did not want to do, so there were few options, they were very competitive to get, that would get you out of going to Vietnam. One was to join the United States public health service as a commissioned officer and be assigned to the NIH for two years. Very very competitive to get such positions, but I had a strong academic record, and I was able to get that, and it seemed like a good thing to do, because like Brian, I pictured myself someday as an academic physician and I vaguely had it in my head that academic physicians did some research. So, I figured, well, I get my research papers and I go. And that is where I got started in research.  Now there is a very interesting and timely piece in, I guess, last week’s issue of *Science*, by [Mike Brown](https://www.nobelprize.org/prizes/medicine/1985/brown/facts/) and Joe Goldstein, in which they review basically the history of that year, and remarkably it turns out between 1964 and 1972, I think is the slice they took, I became the ninth Nobel Laureate to have trained. I actually went through the list. Six of us came between 1967-70 and when I say came, I do not mean there were a hundred of us each year – in a year there might have been eight or ten or twelve – so it was a remarkably high success rate. |
| Q6 | When did you give up on patients? |
|  | Robert J. Lefkowitz: I actually made teaching rounds for 30 years at Duke. I would do one rotation a year, six weeks, from age 30 to age 60, at my 60th birthday, for a variety of reasons, I hang up my stethoscope. |
| Q2 | At Duke, you pursued this difficult task of purifying the β-adrenergic receptor, it took 15 years to purify and clone, that is quite an undertaking. Did you have, as you were on that path, the goal of that purification so that you were always looking that far ahead? |
|  | Robert J. Lefkowitz: Definitely. That was a goal for many, many years. Something interesting that … at least it is my view of things now, and maybe it is revisionist history, but when I look back on that period, my sense is that it almost never occurred to me we would fail. I always believed we would be successful. When I look back on it now, it was kind of crazy, but that is my sense of it now. I always assumed it would all work, I did not know when or how long it would take, but sooner or later we would get there. It never occurred to me that maybe it would not work at all and it would be a total dead end. |
| Q10 | Let’s talk about the lab a bit because you have had an immensely productive lab, both in the sense of papers and discoveries, but also in the sense of people. You have had more than 200 people? You must have got a research environment going which people want to join. What was the secret of it? |
|  | Robert J. Lefkowitz: That’s a very good question. I think there probably are a number of elements. One of course is the old business of success breeds success, if a program is successful then people want to come because there is high visibility research going on. As to why we were so successful, I mean there is a lot of mystical stuff, like I’m a great judge of talent, that’s how Brian came to my laboratory. I say that and we both laugh because when he came to interview as I recall, I was out of town.  Brian Kobilka: Right there, yes.  Robert J. Lefkowitz: I wasn’t there, and I think he even made a second visit, and I was also not there. But in any case, as I wasn’t there, so obviously I’m a good judge of talent, and I took him anyway, sight unseen. I think one of the things about working in a lab is to have good *esprit de corps*, which can’t be 100%, there is always going to be some odd balls or some oil and water mixtures of people just doesn’t get along, but I think in general we had good chemistry of people in the laboratory. I think I always brought to the endeavor a real sense of enthusiasm for what we are doing. Enthusiasm is something that you can’t fake, you can’t fool people. I remember at my 60th birthday party that Brian was at and many of the fellows came to, they were giving various talks about what they remembered. I remember one postdoc from that era, a wonderful guy named Rick Serione, who is now a professor of … has a name chair, in chemistry actually, at Cornell, was saying that one of the things that kept him going is that he always sensed from me that his project, which was a reconstitution of the receptor after it was purified, was the most important project in the lab, and he liked that, until one day he talked to some other guy and he said: No, I felt my project was the most important. It turned out that everybody thought their project was the most, and I guess somehow I transmitted that, because probably I believed it, including Brian’s, which really was the most important project in the lab. |
| Q10 | With Bob sitting here maybe it is not the right place to ask you, or maybe it is the right place, does that rhyme with your experiences of Bob’s lab? |
|  | Brian Kobilka: I would say yes. He was always very enthusiastic and encouraging, and you felt that you could try anything. I don’t actually remember there being any kind of limit on even what we could spend to try something that was completely sometimes crazy.  Robert J. Lefkowitz: I think one of the things I taught Brian was how to go into debt in the laboratory, and he has been very god at that, the reason he is I am sure he could tell you about. The folks in the lab probably didn’t even know it, bur on several occasions when things really got hot, and we were making progress on a project, I would just overspend, I would just not care about the budget, we would just do what we needed to do. I was called on the carpet on several occasions, both by the chairman in medicine, named Jim Weingarten, and also by the head of the Howard Hughes medical institute. The administrator of the Hughes institute, a guy named Kenny Wright, he was a good old Southern boy, and I remember on two occasions they sent him down specifically, as he put it, to ‘slap me on the wrist and take me up behind the woodshed’ because I had totally overspent my budget and he was there to sort of arrange things in. On the other hand, we were doing good work and he was kind to give me a wink, but he brought the message anyway. |
| Q5 | When you pick people to join your lab, what do you look for? People you can get on with foremost? |
|  | Brian Kobilka: It’s very important that not only I get along with them, that they get along with other people in the lab, it’s really important to have chemistry in the lab. I would say that the lab has been most successful when people work together on again, very challenging projects, sharing ideas, sharing reagents, really take teaming on projects – I think that’s really key to having a productive and enjoyable experience.  Robert J. Lefkowitz: I think something that is very important both to Brian and myself is the mentoring of the young people. People often ask me, because I have been successful in training so many people, ‘What are the keys to mentorship?’ It’s like everything else, there’s not one right way to do it, just like there’s not one right way to do science. I think many people consider both Brian and myself for good mentors but our personalities couldn’t be more different, so obviously we can’t possibly mentor people in the same way, and yet we both seem to wind up doing a fairly good job of it. I think a lot of this is just a matter of are you willing to invest yourself in people and really care about them and care about their careers and success. And challenge them! To put things in front of them which they really have to reach to get to. If you can give somebody the experience of working right at their potential, really doing something which tests them and extends their limits and let them feel what it is like to succeed at that level – then you have done it, because then they know what it feels like, they know what they are capable of and they are willing to challenge themselves in the future. |
| Q5 | You have to know them pretty well to know what to challenge them with? |
|  | Robert J. Lefkowitz: Exactly. For me personally getting to know people, getting in their head, because you challenge different people in different ways, it takes different kinds of things. The whole issue of how much to direct people, it’s a delicate balance, you can direct them too much, they may be successful in the short term, but they never gain the confidence that they can really do it by themselves. Or you can direct them too little, and they just drift and become unfocused etc. So the question is to provide enough direction but not too much direction. Of course, there’s nobody who can tell you what that is, you just have to figure that out individually. |
| Q2 | If we just return to the lab. You came into the lab and were involved in other stages of this β*–*adrenergic purification and cloning experiment where the structure of the β*–*adrenergic receptor was revealed. That acted in a phrase that seems very appropriate, as the Rosetta stone unleashing lots of other G-protein coupled receptor structures and revealing that there was this super family. I have often heard people say that in retrospect of course there was a super family, it was obvious, but was it obvious as you went into it? |
|  | Robert J. Lefkowitz: Not in the least. When we were cloning, we had first been successful in getting what we knew to be valid clones for the receptor. It’s not like today, it’s amazing to think back. How many nucleotides were there in the open reading frame … a couple of thousand?  Brian Kobilka: Yes, 1,500.  Robert J. Lefkowitz: And how long did it take between us and Merck to sequence that piece of DNA?  Brian Kobilka: I don’t remember.  Robert J. Lefkowitz: That wasn’t a day or two, was it?  Brian Kobilka: No, wasn’t a day or two.  Robert J. Lefkowitz: It was probably a matter of weeks.  Brian Kobilka: Probably between 100 and 200 base pairs.  Robert J. Lefkowitz: While we were sequencing it, word began to get around on campus, I don’t know if you know this story… Word got around the campus: we had it. OK. And I don’t remember who, but somebody … We had part of the sequence, I don’t know how many base pairs, and we knew we had the right thing because we already could see some of the five peptides that we knew were in there from our sequencing of pure protein. And a colleague said: ‘What does it look like?’ And I remember distinctly saying to him ‘It doesn’t look like anything, why should it look like anything, this is the first one’. So that shows you the extent to which we were not expecting what we eventually found which was the homology with rhodopsin. This even now, the functional analogies between rhodopsin and transducin and the /- – -/ with the βreceptor, the G protein, those functional analogies were clear, and I think by then it was probably clear that transducin and Gs were members of a family. Nonetheless, nobody was expecting the βreceptor and rhodopsin to look alike, it was only later, after the full sequence emerged that these homologies became clear. But in the early going I thought we were describing the very first … they were so generous. |
| Q6 | Was it with great pleasure that you realized that you were suddenly opening up this super family, or was it in fact a sense of oh, other people knew this already, other people could have tweaked this? |
|  | Robert J. Lefkowitz: Shortly after we reported our clone, about four months later, Elliott Ross, Dallas, reported on another, the β*1–*adrenergic receptor, from a turkey, and it looked very similar. Then /- – -/ Anouma, a little bit later, reported on two muscarinic receptors. Very quickly, within a year or less, we had those, and then we, Brian, cloned the α2*–*adrenergic receptor again, within about a year based on protein sequence that we had. Very quickly it was filling out that there was this family. I think in the moment we cloned the β2 I think it was a Heureka moment, but I don’t think any of us … and we /- – -/ right enough for a paper maybe they are all going to look like this, but I don’t think any of us really conceived just how large and diverse this family was going to be. And certainly of course the olfactory receptors which came four, five years later doubled the number of receptors right on the spot. It’s like all discoveries – many discoveries – you don’t fully appreciate the significance in the moment, it becomes clearer and clearer and clearer over the years. |
| Q15 | Everybody needs a sounding board; you obviously have an appetite for these high-pressure situations. We don’t have very long left, but I would like to just touch very briefly on the medical aspects. As I said in the beginning, about 50% of medicines acts through GCPRs, but there are a lot of off target effects and side effects. Would you like to say how the work that you do has impacted, or will impact, the development in medicines? |
|  | Robert J. Lefkowitz: I think that in particular the recent work that both Brian and I have been doing – totally different kinds of work – each in their own way has implications for potentially developing more specific medications, by which we mean medications which have less side effects. If you look back over the history of pharmacology at least during the 40 years that I have been involved, there have been several advances that have helped us to … by “us” I mean others, I mean the drug /- – -/, the tailor GPCR targeted drugs with less side effects. The first development was the elucidation of previously unknown receptor sub-types. The cloning revolution changed everything. When I started my career I think there were three adrenergic receptors and then early on, I guess around the time in the early med-seventies a fourth was discovered. By the time we got done with our cloning we had eight and then a ninth was added. There was one dopamine receptor, it went to five; there was one muscarinic, it went to five; there were one or two or three or – I forget – tone receptors that went to 15. With the advent of these greater and greater receptor subtype you could get more and more specific actions because you didn’t have to get the off-target effects from a different subtype. But now I think there may be even other ways in which we can get greater specificity.  One of the things I’ve worked on during the past decade has been the fact that in addition to signaling to the inside of cells through G-proteins the receptors can also signal through a different molecule called β-arrestin. This is a molecule that we discovered about more than 20 years ago as a key part of the mechanism which turns the receptors off, it turns them off with respective G-protein signaling but at the same time, we’ve only come to appreciate recently, serves as an alternate signaling mechanism. Now it turns out that you can design drugs which will activate signaling either through the G-protein or the /- – -/ through the same receptor. For some drugs it turns out that the desired effect through that drug actually is being mediated through G-proteins, but some of the side effects are being mediated through β-arrestin signaling or vice versa. If you had a drug which can target one or the other mechanism you may be able to get a few side effects, in fact there are several examples of such compounds which are now on early phase clinical trials. So that may be an example of how my work in recent years may have implications for getting even more specific drugs with less side effects than we’ve had. |
| Q15 | And as for the crystal structure? |
|  | Brian Kobilka: I think there are two ways that we might facilitate the development of more selective drugs. One is as we learn more and more about the binding pockets particularly how related receptors are so similar to each other in terms of /- – -/ assets from the binding pocket. We’re discovering that just outside of the binding pocket there’s greater diversity that could be sampled and in some drugs do sample this, for example it’s a structure that we recently obtained that hasn’t been published yet, it’s a drug called /- – -/ which is used to treat asthma. It’s extraordinarily selective for the β2 over the β1 and it is partly because it extends out of the, what we call /- – -/ pocket into more of the /- – -/ surface samples between β1 and β2. I think that’s an opportunity for the structures will give us an opportunity to actually design drugs that might be more selective. The other is to take advantage of unconventional binding pockets. First of all there are also allosteric binding pockets that are for example the most clinic receptors are well-known. There may be other druggable surfaces on the receptor including surfaces on the inside of the receptor that we might explore, that will also have greater structural differences from even close related receptors, say for β1 and β2. Those are a couple of opportunities to develop more selective drugs. |
| Q15 | So for the first time it is really possible to use the structure to do structure aided drug design? |
|  | Brian Kobilka: Yes, and I think a colleague of ours, Brian Shoichet, has really been at the fore front of using computational /- – -/ and shown, as he likes to say, that GCPRs is really great binding pockets for /- – -/ screening. |
| Q9 | I was going to ask the last question, does it matter how it is labelled, does it matter whether it is chemistry or biochemistry? |
|  | Robert J. Lefkowitz: I think in a sense not. I think what it shows is just how the interface between chemistry and biology and medicine … I have been called a lot of things in my time, not all pleasant, but I can handle chemist. Over the years, people have always gone: Well Bob, you’ll win the Nobel Prize someday. It was nice to hear although it didn’t seem to be happening, but if it happened, I always assumed it would be in medicine and not in chemistry. I think I have Brian to thank for that.  Brian Kobilka: I think I might even take a little at it to like in being awarded the chemistry prize. I think medicine and physiology are wonderful as well, but I’ve sort of been a chemist and want to be for the years. |

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| **Telephone**  **interview** | [DS]  [Dan Shechtman] Dan speaking.  [Adam Smith] Oh, hello. This is Adam Smith from Nobelprize.org. Am I speaking to Professor Shechtman?  [DS] Yes, speaking. What country are you calling from?  [AS] From Sweden. From …  [DS] Oh, yes, yes.  [AS] … The official website of the Nobel Prize. Many congratulations.  [DS] Thank you so much. This is really wonderful, wonderful news for me, and for my colleagues.  [AS] It’s marvellous news. And, although many scientists are used to meeting some healthy scepticism, you, when you made your discoveries, met an unbelievable degree of scepticism, didn’t you?  [DS] That is correct! You heard that Sven Lidin describing it?  [AS] Yes, indeed. And, you were even expelled from the lab you were working in?  [DS] Yeah, that is correct.  [AS] What do you think your experience of discovering quasicrystals taught you about science?  [DS] Oh, it taught me … This is a very good question! You know, it taught me that a good scientist is a humble scientist, somebody who is willing to listen to news in science which are not expected. Because discoveries today are really not expected – if they were expected they would have been discovered a long time ago. So something new, that is forbidden by some laws … people have to listen to this. In most cases, the news is not really news. But in some cases, discoveries are made and should be listened to. So, I think the main lesson that I have learned is that a good scientist is a humble scientist who is open-minded to listen to other scientists when they discover something.  [AS] That’s a lovely message. And also, I suppose, open-minded to listen to what nature is telling them because quasicrystals have changed our view of what matter can be.  [DS] That is correct. You know there was a paradigm shift in the community and like many discoveries it was difficult to convince many people, especially the old established generation of X-ray crystallographers, because the discovery of was made by electron microscopy, and electron microscopy was not a privileged tool among the crystallographers. Crystallographers believed in X-ray results, which are of course very accurate. But the x-rays are limited and electron microscopy filled the gap and so the discovery of quasicrystals could have been discovered only by electron microscopy, and the community of crystallographers, for several years, was not willing to listen. But then we had the results from X-rays on quasicrystals and then the community joined. And that process took a few years.  [AS] Just a last question, you are now at the Technion – you studied at the Technion – it must be very nice to be receiving the Nobel Prize there?  [DS] Yes. Absolutely. You know we have two other Nobel Laureates at the Technion?  [AS] Indeed. [Aaron](https://www.nobelprize.org/prizes/chemistry/2004/ciechanover/facts/) and [Avram](https://www.nobelprize.org/prizes/chemistry/2004/hershko/facts/), yes.  [DS] Yes! Have you met them when they were in Stockholm?  [AS] Yes, I have indeed. And, I have even travelled to the States with Aaron. So, I imagine … will the three of you be getting together this afternoon for some joint celebration?  [DS] Yes, well, I don’t know if they have time to join, but I would, of course, love to see them. And, yes, there is a press conference today at two o’clock at the Technion.  [AS] Yes, marvellous news for the Technion. When you come to Stockholm in December, happily we’ll have a chance to speak more about your discoveries.  [DS] Oh, I’d love to do that. You know, I’ve visited Stockholm quite a few times and it will be wonderful to be there again for this occasion, of course.  [AS] Okay, well we very much look forward to receiving you here. Thank you very much for speaking to me.  [DS] Okay thank you. Bye, bye.  [AS] Bye, bye. |
| **Interview** |  |
| Q2 | And this is because this picture you had seemed to defy the possibilities that were allowed under crystallography in those days? |
|  | Dan Shechtman: That is correct. But it was not one picture, it was a long series of experiments. The famous diffraction picture is one of very many experiments, all done by electron microscopy, transmission electron microscopy. So, he gave me the book and said, Please read. I said, I know this book, I am a teacher at the Technion I teach these things and I don’t need to read it. I am telling you this is something different, it’s not in the book. He took the book and sometime later – now I don’t remember how many days or how many hours it was – but he came back and said, Danny, you are a disgrace to my group and I want you to leave my group, I don’t want to be associated with this. So he moved to another group. This didn’t mean much, it sounds traumatic but it was not, I just had to find another group leader who would to adopt me – the orphan, the scientific orphan – and somebody did. The only amendment was instead of reporting to this secretary I reported to that secretary. I didn’t move from my office or from my laboratory, it was just about the same, so it was not very traumatic – now when people hear about it, Wow, thrown away from your group! Yes, but it was, not for me at least, it was not traumatic. It was not nice, I didn’t feel very good about it, but … This was a span of reactions between encouragement and rejection – and everything was somewhere in between. |
| Q2 | What was the project that you were actually doing, because you weren’t looking for quasicrystals, you were making these alloys. What were you off looking for? |
|  | Dan Shechtman: My project … Let me start a little bit earlier. I came to NBS for my first sabbatical from the Technion. This is six years after I became a faculty, on the seventh year we have a sabbatical. I went there and actually stayed for two years, I requested one year of leave of absence. The sponsor was DARPA, Defense Advanced Research Projects Agency. They wanted me to develop aluminum base alloys for aerospace applications. I did it with a technique called rapid solidification in which you take a metal, you melt it and you solidify it, but very quickly, very rapidly. We had some instruments to do that, to solidify. When you rapidly solidify you move away from the /- – -/ stability, it is not /- – -/ to make them stable. You receive structures, meaning atomic arrangements which you cannot receive if you slowly cool. |
| Q4 | You capture different structures? |
|  | Dan Shechtman: They form, different structures form. I started to work on an alloy that they gave me upon my arrival, it was an aluminum alloy. They said, Oh Danny, before you prepare your own alloys, here is something that we have for you, we already prepared this, so I started to work on aluminum alloys. Then there was a phase there which was close to aluminum six iron that was not stable. I wanted to see how it looks when it is stable, so I prepared alloys from, instead of aluminum iron aluminum manganese and I prepared a series of alloys – 1 % manganese, 2 %, 5 %, 10 % – maybe 10 alloys. In the aluminum 25 % manganese there it was. Let me tell you something that is a little bit educational. The person who sponsored me in DAPA – now this is department of defense of the United States – he knew me, and he said, Danny, you have a very nice proposal which I am sponsoring, but I am telling you run wild. Do whatever you want! Don’t just stick to the proposal, just run wild. What did it mean? You see, aluminum 1 % manganese, maybe up to 5 % manganese can be used for, but 15 %, 25 % is almost powder. You cannot make anything useful for aerospace from that. But I felt free to do whatever I wanted. You start from applications, but you end up in good science. |
| Q1 | That’s a lovely thing to bring up because so often we sit talking to Nobel Laureates who have been doing basic science and they have come up with a basic discovery, and naturally people start asking, What is the application? In your case you were doing applied research, and the basic research was your side piece – it’s very nice. Is the lesson to learn from that even when thinking that you are directing people down the applied search tracks there should always be the space for play? |
|  | Dan Shechtman: You should look around and pay attention to something odd. When I talk to young students, I can give them ten advice but I always give them one advice. If you want to succeed in something – become an expert in that field. You can start becoming an expert now, when you are a high school student. Choose a subject that may interest you and in today’s world information is regularly available to everybody everywhere. Choose a subject and become an expert. If you have questions call a professor in the university, he will talk to you, he will explain to you. Find out who are the people who are the masters of that field and talk to them. Become an expert and it will carry you a long way. |
| Q1 | Because expertise will always be sort out by others? |
|  | Dan Shechtman: No, because as an expert you will … When you will discover something you will trust your findings. Also you are right. It pays to become an expert and sometimes it doesn’t. Let me give an example. In my early days in academia, I was going to the US every summer to work there. I am a material scientist and I wanted to be labelled material scientist, but I was labelled as an electron microscopist instead. One summer I called them and asked, Can I come this summer? He said, No, this summer we don’t need any electron microscopist. I said, Now wait, I am a material scientist. No, no, but you are a good electron microscopist. I was labelled as an electron microscopist. Sometimes it is good, sometimes it is not very good to put a label on somebody in a narrow filed. |
| Q2 | We’ll come back to quasicrystals in a minute, but I just wanted to make a brief digression into becoming an expert because how did you become an expert yourself, how did you become a material scientist? |
|  | Dan Shechtman: Let me tell you. When I was very young, in the fifth grade in elementary school, I was very interested in nature and science. The nature teacher – we had a subject called nature – which is now called science – then it was called nature – said to the children, You know we have a microscope in school, and my eyes opened like that. What? Can you bring it to the class? He said, Yes, of course. The next week he didn’t bring it and the next week he didn’t bring it and I begged him and begged him, so finally he brought it to the class and put it on the table. It was a microscope like this, a very primitive one, but I had never seen one before. He put a sample of a leaf or an insect, I don’t know what it was, I think it was a leaf or something. He said, Dan, you showed an interest in this so you will be first to look. I came and I stood at his desk and I was looking, Wow, it was so amazing. He said, OK Dan, sit down. I said, Wait a minute, I was so fascinated. Then I said, Maybe you could bring it to the class every week or may I come to the warehouse where you store it, can I work on it? No, he said, one time is enough, and he never brought it again.  This was my first encounter with a microscope, it was a small, primitive optical microscope. When I did my master’s degree at the Technion the first transmission microscope arrived at the Technion and I immediately pounced on it. I was circling around when they assembled it, asked so many questions, and looked at it – more like a mechanical engineer than anything else, just wanted to see the construction. Then I became one of the first operators of the electron microscope. At that time we were used to fix the electron microscope ourselves, there was no technician, we did it. People ask me, Did you spend time on the microscope or under the microscope? It was equal time, but I learned how the microscope works, really, learned the technique. Then my PhD was already on electron microscopy. |
| Q5 | There was a gap in your history between the microscope you were showed once and then was taken away and your master’s degree. Somebody else must have encouraged you. Was there one person or someone who pushed you? |
|  | Dan Shechtman: Yes, I can say that there was one professor that arrived at my department from Cambridge in England. He was /- – -/ microscopy, one of the first in electron microscopy, David Brandon. He was my thesis supervisor for PhD. I came to him when I did my master and said, Will you instruct me for a PhD and he said, Of course, why not. This is the way we started, and he gave me the first lessons about electron microscopy. He did some other thing that should be told, he introduced me to the masters of electron microscopy of the time. Most of them were from England and from Belgium. They came to visit him and he invited me to his home every time somebody came to visit. He introduced me to this community. This is important, this is a lesson to be learned. Later on, he sent me to an international school of electron microscopy in Erice, Italy – Sicily actually. That was another important thing – send your students to become experts. |

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| **Chemistry\_2024-2000** | |
| **ID** | 0337 |
| **Biographical** | Richard F. Heck was born in Springfield, Massachusetts, U.S.A. on August 15, 1931. The only son of a housewife and a salesman, he moved to Los Angeles, California at the age of eight. His passion for chemistry began in his early teens and stemmed naturally from his interest in growing orchids. His interest developed throughout high school and culminated in his majoring in Chemistry at the University of California, Los Angeles (UCLA). He received his bachelor’s degree in 1952 and immediately commenced his graduate studies under the supervision of Professor Saul Winstein. Heck was drawn to the complexity and versatility of the area and particularly enjoyed the “way you can make all sorts of compounds”.[1](https://www.nobelprize.org/prizes/chemistry/2010/heck/biographical/#not1) He received his Ph.D. in 1954 in physical organic chemistry, and his main research area was neighboring group participation in the solvolysis of arylsulfonates. A National Science Foundation Postdoctoral Fellowship took him to the Swiss Federal Institute of Technology in Zurich, where he worked with Professor [Vladimir Prelog](https://www.nobelprize.org/prizes/chemistry/1975/prelog/facts/), who became a 1975 Nobel Laureate. During his one year stay he carried out research on the solvolysis of medium sized cycloalkyl arylsulfonates. In 1955, Heck returned to UCLA and continued his research on neighboring group effects, an area which is now included in all organic chemistry textbooks.  In 1956, Heck went to work for the Hercules Powder Co. (now Ashland Inc.) at their research center in Wilmington, Delaware. His strong physical organic chemistry background undoubtedly inﬂuenced their decision to hire the then 25 year old. His first project involved working on the development of a commercial process for producing polymers using [Ziegler-Natta](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1963/) catalysts (this process is still used today to produce large volumes of rubbers and plastics). Although Heck accomplished “little of scientific value in the two years that I was in this program”[2](https://www.nobelprize.org/prizes/chemistry/2010/heck/biographical/#not2) the experience he gained in transition metal chemistry would prove to be invaluable in his next project. In a defining moment, his supervisor, Dr. David Breslow, suggested that Heck “do some thing with transition metals”. Few could have foreseen that this suggestion would transform modern organic chemistry and give rise to the vast and important field of transition metal catalysis.  In 1958 organotransition metal chemistry was still in its infancy. There were several important transition metal-catalyzed processes used commercially, but very little was known about the actual chemistry involved. Heck’s initial idea was to investigate the chemistry in one of these processes and to use this knowledge in the development of new chemical transformations. This work began with an investigation of the hydroformylation process, which ultimately resulted in a mechanistic rationalization of this reaction. Today Heck’s work on the hydroformylation reaction is widely regarded as the first correct transition metal-catalyzed reaction mechanism. This was a significant achievement and provides an excellent insight into the way Heck approached his research. At a time when most people saw transition metal catalysis as a ‘black box’ (an unknown method that could be used to aid certain chemical processes), Heck concerned himself with finding out what was inside the box (i.e. how these reactions worked) and using this information to discover new chemistry.  Despite the discovery of many new chemical reactions based on his newfound mechanistic understanding, Heck had no idea how Hercules could profit from these discoveries. This forced Heck to take his research in a new direction and, once again, it was a discussion with a colleague that would dictate Heck’s next move.  Pat Henry, who worked in the laboratory opposite Heck, was studying the mechanism of the industrially important Wacker Process. Heck was intrigued by Henry’s notion that decomposition of the intermediate palladium species occurred via a β-hydrogen elimination. Heck then proceeded to “see what would happen” if an organopalladium species, which lacked a β-hydrogen, was prepared in the presence of another molecule. His very first experiment was an overwhelming success (Figure 2). In a description of this seminal study Heck stated that he added  phenylmercuric acetate to a stirred solution of tetrachloropalladate … under an atmosphere of ethylene. An immediate reaction occurred. Palladium metal precipitated and ethylene gas was rapidly absorbed. Analysis of the reaction mixture showed that about an 80% yield of the styrene and 10 % yield of trans-stilbene had been formed.[2](https://www.nobelprize.org/prizes/chemistry/2010/heck/biographical/#not2)  This was an incredible finding and marked the discovery of a new carbon-carbon bond forming reaction, which we today know as the Heck reaction. Heck then proceeded to systematically investigate the unique reactivity of these organopalladium compounds with carbon monoxide, alkenes and dienes. This work was documented in a remarkable series of seven consecutive articles in the highly regarded *Journal of the American Chemical Society*. Of great synthetic importance was the compatibility of these processes with almost all common organic functional groups. However, the reaction had a number of significant drawbacks. It required the use of highly toxic mercury or tin salts and stoichiometric amounts of expensive palladium, two factors which significantly limited the usefulness of this reaction. These issues became the focus of Heck’s next research phase.  In 1971, Heck left Hercules and accepted a faculty position at the University of Delaware. Over the next few years Heck worked towards developing conditions to make the reaction more ‘user friendly’. Inspired by reports on the successful formation of the haloaryl palladium-phosphine complexes, Heck explored whether these intermediates could replace the problematic stoichiometric arylmercury-palladium combination. He also investigated the effects of certain bases on the reaction, which led to the development of a reaction that was catalytic in the amount of palladium required. This discovery, reported in 1972, formed the basis for a number of systematic studies on the application of this reaction in organic synthesis. Today, this reaction is known by chemists all over the world as the Heck reaction (or Heck-Mizoroki reaction). In addition to the discovery of the Heck reaction, Heck and his team also invented three other very useful palladium-catalyzed carbon-carbon bond forming reactions over the next few years. The palladium-catalyzed arylation of alkynes was reported by Heck in 1975 and later that year Sonogashira reported that the addition of copper salts resulted in a faster reaction. This reaction is known today as the Sonogashira reaction and is one of the premier methods for functionalizing alkynes. Heck also developed a novel carbonylative methodology for the preparation of aryl carboxylic acid derivatives from an aryl halide, a nucleophile and carbon monoxide. Finally, Heck reported the coupling of vinylboronic acid with acrylates. This can be seen as a precursor of the extremely important Suzuki coupling and the oxidative Heck reaction.  The importance of the Heck reaction grew slowly among organic and medicinal chemists. The current impact of Heck’s discoveries can be clearly seen by performing a full text search in a chemical database. A search of Heck’s name in SciFinder gives 1,298 hits for the years 2000−2005 and 3,845 for 2005–2011 (as of April 27, 2011). The continued development and use of the Heck reaction has now been summarized in more than 40 reviews. The first special issue of a scientific journal focusing only on the Heck reaction was published in 2006 and the first book on the Heck reaction was published in 2009. Today, the Heck reaction is an important concept and tool for all organic chemists and medicinal chemists. Organopalladium chemistry has achieved a position of prime importance through its operational simplicity, enormous compatibility with sensitive functional groups and broad applicability, from materials science to the synthesis of drug candidates and approved drugs. Almost all sub-disciplines of modern organic chemistry have benefited from advances in the field. Heck’s work can be regarded as a precursor to a number of other Pd-catalyzed cross-couplings, including those with boronic acids (known as the Suzuki cross-coupling), organotin (known as the Stille cross-coupling), organonickel compounds (known as the Kumada-Corriu cross-coupling), organozinc compounds (known as the Negishi cross-coupling) and organosilicon compounds (known as the Hiyama cross-coupling), and linkages with alcohols and amines. Undergraduate students learn about the Heck reaction and perform experiments based on it in the laboratory. Process chemists perform palladium-catalyzed reactions in the large scale manufacture of fine chemicals, fragrances, pesticides and pharmaceuticals. Of all the chemistry developed by Heck, maybe the greatest social impact has been from the Pd-mediated coupling between an alkyne with an aryl halide. This is a reaction that is used for ﬂuorescence labeling of DNA bases, which has contributed to the automation of DNA sequencing and sequencing of the genome. Heck’s work has motivated thousands of researchers to explore the unique possibilities of palladium catalysis in their own work. Richard Heck laid the foundation for virtually all the metal-catalyzed coupling reactions that are an essential component of modern organic synthesis.  After an extraordinary and prolific career, Willis F. Harrington Professor Richard F. Heck retired from the University of Delaware in 1989, where he remains a Professor Emeritus. In 2005, he became the recipient of the Wallace Carothers Award, which recognizes creative applications of chemistry that have had substantial commercial impact. In 2006, he received the [Herbert C. Brown](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1979/) Award for creative research in synthetic methods from the American Chemical Society. That same year he also returned to the laboratory as a visiting professor at Queen’s University, Canada. In 2010, he received an honorary doctorate from Uppsala University, Sweden. Richard Heck has published over 200 scientific papers and has an H index of over 55 (counting from 1987, he retired in 1989).  Richard now lives in the Philippines with his wife, Socorro, whom he met at a Manila restaurant while visiting the Philippines in 1979. Richard’s life has now come full circle and just as he did as a teenager in Los Angeles, he spends his spare time growing orchids. |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** | [RH]  [Unknown] Good evening?  [Adam Smith] Hello, may I speak to …  [U] Hello?  [AS] Hello?  [U] At the telephone? Hi!  Background noise  [U] Hello?  [AS] Hello, is it possible to speak to … Hello can you hear me? Good evening, may I …  [U] Yes?  [AS] May I speak to Richard Heck, please?  [U] Yes, hold on!  [AS] Thank you.  Background noise  [Richard Heck] Hello?  [AS] Good evening, Professor Heck.  [RH] Hello?  [AS] Hello, this is Adam Smith …  [RH] Yes!  [AS] … calling from the official website of the Nobel Prize, in Stockholm. Congratulations on the news of the award.  [RH] Well, thank you very much.  [AS] We, at the website for the Prize, have a tradition of recording very short telephone interviews with new Laureates. Would you mind if we spoke for just a few minutes?  [RH] No, that’s alright with me.  [AS] Thank you . So, I gather we’re calling you in the Philippines. Is that where you now live?  [RH] Yes.  [AS] And, what were you …  [RH] Yes, that’s where we’re living at the moment.  [AS] And what were you doing when you heard the news?  [RH] I was sitting in my house with the family, not doing anything much.  [AS] You developed the palladium-catalyzed coupling approach when you were working in industry mainly, in the 1960s. It must have been a productive environment?  [RH] That’s correct, yes. That’s right.  [AS] And, remarkably, the series of papers you published on it were single authored papers in the *Journal of the American Chemical Society*. So, one gathers you worked alone on this?  [RH] Yes, mostly.  [AS] Were you happy to be working alone? Was that your style in those days?  [RH] Well, it just … sort of happened that way. I didn’t plan it, or didn’t require it or anything. It just turned out that way.  [AS] Hmm! And, the reaction you developed, now know generally as the Heck reaction, is of course enormously widely used nowadays. But was uptake fast? Did people caught on to its importance early on?  [RH] Well, I don’ t think so. I didn’t have the impression that it happened suddenly. It was a slow development , I think.  [AS] So, how do you feel about being awarded the Nobel Prize?  [RH] I’m extremely grateful. It was a big surprise to me! I didn’t expect it.  [AS] When, when you think about the tool box of available methods for building organic molecules, do you think that we are now well equipped, or do you think we have a long way to go in building the tools we need to build the molecules we need?  [RH] Well, I think there’s … a lot of chemistry still out there that will help developments. And, I have no idea how long it’s going to last, but I think there’s still a lot of chemistry to be developed.  [AS] Are you hopeful that that is being developed, that the resources are being put into, let’s say, basic science to find the tools?  [RH] Well … you know, I’ve been retired for quite a while now, and I’ve not really kept up with things. But, I think there’s still a lot to be done, yes.  [AS] When did you retire?  [RH] Oh, about four … four or five years ago, I think.  [AS] So, what’s your main pursuit these days?  [RH] Since then I’ve just been relaxing and enjoying life, I think!  [AS] Sounds a good formula! And, why did you choose the Philippines?  [RH] Well, because my wife is Philipino. And we’ve been here a few times, and it’s a nice place to live.  [AS] Grand. OK, and are you … Do you think, it’s early days yet, but do you think you’ll come to Stockholm to receive the Nobel Prize?  [RH] Yes, that feels like something that I’d like to do, yes!  [AS] Great, ok! And, what about celebrations for this evening, any plans?  [RH] No, I don’t think that I’m going to do anything, I just enjoy the feeling of having won it. I’m very much surprised … and enjoy my stay here in the Philippines. But, I don’t have any plans for a big celebration here.  [AS] Well, I can hear lots of happy voices around you so, I should leave you to go off and enjoy them. Thank you very much for speaking to us.  [RH] Well, thank you very much!  [AS] It’s a pleasure, OK. I look forward to meeting you in Stockholm.  [RH] Good talking to you. Good bye.  [AS] Thank you, goodbye. |
| **Interview** |  |
| Q2 | It’s a nice way to be made immortal to have a reaction named after you, I think. If we turn to the cross-coupling reaction we’ve just being discussing. It began with you, Professor Heck, in working at Hercules company, I think, and you were exploring palladium’s ability to do interesting things. You weren’t actually looking for a cross-coupling reaction? |
|  | Richard F. Heck: No, I wasn’t, it just happened. I recognised it and I thought it would be something useful so that why I studied it. |
| Q6 | When you publish papers on this, you publish them as a single author, which implies that you were working very much alone, was that the case? |
|  | Richard F. Heck: Yes. Well, I had a non-technical assistant, but I only had to put my name on it. |
| Q3 | Were you left free to play in this industrial environment? |
|  | Richard F. Heck: I was in their basic research group, just a small group that could try anything, I guess, if they thought it might be useful. They left us alone pretty much, at least for a while. |
| Q4 | And were you aware that palladium would act as a catalyst to bring carbon atoms together in this way? |
|  | Richard F. Heck: Well, there were some things in the literature that suggested it might a be useful reagent for doing that kind of chemistry, yes. There were some early people in this field who did some good chemistry, like Koetz, remember? Koetz and Calvin, I remember those people, which was one very early but nobody seemed to follow it up. |
| Q15 | Was your company keen to make money out of your research? |
|  | Richard F. Heck: That is was what it was supposed to do, I don’t think I did much for them, but that’s the reason for why I’m not there anymore. |
| Q15 | You weren’t patenting the method or anything like that? |
|  | Richard F. Heck: They patented everything that they thought could possible conceivably be useful, so some of it was patented I think. |
| Q4 | I guess, but when do you think its power was seen? |
|  | Richard F. Heck: I couldn’t put a date on it. It’s a slow process, it just happens slowly. To make a decision on when it started, I don’t know, it’s hard to say. |
| Q3 | When you moved into organic chemistry as a young man, was it the desire to solve problems such as how to convert CO2 or other things that drove you there or was it general inquisitiveness, were you applied or just curious? |
|  | Richard F. Heck: I enjoyed working with chemicals, I do things and make all kinds of perfumes and things that interested me in my first few years of my studies and I expanded on that and it’s useful to make all kinds of materials that you might want to use, technical materials for example. |
| Q2 | Were you a childhood chemist? |
|  | Richard F. Heck: Yes, that was in my early teenage years I started chemistry. |
| Q5 | And last, Richard Heck. Working alone, maybe you didn’t have a mentor, or was there somebody? |
|  | Richard F. Heck: I worked with Winstein first where I got my degree and he taught me physical organic chemistry and I didn’t follow that up, I got into more organometallic chemistry as I went into industry. So, in industry I tried to make money for the company mostly so they were directing my work more or less. |

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| **Chemistry\_2024-2000** | |
| **ID** | 0338 |
| **Biographical** | I was born on July 14, 1935 in Changchun, China, as a Japanese citizen. My family moved to Harbin when I was one and then to Seoul, Korea, two years before the end of World War II. As I was admitted to an elementary school in Harbin at age six, a year earlier than normal, I then came to Seoul as an eight-year old third grader. Shortly after the end of World War II in 1945, my family returned to Japan and moved into a house in Tokyo which my parents had purchased several years earlier that miraculously survived many intensive bombings. A much more serious problem for my parents was how to feed a rapidly growing family of seven, with five children ranging from twelve to one. Their solution to this food shortage problem was to move to an underdeveloped patch of land of a little less than one acre about 50 km southwest of the center of Tokyo. Although my father’s attempt to become a farmer there was not very successful, this naturally wooded area called “Rinkan” in Yamato, Kanagawa prefecture, became what I consider even now my “first hometown,” where I spent my junior high school (seventh-ninth grades), high school (tenth-twelfth grades), and college years (1953–1958 for five years as I needed to repeat my junior year due to gastrointestinal illness).  Despite all these difficulties, I recall my early school years through ninth grade mostly with positive and enjoyable memories. Although I virtually never studied outside classrooms through the ninth grade, I was quite alert and enjoyed most of the classes with the exception of calligraphy and Japanese language. But, I enjoyed after-school hours before darkness even more. Those short after-school hours in the nearly six-month-long Harbin winters were spent skating in the playground covered with ice. I hardly recall my indoor activities before darkness through ninth grade. Several classmates and I in our junior high school jointly collected naturally growing grasses for rabbits and took care of chickens, which virtually every family in our area was raising for food and minor supplementary income, but we never forgot to set aside some time for playing ball games and so on. For some reason, I found a world atlas in our very modest bookshelf to be to my liking and almost daily looked at it in the evening, especially during my Harbin days. I luckily established myself as one of the top students throughout my elementary and junior high school years.  My first setback, if only a temporary one hit me, when I applied for an “elite” high school in our prefecture called Shonan High School. Despite my superior scholastic standing, I was declared ineligible, because I was a year younger than my classmates. Luckily, several of my teachers at Yamato Junior High School including my classroom teacher, S. Koyama, and music class teacher, T. Suzuki, who was the father of my future wife, Sumire, successfully persuaded Shonan High School officials to accept me. At Shonan, which only the top several of my two hundred plus classmates at Yamato Junior High School attended, my life style described above was no longer satisfactory. Nor was I sufficiently ambitious about my higher education. I soon noticed that the entire school was obsessed with the single notion of intensely training and successfully sending as many students as possible to several of the most highly rated universities, represented by the University of Tokyo, several other former Imperial Universities such as Kyoto, Osaka, and Nagoya, as well as the Tokyo Institute of Technology.  Throughout my first year at Shonan, I was still mostly limiting my studying to that in the classrooms, which led me to earn the 123rd place in scholastic standing among a little more than 400 classmates. After a brief moment of disappointment, I then realized that, whereas there were a little more than 100 students who were ahead of myself, there were also nearly 300 others behind me. Back in those days, about 30–40 students including one-time repeaters were successfully entering the University of Tokyo each year from Shonan. It then suddenly occurred to me that, if I studied as hard as I could, even I might have a legitimate chance of entering the University of Tokyo, which until then appeared far beyond my reach.  For the first time in my life, I instantly became a self-motivated and highly disciplined model student devoting most of my available time to intensive studying. I would wake up a couple of hours earlier than the rest and spend those extra hours in preparation for classes each day. No more solitary explorations of my favorite Shonan seaside area, especially Enoshima Island, after classes. Each evening, I would study until after 11 pm when I heard my mother’s gentle reminder saying: “Isn’t it about time to stop studying and go to bed?” In retrospect, I feel very fortunate that neither of my parents ever told me to study more or harder in my life. For one thing, they themselves were very busy just for our survival, even though I did amply sense their silent but strong mental support for my higher education.  At the end of the first semester of 11th grade, my scholastic ranking rose to the 9th among a little more than 400 students. I then reached the top position at the end of the 11th grade and maintained that position through the 12th grade. Toward the end of the 11th grade and through most of the 12th grade, a series of several mock college entrance examinations were given, and I managed to earn the highest overall scores three out of five times. Naturally, my confidence grew sharply. At the same time, however, I began feeling an intense psychological pressure against never failing in the upcoming real entrance examinations as the top student at Shonan. Indeed, this mental pressure was most intense during the two-day entrance examinations for the University of Tokyo and both my mental and physical conditions were at the worst, short of being outright sick. I really thought my performance on those two days was at its worst, and I felt more than halfway certain that I failed. Fortunately, I did pass, perhaps barely, and became one of the youngest college entrants at age 17 in the stiflingly rigid Japanese system. Fortunately, there was no age-based opposition this time.  In retrospect, I now consider the oft-criticized rigorous college entrance examination system in Japan to be a highly valuable and effective training of teenagers in preparation for their research and other professional careers, especially in science and engineering areas. Even today, 55–60 years later, I very frequently resort to my mathematical and scientific background, which I quite firmly built in my high school days in preparation for the college entrance examinations.  Having accomplished my high school goal, my eccentric and erratic lifestyle took another 180-degree turn. Even though my major in college was non-biological science and engineering, our curriculum for the first two years at the Komaba campus, designated as General Education, was full of non-scientific classes including a second foreign language − German for myself − law, economy, psychology, and so on, along with a limited number of mathematics and natural science classes. With some exceptions, neither students who had just survived very demanding college entrance examination, nor professors, who probably were mostly interested in and preoccupied with pursing their own professional interests, appeared to be sufficiently interested in learning or teaching the subject matter. For example, there were two different German classes in my curriculum. Most of the students in these classes were taking German lessons for the first time in their lives. One class dealt strictly with German grammar. In the other class, we were asked to deal from the very beginning with German novels and poems. I recall our trying to read and interpret Goethe’s poems, while consulting a German-Japanese dictionary for almost every word with little grammatical knowledge. This was clearly a very poor way of learning any foreign language. Coupled with a serious lack of effort on my part, my knowledge and ability in German are even today very limited and poor. Nearly the same can be said about most of the other subjects as well . In the meantime, I quickly diverted my time, interest, and efforts to some off-campus activities, such as (1) listening to Western classical music, especially Mozart, Beethoven, Brahms, Chopin, Dvorak, Grieg, Tchaikovsky, and so on, (2) singing in and conducting a small choir group mostly performed at the small house of my music teacher at Yamato Junior High School, Tsuguo Suzuki, who later became my father-in-law. Kenji Suzuki, Tsuguo’s eldest son and one of my classmates at Shonan High School and also at the University of Tokyo, was the other leader of the small choir group. To my disappointment, Sumire, the older of two daughters of Tsuguo Suzuki and my future wife, would stay away from our choir activities, even though she was undoubtedly forced to listen to the sounds we generated in the small house. For one thing, she was younger by three years than most of the choir group members (two years younger than myself), and she probably felt she did not belong to our choir group. Even so, Sumire and I started dating during my freshman year, and we rapidly got closer with time.  As I spent much of my available time in these extra-curricular activities, I all but forgot my self-motivated studying. Even today, I occasionally regret my lack of continued efforts, which I acquired during the latter half of my time at Shonan High School. Clearly, I was primarily responsible for this academically non-productive two-year period at the Komaba campus of the University of Tokyo, but I also believe that there was considerable room for improvement in many areas of curriculum development.  Despite my failure to make due efforts, I was surprised with much relief when I learned that my scholastic ranking at the end of the first year was barely in the top third among ca. 450 non-biological science and engineering majors. This permitted me to choose one of the most highly coveted departments at that time, applied chemistry specializing Industrial Chemistry, for my Junior and Senior years. In and around 1955, ten years after the end of World War II, the Japanese economy was growing rapidly − in part because of the unfortunate Korean War near Japan. In particular, the newly rising non-natural polymer industry was booming and attracting young scientists and engineers such as myself to join this field.  Despite all these promising developments, I experienced probably the hardest and least productive time in my life. First of all, it required almost two hours one way or four hours both ways to commute between my home in Yamato and the Hongo campus of the University of Tokyo. Our class schedule in my junior year was packed with a series of lecture and laboratory classes full of superficial discussions and experiments on various industrial chemical processes from 8 am to about 5 pm every day. Only in a relatively small number of classes did we learn some fundamentally important chemistry. Unfortunately, however, most of these classes were, in my opinion, rather poorly taught. In a class on quantum chemistry, for example, a widely known textbook (the Japanese version) entitled “Valence” by Coulson was chosen, but virtually no penetrating and nourishing discussions were presented in class. In fact, I needed to wait for four more years until I took a class on this same subject with the same textbook (the original English version) at the University of Pennsylvania, which finally permitted me to acquire the important quantum chemical background at an adequate and useful level.  Between physically demanding commuting − which required almost four hours of standing in jam-packed commuter trains − and highly time-consuming but seemingly non-nourishing lecture and laboratory classes, I began suffering from gastrointestinal problems by July of 1955. The problems got worse during the latter half of that summer break, and I was finally hospitalized for a few weeks, which prevented me from taking all of the mid-year tests. Eventually, I was forced to repeat my junior year.  In retrospect, this major setback proved to be a blessing in disguise. For one thing, I had plenty of my own time to think, plan and do some new things for myself according to my own plans. I read almost indiscriminatingly a wide range of books ranging from the Bible, although I was not a Christian, to “how to …” publications. Through all these reading and thinking activities, I reached my own notion that “happiness” must be the ultimate goal for each of us and that the following are the four essential components of it: (1) good health, (2) happy surroundings including one’s own family and beyond, (3) selection and pursuit of a worthy professional career, and (4) one or more enjoyable and lasting hobbies.  With my renewed life goals, I restarted my junior year in April, 1956. This time, I decided to rent a small room across from the Hongo campus, but I would go home almost every weekend from Friday evening to Sunday evening. Another new item I added to my plans was learning conversational English, which I considered to be critically important for my career development. Throughout my junior and senior years, however, I remained critical about the combination of mostly superficial descriptions of various chemical processes and a smaller number of fundamentally important subjects that were, in my opinion, rather poorly discussed in classrooms. Clearly, I was also responsible for my inability to make better use of these classes. My music-related activities were maintained and exercised over the weekends, and I began steadily dating with Sumire with a growing notion of our eventually getting married.  During the latter half of my junior year, I applied for a lucrative scholar ship from one of the leading synthetic polymer companies, Teijin, Ltd. and successfully obtained it with the agreement that I would join Teijin upon graduation. This virtually eliminated my concerns over various financial matters including the costs of dating with Sumire. I regret very much that amid all of these activities, my efforts in my Senior Research project based mostly on experimental work were kept minimal.  On the day of graduation with the degree of Bachelor of Engineering in March, 1958, Sumire and I announced our engagement to our parents in a small restaurant near Akamon (“Red Gate”) of the Hongo campus.  At Teijin, I was assigned to be a research chemist at the Iwakuni Research Laboratories, then the main research facility of Teijin, which was located near Hiroshima in the Inland Sea area. One of my superiors there asked me to systematically explore chemical reactions of polymers to come up with modified polymers of superior properties. It soon was apparent to me that my synthetic organic chemical background was woefully weak. I immediately told myself, “I should rebuild almost from scratch my synthetic organic chemical background,” something I already had been vaguely hoping to do independently of this episode. The most obvious thing to do was to return to the University of Tokyo as a graduate student pursuing a master’s degree. The main difficulty was how to raise the tuition fees, as virtually no graduate teaching assistantships were available back then in Japan. I recall the welcome speech by the President of Teijin, Mr. S. Ohya, in which he strongly urged all new members of the company to study and master some foreign languages, especially English, German, and French. He also told us about the Fulbright-Smith-Mund All-Expense Scholarship permitting highly qualified recipients to study in the U.S. for up to three years, and he further indicated that, if anyone at Teijin won this scholarship, Teijin would grant a leave of absence with some additional financial support. As indicated earlier, I had been studying conversational English on my own for about three years. So, I decided to pursue the recommended course of events. In fact, the Teijin Iwakuni Research Laboratories soon hired a native English-speaking foreign tutor and I started taking an English conversation class, which proved to be a most useful experience for me to acquire a solid foundation of conversational English. Once again, my self-motivated diligent study habits came back, and I quickly became quite proficient in practical English.  The two-stage Fulbright Examination on written and conversational English was by far the most competitive examination up to that point in my life, but I was luckily chosen as one of the only two who passed out of a little more than 150 applicants. Looking back, I consider my winning a Fulbright Smith-Mund All-Expense Scholarship to come to the U.S. in 1960 and study toward my Ph.D. degree in Synthetic Organic Chemistry to be the single most important turning point in my professional career.  The Fulbright Commission asked me to list three universities. The final one would be selected through negotiations by the Fulbright Commission with the listed universities. With almost zero knowledge about American universities, I consulted the Journal of Polymer Science, which I was most frequently reading, and noted the names of three editorial board members who were at Princeton University (A.V. Tobolsky), the University of Pennsylvania (C.C. Price), and the Brooklyn Polytechnic Institute (C.G. Overberger). The Fulbright Commission chose University of Pennsylvania for me.  After 8 weeks of English orientation classes at the University of Hawaii in August and September, 1960, I came to the University of Pennsylvania in Philadelphia. I spent three years there for my Ph.D. degree, which I obtained in December, 1963 under the guidance of Professor A.R. Day.  Before 1960 Japan had produced just one Nobel Laureate, [H. Yukawa](https://www.nobelprize.org/nobel_prizes/physics/laureates/1949/), who won a Nobel Prize in Physics in 1949 only four years after the end of World War II. Although I vaguely knew of him, he was a physicist in Kyoto, which is some 500 km away from Tokyo. So, he was like a figure in a fairy tale to me. On the other hand, a series of a dozen or more Nobel Laureates in sciences as well as those who had not won but were clearly destined to win Nobel Prizes visited Penn to give lectures during my stay there. On some other occasions, several of us at Penn would get together and drive to other universities within several hours’ driving distance to attend lectures by Nobel Laureates. In this way, I attended easily more than a dozen lectures by Nobel Laureates including [G.T. Seaborg](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1951/), [H. Staudinger](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1953/), [L.C. Pauling](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1954/), [M. Calvin](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1961/), [M.F. Perutz](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1962/), [J.C. Kendrew](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1962/), [K. Ziegler](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1963/), [R.B. Woodward](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1965/), [D.H.R. Barton](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1969/), and [H.C. Brown](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1979/). I even personally talked to them. They were no longer figures in fairy tales.  Through these opportunities, the Nobel Prize became something of reality to me. I must confess that, in my usually quixotic way, I even began thinking that if I keep trying in the right direction and on the right track, I might even have a remote chance of winning one some day.  As a first-year graduate student at Pennsylvania, I was a reasonable Ph.D. student in class. However, I am much more proud of the fact that I earned 8 consecutive grades of excellence in the Organic Cumulative Examinations, a feat essentially unheard of back then. This indeed gave me a tremendous amount of confidence in myself and in my potential research capability.  In the laboratories, however, I was at least initially rather clumsy and failed in a fair number of experiments. I then began questioning many aspects of organic synthesis, as it was known then. “Why are so many organic synthetic reactions esoteric?” “Why are so many of them including acetoacetic ester and malonic ester syntheses roundabout and yet of limited synthetic scope?” It was around those days that the following dreamy, if childish, notion occurred to me. If we could come up with widely applicable, straightforward LEGO-game like methods for hooking up together two different organic groups, R1 and R2, to produce R1–R2, the entire task of organic synthesis would be vastly simplified and generalized. In fact, the [Grignard](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1912/) cross-coupling reaction shown in Eq. 1 had long been known, even though it might have been a relatively unimportant reaction of very narrow synthetic scope within the vast scope of Grignard’s Nobel Prize winning work known about a century ago.  In the Grignard cross-coupling reaction shown in Eq. 1, Mg and halogens are used to promote the desired formation of R1–R2 both kinetically and thermo dynamically. Through such simple but unmistakable considerations, I soon became obsessed with the notion of exploring organometallic chemistry in order to solve a wide range of problems in organic syntheses, which eventually led me to join H.C. Brown’s group as a Postdoctoral Associate for two years (1966–1968) and then as his Assistant with the rank of Instructor for four more years (1968–1972). During the latter four-year period, I was given a considerable amount of freedom to pursue my own ideas and plans. Indeed, it was during this four-year period that I became interested in the possible uses of *d*-block transition metals as catalysts for promoting main-group metal-containing organometallic reactions, such as those shown in Eq. 1. In addition to some pioneering works of M.S. Kharasch, which led to the Cu-catalyzed alkylation of Grignard reagents by J. Kochi in 1971 and its Ni-catalyzed version by K. Tamao and M. Kumada as well as by R. Corriu in 1972, some other initially stoichiometric reactions of organometals containing (i) Cu by H. Gilman, which was extensively further developed by E.J. Corey, (ii) Pd, mostly π-allylpalladiums by J. Tsuji and by B.M. Trost, as well as arylpalladiums by R.F. Heck, and (iii) Ni, mostly π-allylnickels by [E.J. Corey](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1990/), M.F. Semmelhack, and L.S. Hegedus became widely known since the late 1960s. Despite all these mostly stoichiometric reactions of organotransition metals, containing Cu, Ni, Pd, and some others, widely applicable methods for C–C bond formation that are highly catalytic (TON ≥ 103 – 104) in transition metals were virtually unknown at the time I started my independent career as Assistant Professor at Syracuse University in July, 1972. I therefore chose with much enthusiasm “Discovery and Development of New Organic Synthetic Reactions Catalyzed by Transition Metals” as the central topic of my life-long research projects. One important aspect of it is the subject of my [Nobel Lecture](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/2010/negishi-lecture.html), presented below. |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** | [EN]  [Ei-ichi Negishi] Hello?  [Adam Smith] Hello, may I speak to Professor Negishi please?  [EN] Yes, speaking.  [AS] Hello, this is Adam Smith calling from the Nobel Prize website, in Stockholm.  [EN] Ah ha!  [AS] My congratulations on the …  [EN] Well, thank you very much!  [AS] We have a tradition of recording just very brief telephone interviews with new Laureates  for the Nobel Prize website on the day of the Announcement. Would you be free to speak for a few minutes?  [EN] Ah, yes!  [AS] Thank you so much. So, I gathered from the Press Conference at the KVA that you were asleep when the call came?  [EN] Right.  [AS] And this came as unexpected news I imagine?  [EN] Ah, if I say totally unexpected, then maybe I will be, you know, lying. But, ah, I was telling my wife that perhaps I may be one out of hundred, at this point. You know, because there had been some nominations, some activities beforehand. So that’s the sort of level that I was expecting.  [AS] And, you’re at Purdue. And, indeed you worked with [Herbert Brown](https://www.nobelprize.org/prizes/chemistry/1979/brown/facts/).  [EN] Exactly, yes.  [AS] So, he also, of course, was a Nobel Laureate. So there is a chain there.  [EN] Ah, definitely. Because, as you may know, another recipient, Akira Suzuki, is several years older than me, and he also was a post doctoral associate in Professor Brown’s research group.  [AS] Indeed. And he of course continued the organoboron chemistry …  [EN] Continued, but, I must say he … what he has done has literally nothing to do with what Professor Brown has done. Expect that both dealt with organoboron compounds.  [AS] And, so did you overlap in the Brown laboratory?  [EN] No, no, we did not overlap. But, later, we became closer and closer!  [AS] Was Herbert Brown a very special mentor?  [EN] Very much so! He really … In terms of research, he is my only mentor, research mentor. I have had other professors, but he taught me just about everything as to how to do research.  [AS] What did you learn from him?  [EN] Well, I must say, true way of doing research.  [AS] What is the true way of doing research? Can you encapsulate it?  [EN] Well, so, in many ways, when you pick your subject, or target, or whatever, then we dig out the truth. But, in reality, nobody knows what the truth is. So, we try to do many things to make sure that what we dig out is true. And, many people, in many other cases, people may fall short of that. That will lead to many confusions, of course. And, this search for truth, one finding will lead to another so there’s  this tremendous scope expanding, you know, in front of you. And, then we continue. So, one of the things that he liked to say is ‘a little acorn grow into a tall oak’.  And, indeed, that’s the mode of our explorations. And, I believe, we some of us, have learned this and how to do it, from him.  [AS] Yes, well, that certainly seems to be the case with palladium catalyzed coupling. It’s very interesting to hear the reference to truth, because often when one talks about synthetic organic chemistry, one talks about the development of new methods to make new molecules. And, the question of exploring truth, or nature’s truth, doesn’t really get discussed. But, that’s a fascinating way of looking at it.  [EN] Uh-hmm. So, I was just engaged in a along conversation a moment ago, but, you know, organic chemists focus their attention only on so-called organic elements. There are about ten or a dozen: Carbon, Hydrogen, Nitrogen, Oxygen, Halogens, and so on. And, then, of course, we all know that there are a hundred, hundred elements available to us. And, so, one of the dreams that we have turned into reality is to make good use of about fifty others. All the others are so-called metals. And, we … One of our findings is that metals are truly reactive, useful elements at least for synthesis. And, especially transition metals, especially so called D-Block transition metals, about half of the transition metals.  So, along this line, actually your Committee, the Nobel Committee, has awarded three times in the last ten years. First in 2001, to [Noyori, Sharpless](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/2001/) and, ah, what’s the name of the third one. I forgot. And then, what was it 2005 to [Grubbs, Schrock and Chauvin](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/2005/). And, now, us three. So, nine of us, actually, are in general area of transition metal catalysis. And, this has been less vaguely, or less well recognized principle.  Transition metals can catalyze so many different organic transformations.  And, we believe … you know between, Akira and myself and then probably ten or more others, luckily have come up with one of the most versatile, one of the most widely applicable methods for synthesizing … yeah, ok, so!  [AS] Yeah, yes, yes indeed. And, when one thinks of the currently available methods to synthesize new molecules, do you think that we are in the position of being able to do what we want, or is there much more to be discovered. Are we …  [EN]  Obviously, much more to be discovered. For instance, asymmetric synthesis, where Noyori and  Sharpless and others made a significant contribution, is still in its, I shouldn’t say infancy, but in its youth.  So, when it comes to how we control detailed stereo chemistry, the synthetic community, or we all, are still struggling a lot. And that will hinder the progress in drug synthesis and so on. Many things are still extremely difficult and it only started twenty, thirty, forty years ago, but it was probably first recognized in 2001. And, I would imagine that more will be recognized. But, definitely more needs to be done!  [AS] And, do you think that transition metals will be the sort of leading front?  [EN] I have no doubt about that.  [AS] Yeah.  [EN] So, this thing goes back to Hoffman, you know [Roald Hoffman](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1981/) who won the Nobel Prize in 1980 or 81, [Woodward](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1965/), of course, and then, in UK, Dewar, who did not win, but these chemists (Oh, [Fukui](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1981/), Fukui in Japan, also won the Prize with Hoffman), they told us. But, few people fully understood the true meaning of this magical thing that the transition metals offer us.  But of course many of us eventually understood. And, the names that I just mentioned earlier, including Noyori, Sharpless and Grubbs and Schrock and us all, we are now, or at least I am, in awe of the power of transition metals. And there is a very, very simple – it’s based on a very simple principle which we, the chemists, should all know. But, my guess is that, at the moment, it is even to most chemists ‘black magic’! That’s what they use, as a phrase!  [AS] And, for the non chemist, can you encapsulate the simple principle?  [EN] Ah! Simple principle is … I call this one the magic of combination of empty orbital and filled, non-bonding, but filled orbital. Of course, this combination, you know we need Lewis acidic compounds, but more, we have a term carbinoydal, carbene. And carbenes provide simultaneously empty and filled non-bonding orbitals. But carbenes are, you know, very fleeting species.  But transition metals, with the transition metals we can have highly reactive, yet stable, even commercially available, compounds with this fundamental property. Which Dewer reported in the early 1950s. Fukui, I understand, was doing this during the World War II! And, then of course, Woodward and Hoffman popularized in organic area this concept of frontier orbital theory, HOMO / LUMO theory. And some of us, many of us, recognized this, including all nine of us I suppose, perhaps in the late 60s and early 70s. And, I believe, those have propelled us to the current level and I think it is continuing.  So, there is basic principle, or story, I think is very, very clear.  [AS] Right, it just needs recruits to champion the principle.  [EN] Right.  [AS] May I ask you a last question, a bit of a strange question, but as a synthetic organic chemist, do you think you were born – or organometalic chemist – do you think you were born at the right time? Has this been the perfect time to be practicing your art?  [EN] I believe so! Someone, one of the very famous chemists, I believe he himself has been, I’m sure, a candidate for this Nobel Prize, said in around 1970, forty years ago, ‘organometalic chemistry …’ Yes?  [Background noise}  [EN] So, he said that this field is already on its way down. But I believe, looking back, that he was too futuristic. And, I think the next three decades maybe, that was a period of major growth.  [AS] I suppose things always take longer than one thinks.  [EN] Yeah! I believe so! And, I, myself, believe that my mission is probably half way through. But, I don’t think that I have the time for the other half.  [AS] Will the award of the Nobel Prize help make things happen faster?  [EN] I hope so! I hope so. But I, you know, I have to be well aware of my own age. Age factor, of course, you know everybody’s subject to that!  [AS] And, I suppose also aware of the danger of having your time taken up by having to speak to people on the telephone like me.  [EN] Well, that’s just today! I have with me a couple of other people waiting!  [AS] I can well imagine. So, I shall let you get on, and I hope at some point you have the chance to..  [EN] Well, I think what you’re doing is very important and coming from Sweden, you know, I very much appreciate it!  [AS] Well, thank you. When you come to Stockholm to receive your award we will have the chance to speak at greater length.  [EN] My pleasure.  [AS] Thank you. Ok, well, enjoy the rest of your day and thank you for speaking to us.  [EN] Yeah, thank you very much!  [AS] Bye, bye. |
| **Interview** |  |
| Q9 | **Richard Heck, Ei-ichi Negishi, Akira Suzuki, welcome to Stockholm and Nobel week. Professors Negishi and Suzuki, you have just arrived from Japan where you were together, being feted. Do you enjoy all the attention that this brings?** |
|  | Akira Suzuki: Well, I think maybe I want to enjoy it. How about you?  Ei-ichi Negishi: I feel that it’s part of the prize and probably the best thing is for me to enjoy it and provide hopefully my best service too. |
| Q4 | **Yes, but within the chemical world, very important world, there is so much of carbon-carbon chemistry is done using these reactions. It’s a nice part of chemistry, organic chemistry, that the reactions named after their inventors. So, all these characters live on through the pages of the organic synthesis textbooks. Do you know where that convention came from, that reactions should be named after the people who made them?** |
|  | Ei-ichi Negishi: No, I don’t, but there are several books based on so-called name reactions and I had an occasion to go through some of them and after the World War II, there have been just about 100 names, given to 100 reactions. So that means maybe two per year. |
| Q2 | **I want to pick up on this halfway point, because there is this marvellous abundance of molecules out in nature, that we look at and try to emulate and sometimes build and sometimes try to improve upon and then there are textbooks full of reaction schemes which allow one to think about how to put things together to make them. And you’re saying that we’re about, as an estimation, halfway towards the goal of filling those textbooks to the absolute limit. How does one estimate how many reactions there are to be discovered?** |
|  | Ei-ichi Negishi: Halfway means not necessarily in sort of a volume of things that we cover. Typically, organic compounds, we can consider in terms of ten or so dozen different kinds of functional groups – alkyl, alkene olefin, acetylene, aromatics, acyl, etcetera. About ten or a dozen. If you take a look at the organic chemistry textbook, then you see their discussion, discussions of them, in a dozen or twenty chapters, so that’s organic chemistry. If you consider ten or so as R1 group, and then similar ten or so, as R2 group, then you have ten times ten, a hundred combinations. If you can hook them at will, as you wish, then that’s the whole organic framework construction. You understand? Forget about other functional details but in this, in our approach, functional groups can be there, can be placed as needed. And then, when time for coupling the two together, we do that. |
| Q14 | **So, as well as varying the substituents that goes into the reaction, one can also vary the transition metal catalyst and then that just opens up a whole new spectrum of possibilities. The idea that we can solve all these problems of how to link the different functional groups together, suggests that there might be an end to the development of organic chemistry, that organic chemistry, the synthetic methodology, could reach a point which you say right, it is, we have what we need and then it just building what we need. Do we really foresee such a time?** |
|  | Ei-ichi Negishi: In a very, very long time … This is only one mode of organic synthesis, very, very general, very important mode, but I have been recently telling people, organic synthetic chemists have a major, major task right now which we want to solve. That is, how to convert carbon dioxide and water into carbohydrate, which nature does in a biochemical way, biological way. But no synthetic chemist has yet to claim this laboratory way, or factory way, of doing the same thing. I think this is a very, very important task because if we can do that economically, which we should be able to do, then we will solve a food problem, energy problem and a pollution problem, because CO2 is a starting material, we need more rather than less. And I cite this one because I believe, firmly believe, as in nature, D-block transition metals, in the case of biological process, it’s iron, iron is a D-block transition metal. It is going to be critically needed, probably one electron transfer process, radical kind of chemistry, rather than our nice two electron transfer processes, like the Heck-reaction or the Suzuki. Because there are two electron transfer process reactions. |
| Q14 | **So you would promote the study of and research on the D-block transition metal as a major area?** |
|  | Ei-ichi Negishi: I’m just presenting this as an example of a major goal, right in front of us. We want to solve this today or maybe in a year’s time or ten years’ time and no one right now we have a feeling that we should be able to do that because nature does, nature has been doing that for billions of years. It’s a big shame for the entire group, including ourselves. What I’m saying is that, this is just one of the major pending goals. You talked about our tasks being reduced, eventually to zero. I don’t think that time will come pretty soon. |
| Q3 | **That’s a good message. I don’t suppose that is was money who drove you to chemistry originally? What was it that made you adopt chemistry as your subject?** |
|  | Ei-ichi Negishi: Well, as an elementary school kid, I liked maths, very crisp. Then I thought I was going to major double E, electrical engineering, fascinating electronics, then I switched to chemistry, perhaps a little bit for money, because someone told me in electrical industry, the pay is not so good. So, my motivation was very impure but looking back I think that I chose the right field for me, because it’s not so mathematical, you know, it’s not like maths, it’s not cut and dry. And yet I didn’t develop my liking towards biologically oriented areas, because there were so many unknowns, so many nebulous kinds of things, many things were so in between, so they didn’t appeal to me. And now chemistry is sort of in between, between two extremes and I love that and I think this is an area where we can exercise our imagination and we can have many useful discoveries and development and then overall impact is, the works for the benefit of mankind. So, looking back I am very glad that I chose chemistry and I am recommending this to many young people, by saying that. |
| Q11 | **Sort of feet on the ground and head in the air. Do you find young people are coming to chemistry to a sufficient degree in the States? You have been teaching in Purdue for many years, do you find that?** |
|  | Ei-ichi Negishi: From our perspective, probably we are finding fewer and fewer younger people to be sufficiently qualified to be trained by us at the graduate level, that’s what my main interest is in and that’s been one of my concerns. |
| Q11 | **It’s no longer seen as a better paid alternative. Why do you think they are not coming?** |
|  | Ei-ichi Negishi: As you said, probably they are gravitating towards the areas that obviously look more lucrative. One of my grandchildren, he is major in business, not chemistry, not science, maybe for that reason. |
| Q5 | **Herbert Brown was obviously an enormous influence on you as well, Professor Negishi. Is there something in particular that you remember about him that encapsulates his approach?** |
|  | Ei-ichi Negishi: There are many, many, but I think he is a master of how to handle difficulties or failures and turn them into success. And I believe we all learned how to deal with those hard situations, and he had many, many, so usually he had so many plans. |
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| **Chemistry\_2024-2000** | |
| **ID** | 0339 |
| **Biographical** | I was born on September 12, 1930, in Mukawa – a small town in Hokkaido, Japan. I attended primary school there and entered a secondary school in Tomakomai, which is home to one of the biggest paper companies in Japan. At high school, I was interested in mathematics. Consequently, when I entered Hokkaido University in Sapporo, I wanted to learn more about the subject. In my freshman year, I became interested in organic chemistry after reading *Textbook of Organic Chemistry* by L. F. Fieser and M. Fieser. Finally, I decided to major in organic chemistry.  The title of my doctoral thesis was *Synthesis of the Model Compounds of Diterpene Alkaloids*. In the study, I used organometallic compounds, [Grignard](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1912/) reagents and organozinc compounds as synthetic intermediates and realized that organometallic compounds are interesting and versatile intermediates for organic synthesis. After completing the PhD program at Hokkaido University’s Graduate School of Science in 1959, I was employed as a research assistant in the Chemistry Department. Two years and six months later in October 1961, I was invited to become an assistant professor of the Synthetic Organic Chemistry Laboratory at the newly founded Synthetic Chemical Engineering Department in the Faculty of Engineering. In April 1973, I succeeded Professor H. Otsuka of the Third Laboratory in the Applied Chemistry Department. In total, I have spent 35 years at Hokkaido University as a staff member – 2 and a half in the Faculty of Science, and the other 32 and a half in the Faculty of Engineering. Other than about two years of study in America and a few months in other places overseas, most of my life has been spent at the Faculty of Engineering. Including my nine years as a student, the majority of my life has been at Hokkaido University. After my retirement from the university in 1994, I served at two private universities in Okayama Prefecture – Okayama University of Science and Kurashiki University of Science and the Arts – before retiring from university work in 2002. In the following, I would like to describe a few memories of my life in chemistry.  **A FEW MEMORIES**  **Professor Herbert Brown and Purdue University** As I reflect on these years, I see that there were many difficult periods as well as joyful ones. Memories of tough, trying experiences tend to fade with time. I think now mainly about the fun things, and here I describe a few memories that I have from my work.  It was a Saturday afternoon in 1962 when I visited the Maruzen bookstore in Sapporo. As I browsed the chemistry books, I discovered a very unacademic-looking volume bound in red and black. This book was *Hydroboration* by [H. C. Brown](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1979/), the 1979 Nobel Laureate in Chemistry. I took the book in my hands and began looking through its pages to find words written in Professor Brown’s unique style. I purchased the book and returned home. I still remember clearly picking it up after dinner that evening and not being able to put it down. It is not very long, but it remains one of the few scholarly books that I have stayed up all night to read. At the time, I had just transferred to the Faculty of Engineering from the Faculty of Science, and I wanted to begin research in a fresh field at my new workplace. This is perhaps one reason why this book had such an impact on me.  Inspired by this experience, I went to Purdue University in Indiana in August of 1963 (Figure 1) and spent almost two years at Professor Brown’s laboratory researching the newly discovered hydroboration reaction as a postdoctoral research associate (Figure 2). It was my first time in a foreign country, and one of the things that left an impression on me was the affluence of America at that time. For instance, one American dollar was worth 360 yen. My monthly salary as a doctor researcher was four times what I received even as an assistant professor in Japan. There was also little difference in diet between the rich and the poor. I found many such things that were unimaginable in Japan. Purdue University has a strong relationship with Hokkaido University. In the past, the former president of the university, Professor S. Ito, studied at Purdue. Professor S. Nomachi and Professor T. Sakuma were at Purdue at the same time as I was.  I learned many things from Professor Brown, including his philosophy toward research, but there is one thing he said that I recall with particular clarity: “Do research that will be in the textbooks.” It is not easy to do such work, but this has remained my motto. Professor Brown was 51 years old and was an extremely active researcher. He visited Hokkaido University three times. I had the opportunity to meet him and Mrs. Brown more than ten times (Figure 3), but unfortunately we lost them in 2004 and 2005.  Hydroboration is the reaction of alkenes with borane to produce organic boron compounds, which differ from other organometallic compounds in that they are chemically inactive, particularly in ionic reactions. For example, organic boron compounds are stable in the presence of water and alcohol, and do not undergo Grignard-type reactions. It was therefore thought that such compounds would be unsuitable as synthetic intermediates. Between 1963 and 1965 when I was at Purdue, there were more than 30 doctoral researchers and graduate students from all over the world at the Brown Lab. Many of these friends shared the opinion that boron compounds were inactive. In contrast, I thought that the stable character of organoboron compounds could be an advantage in some cases. For example, they could be used in the presence of water without any special precautions. I considered to find some way to use these compounds in organic reactions, and created a new research plan upon my return to Japan in April 1965 (Figure 4).  **DISCOVERY OF ALKYL RADICAL FORMATION FROM R3B**  At the time, I focused on three characteristics of organoboron compounds. First, compared to other organometallic compounds, the difference in electronegativity of the C-B bond is small, making it an almost-perfect covalent bond. Second, boron atoms have an empty ρ-electron structure, meaning that they may be susceptible to nucleophilic reagents. This suggested that the compounds might undergo the reactions shown by Eq. 1. Third, studies of the C-B bonding distance showed that it was almost equal to the C-C bonding distance.  In consideration of these three points, I decided to study the reaction of organic boron compounds with α, β-unsaturated ketones. In other words, I hypothesized that the intermediate (I) in Eq. 2 could be obtained through a quasi-hexagonal transition state, which could be hydrolyzed to give a saturated ketone. When we examined methyl vinyl ketone in the reaction, we found that the predicted corresponding saturated ketone was produced with a quantitative yield (Eq. 2). We obtained these results in 1966, and when I notified Professor Brown of our findings in a letter, he was extremely interested. He told us that he wanted to explore the results at Purdue as well. I supported his proposal, and we continued to study α, β-unsaturated ketones in Hokkaido, while α, β-unsaturated aldehydes were investigated at Purdue. We analyzed the scope of the reaction and tried several types of α, β-unsaturated ketone reactions, finding that each produced favorable amounts of the corresponding saturated ketones at room temperature. Although we discovered that compounds with a substituent in the β position (such as II compounds) did not react at room temperature, we found that the expected proportions of products were formed in a THF (tetrahydrofuran) solution at reflux temperature. I received a letter from G. Kabalka (now a professor at the University of Tennessee), who was then a graduate student performing related research at Purdue. According to the letter, something similar had been found with α, β-unsaturated aldehydes. None of the corresponding saturated aldehydes were produced by the reaction of compounds such as III, which had a substitution group in the β position, even though many similar compounds (such as acrolein) reacted readily at room temperature. I proposed that each laboratory confirm the results of the other, and we began experiments on III, finding that the reaction proceeded in THF at reflux temperature. However, subsequent experiments at the Brown Lab did not manage to reproduce our reaction. I remember a sentence in the letter I received from Professor Brown reporting their results: “Chemistry should be international. Why do we have such a big difference between two places, Sapporo, Japan, and West Lafayette, U.S.A.?”  When we looked more closely at these contradictory results, we discovered something quite unexpected. A trace amount of oxygen contaminating in the nitrogen gas we used in our reaction system was catalyzing the reaction. At the time, we knew that organoboron compounds reacted with oxygen, so both we and the Brown Lab conducted the reactions in nitrogen gas. In our laboratory, we used nitrogen purchased from Hokkai Sanso (now called Air Water Inc.), which we further purified ourselves. Nevertheless, trace amounts of oxygen were still present in our nitrogen gas. The oxygen acted as a catalyst and promoted the reaction. In the U.S., extremely pure nitrogen could easily be purchased in those days, and did not contain sufficient amounts of oxygen to cause the reaction.  From such unexpected results, we found that with small amounts of oxygen catalyst, organoboron compounds produced alkyl radicals. Furthermore, the reaction followed the radical chain mechanism as shown in Eq. 3 rather than the coordination mechanism we had inferred previously (Eq. 2).  **Serendipity** The concept of serendipity often crops up in research. Serendipity is the faculty or phenomenon of finding valuable or agreeable things that were not being sought. I believe that all researchers can be serendipitous. However, in order to make the most of such opportunities, a researcher must have the humility to see nature directly, an attentiveness that does not let even the dimmest spark escape, and an insatiable appetite for research. Some amount of luck is also needed, but we can say with certainty that little will come of half-hearted efforts.  **Quick publication** In 1970, we were performing experiments to directly produce carboxylic acid from organoboron compounds. One possibility we explored was to use complexes derived from such compounds and cyanide ion, which react with protonic acids. We were not able to obtain our intended result, but discovered that these cyano complexes produced symmetrical ketones with a good yield when they reacted with electrophilic reagents like benzoyl chloride. Nonetheless, I was busy preparing for a presentation at an international conference to be held in Moscow in 1971, and we left for the conference without finishing our paper on it. After I had successfully given my invited lecture, I left the lecture hall to quench my thirst with a glass of water. At that time, a tall foreign man introduced himself to me. It turned out to be Professor A. Pelter of Manchester University in the U.K. He later transferred to the University of Wales in Swansea, and served as the chair of the Department of Chemistry as well as the Vice-Chancellor of the university. At our first encounter in Moscow, I had no idea that he was studying organoborane chemistry. We spoke about many things that day, and to my surprise, I learned that he had already completed the very research that we had been working on, and that his results had been published the previous month in *Chemical Communications*. As a result, our work remains unpublished. Today, that reaction is sometimes called the Pelter reaction. Knowing about our situation, Professor Pelter sympathizes with us and consoles us, but no one else knows anything about it. We learned from this experience. When doing research, we must keep three things in mind. First, we must study existing literature carefully and comprehensively. Second, we need to be aware that other researchers, near and far, are thinking about the same things that we are. Third, we must quickly publish papers on our results (rather than just giving oral presentations).  **Tragic accident** When I remember that conference – the International Conference on Organo-Metallic Chemistry in Moscow 1971 – I cannot help but think of the tragic accident in which an ANA passenger jet collided with a Japan Self-Defense Force aircraft in the skies above Shizuku-ishi in Iwate Prefecture. On that day, I had flown from New Chitose Airport in Sapporo to Haneda Airport in Tokyo to stay the night before boarding an Aeroflot plane to Moscow the next day. I took a Japan Airlines flight in the afternoon, unaware that the plane that had departed only 30 minutes earlier would be involved in such a terrible accident. Knowing nothing of the tragedy, I landed at Haneda and headed to the Haneda Tokyu Hotel near the airport to stay, and then learned about the accident. All passengers and crew – 162 people in all – were killed.  **Haloboration reaction** Next, our group carried out research on the synthesis of organic compounds through haloboration. This research was based on the discovery that a certain type of haloborane derivative adds to terminal carbon-carbon triple bonds. The reaction was discovered in 1981, but we first released part of this research in the United States in 1982. That fall, the American Chemical Society hosted a symposium in Midland, Michigan on organic synthesis using organoboron compounds. I was one of the special invited speakers, and was preparing to travel to the U.S. when I received a letter from Professor Brown. It was an invitation to visit Purdue to give a lecture on haloboration before the symposium. Professor Brown listened to my presentation intently, and raised his hand to comment the moment I finished speaking. He said that his group had studied the possibility and usefulness of the same reaction at almost the same time as we had. They had looked at haloboration reactions for acetylene compounds, but had only investigated the reactions of internal acetylenes as substrates. Their work was unsuccessful, and they ended the research. The goddess of fortune is capricious, indeed.  Over the years, I have had a variety of different experiences. I have made many friends at Hokkaido University’s Faculty of Engineering, especially among many of the people who continue to work at the Third Laboratory of the Applied Chemistry Department and the Organic Synthetic Chemistry Laboratory in the Synthetic Chemical Engineering Department. They have allowed me to enjoy a long career in research. I conclude by expressing my sincere gratitude to these students and colleagues. |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** | [Suzuki]  [Akira Suzuki] Hello?  [Smith] Hello! Professor Suzuki?  [Suzuki] Yeah.  [Smith] Congratulations, of course, on the award.  [Suzuki] Yeah, thank you very much. Yes, thank you very much!  [Smith] It was announced yesterday, so how have the last twenty-four hours been since the announcement?  [Suzuki] Last night, it was very nice day, but a very hard day for myself because I knew the Nobel Foundation give us very big honour. But, they phone me at 6:30pm, around 6:30pm. But, they say, “You cannot tell this thing until after 6:45”.  [Smith] Yes, in the evening, yes.  [Suzuki] I’m supposed to keep it a secret. So, many of the, you know, the press people visit my home – so many – I don’t know, maybe more than twenty or twenty five. Then, our university, Hokkaido University, kindly sent me a car, taxi, to pick me up to the University. University arranged the group interview of many of the newspaper companies. So, I stay in the University almost midnight! Then I’ll be back to my home. And, I arrive 12:30. Then, I checked my e-mail, and I found I had almost more than eighty such e-mail messages, half from Japan, half from the other countries, including the United States and Europe and so on.  So, I checked it. And, finally, I finished check them at 4:30 am. Then, I want to get in the bed. But, I cannot sleep! That means last night, I don’t have no time to sleep. So, I’m really very tired and this morning from 11 o’clock, we started again such a group interview of press companies. So, we are still continuing such a, you know, serious discussion about my Nobel Prize, this time. OK, that is the real situation.  [Smith] It’s good to have an honest account of it. But, it sounds like you’re holding up well? Are you enjoying it?  [Suzuki] Yeah, yeah, of course, I am very happy to have such a great honour. But, also, fortunately, I’m still very healthy. So, I don’t have any problem at this moment. I’m really overjoyed and very happy to have such a great Prize from your Nobel Foundation.  [Smith] Good, good. So, the Prize will focus the world’s attention on organic chemistry.  [Suzuki] Yes?  [Smith] What for you is the joy of being an organic chemist?  [Suzuki] I think, you know, in organic chemistry, we have so many different kind of field of organic chemistry. But, my major interest is to find new synthetic methodologies. Our case, we used the organometalic compounds. Additionally, we need one important element, that is base. Without base the acidic coupling reaction using organoboron compounds cannot proceed nicely. So, that is very important point in our cross-coupling reaction.  [Smith] And, you worked originally on organoboron compounds with [Herbert Brown](https://www.nobelprize.org/prizes/chemistry/1979/brown/facts/) at Purdue University?  [Suzuki] Yes? Of course, as you know, there … we spend two years as a postdoctoral research fellow at Professor Brown’s laboratory in the Purdue University.  [Smith] Hmm, what did …  [Suzuki] At that time, at that time, Professor Brown asked me, “Akira, why don’t you try these studies, the chemistry of hydroboration reaction?” Because, see, I was there from 1963 to 1965. That was, almost, several years after such a hydroboration reaction was discovered in Brown’s laboratory. Therefore, they ask me to continue the study of the stereochemistry of hydroboration reaction.  [Smith] Was it?  [Suzuki] I get nice results. And, ah, we finally decided hydroboration proceeds through the cis addition, from the less hindered of the c-c double bond. That is our conclusion of our study. We developed it …  [Smith] What …  [Suzuki] Yes?  [Smith] Sorry, what did he … what did he teach you about how to do chemistry? Was he a good mentor?  [Suzuki] Yeah, he give us many important suggestion. Not only in the chemistry but also in our … in my, life. For example, he said many things, but today I only say, ah, tell you one thing that he often told me, “You have to study such a study … such a study what be appears in text book.” You know, the text book?  [Smith] In text books, yes.  [Suzuki] That is, of course, it’s very difficult because not so many studies were cited in the textbook. So, Brown often tell us, our postdoc and graduate students, “You have to find your study, which appears in the text book.” I still remember, and I still often teach such a, you know, philosophy, to our many students. That is … of course, he taught us many things, but that is one of most impressive, chief realization he gave me in his laboratory.  [Smith] And, the tools you build, the synthetic tools you build allow one to create new molecules in new ways.  [Suzuki] Yeah?  [Smith] Do you think that the chemist now has enough methodology to allow them to build the molecules they need, or is …  [Suzuki] Well, yes. I think, you know, of course we, organic chemists, want to makes different kinds of organic compounds. Such a compound has a, of course, as you know, C-C bonding. C-C bonding. For the synthesis, of carbon-carbon bonding … Pardon me? What is it?  I’m sorry, I’m sorry. Ah, people say our schedule is over time.  [Smith] Ah, ok.  [Suzuki] So, we have to stop. If you want to discuss such a thing, I think, you send me your phone …  [Smith] We will speak again, yes.  [Suzuki] If you need, ok?  [Smith] Ok, I wish you the best of luck with the rest of the day. I hope you find some sleep at some point. Thank you.  [Suzuki] Ok, thank you very much.  [Smith] Thank you so much. Bye, bye.  [Suzuki] Bye, bye. |
| **Interview** |  |
| Q9 | **Richard Heck, Ei-ichi Negishi, Akira Suzuki, welcome to Stockholm and Nobel week. Professors Negishi and Suzuki, you have just arrived from Japan where you were together, being feted. Do you enjoy all the attention that this brings?** |
|  | Akira Suzuki: Well, I think maybe I want to enjoy it. How about you?  Ei-ichi Negishi: I feel that it’s part of the prize and probably the best thing is for me to enjoy it and provide hopefully my best service too. |
| Q3 | **What about you Professor Suzuki, what lead you to chemistry when you were young?** |
|  | Akira Suzuki: Well, I think, recently I don’t know … as a young student in Japan … people say young Japanese boys and girls they never feel so much interest in the science, including the chemistry, physics and so on. But, so this time, after I get the Nobel Prize, decided I received the Nobel Prize, I have a main chance to talk with press people, they say in Japan, the young people they don’t like science and technology, but I think, in Japan of course as you know, in Japan we don’t have any enough resources. We don’t have any petroleum, not have any iron resources, we only have coal mining resources but that is located so deep under the ground, so it takes lot of money to cut from down to up. So, in Japan the important thing is, we, they make a very nice product, then we sell such a product to all over the world. That is the only way Japan people, we continue our country, in such a meaning, we have to say to young people, you have to explain our situation. And one way we can continue our Japan is, to feel very much interest in science and technology, to make very nice products to sell to the world.  In such a meaning, I say, the Japanese government and the professors, we say such a thing to the younger people and he join us to pay much interest in our chemistry, not only the chemistry, the science and the physics. But in such a meaning, I always say, the other day, I got the chance to talk with Prime minister of Japan, after I received the Nobel Prize, so I emphasised this thing to our Prime minister. He is also a scientist, physics is his major, so he understands very well, but unfortunately many of the people in our government, don’t understand very much more of science and technology, so I think it’s important in the government to understand such a situation and to give lot of research money. Of course, at this moment, Japanese, our economical situation is very, not so nice, even though I asked the Prime minister our government understands such a situation to support the science and the technology and to give research money for such a field and also reasonable money to the education That is very important. I just say such to government people recently. |
| Q3 | **Let’s return to Herbert Brown, Professor Brown, what was it that he taught you?** |
|  | Akira Suzuki: I think, he gave us many things, one thing I still knew about that he said that is, “You have to study, your research leader should be in textbook”. So, that means, you have to find your chemistry just new field of the chemistry, so, if such a new chemistry should appear on the textbook, so he always says you have to do your study which appears in the textbook. And also, I often say, the thing is a little bit different, but I always say to students, you have to do the basic, in Japan we have a special box. In the box we put the rice, how do you say in English? That is a kind of the rice box or something like that. |

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| **Biographical** | Childhood I was born in 1952 in Chidambaram, an ancient temple town in Tamil Nadu best known for its temple of Nataraja, the lord of dance. When I was born, my father, C.V. Ramakrishnan, was away on a postdoctoral fellowship in Madison, Wisconsin, with the famous enzymologist David Green. Because he came from a poor family, he did not think that he could support my mother and me on his postdoctoral income, so he went alone. I often joke that but for this, I would have been born in Madison and could have gone on to become President of the United States. In fact, I first saw him when I was about six months old. My mother, R. Rajalakshmi, taught at Annamalai University in Chidambaram, and during the day, I was well cared for by aunts and grandparents in the usual way of an extended Indian family. When I was about a year and a half, my father left again, this time with my mother, to go to Ottawa on a National Research Council fellowship. They returned a little over a year later, and during their absence I was brought up by my grandmother and my aunt Gomathi, to whom I remain close to this day.  When I was three, my parents moved to Baroda (now appropriately called by its Gujarati name of Vadodara, which refers to the abundance of banyan trees that the city used to have), where my father was appointed at an unusually young age to head a new department of biochemistry at the Maharaja Sayajirao (M.S.) University of Baroda. When he started the department, there was just some empty lab space with no equipment or people. He managed to acquire a low-speed table-top centrifuge, and would get blocks of ice from a nearby ice factory, crush them, and place them around the centrifuge so that his samples would remain cold during enzyme purification. With this setup he managed to publish two papers in *Nature*in quick succession. Within a few years, the department was well established in both teaching and research, and equipped with instruments, a cold room and an animal house.  Unusually for an Indian man of his generation, my father, being aware of my mother’s intellectual abilities, encouraged her to go abroad by herself to obtain a Ph.D. She obtained a fellowship in McGill University to do a Ph.D. in psychology, where one of her mentors was the famous psychologist Donald Hebb, whose theories presaged modern ideas about synaptic plasticity as a basis for memory and behavior. Probably because she felt guilty about leaving my father and me behind, she finished her Ph.D. in under 18 months, which must be something of a record. When she returned, she could not find a suitable position in the Psychology Department in Baroda. Instead she used her analytical skills to help my father in his research, working initially as a CSIR pool officer, which was a temporary scheme by the Government of India to support scientists returning from abroad. This was the beginning of a lifelong collaboration in their work. My childhood and adolescence were filled with visiting scientists from both India and abroad, many of whom would stay with us. A life of science struck me as being both interesting and particularly international in its character.  My move to Baroda was something of a culture shock initially because until the age of three I only spoke Tamil, a language that I unfortunately no longer speak well. One of my earliest memories is of standing in a playground not being able to understand a word of the Gujarati the children were speaking. This feeling of being an outsider has remained with me for much of my life as my career has taken me to various countries. Because my parents did not speak Gujarati either, they enrolled me in what was then the only English language school in town, the Convent of Jesus and Mary School, which was located next to a large military base. After kindergarten, my mother persuaded the school to let me skip a grade. Shortly after my sister Lalita was born in 1959, my family went to Adelaide, Australia in 1960–61 where I studied in fourth and part of fifth grades. I remember the year in Adelaide as one of the most carefree years of my childhood, and returned with an Australian accent that my former schoolmates could hardly understand. Because of the six month difference between the Australian and Indian school years, I effectively again skipped a grade on my return. The rest of my schooling was at the Convent School. By that time, there were other English schools in Baroda, and the nuns who ran the school decided to convert it to a girls’ school and no longer admit boys. They allowed those boys who had enrolled to stay on, but by attrition, our class kept losing boys, so there was a roughly four to one ratio of girls to boys when I graduated. Perhaps because of this and the fact that my mother and sister both went into science, I have felt perfectly comfortable among women even when I am the only male present, and there have been times when my lab has consisted almost entirely of women.  During the 7th – 9th grades, I dropped from being at or near the top of my class to being in the bottom third. Rather than studying, I spent my time playing and reading novels and other extracurricular books. Luckily, in my last two years I had a dedicated science and mathematics teacher, T.C. Patel, who made those subjects come alive. A strict disciplinarian, he nevertheless had a twinkle in his eye as he would expose us to clever ideas and difficult problems. This sparked my interest in my studies again, and I graduated second in my class overall despite the fact that I did very poorly in Hindi, a language that I never managed to learn well.  **Choosing Basic Science** By the time they finished high school, students in India were separated, as they are in England but not in America, into those who are going into science, medicine or engineering, and those who plan to study the arts or humanities. Although I liked literature and did well in my English class, studying English was never really an option I considered seriously, especially given the scientific environment in which I grew up. Additionally, the cultural climate in India makes it difficult for good students to choose to study the humanities unless they are particularly strong willed, because parents are too often opposed to what they see as a risky career choice. Accordingly, I enrolled in the pre-science course at my local university, the M.S. University of Baroda. This was a one-year preparatory course before students chose to go into medicine, engineering or basic science. The pre-science course had an excellent curriculum in both physics and mathematics, largely due to forward thinking faculty in those departments. However, the teaching of botany and zoology was very old-fashioned and involved memorization of lots of facts in a relatively unconnected and tedious way. As a result, I was not particularly interested in the life sciences at that stage.  A critical decision that students have to make after their pre-science year is whether to go into medicine or engineering. Generally, those students who did not get accepted into either of these went into basic sciences as a last resort. My mother, however, had just become aware of the National Science Talent Search Scholarship by the Government of India, which was modeled after the Westinghouse (now Intel) Science Talent scholarships in the U.S.A. A condition was that the recipient had to major in a basic science. She encouraged me to take the scholarship exam, and arranged for me to do the required research project with a colleague of hers in the Biochemistry Department on quantifying nitrogen fixation by leguminous plants, which was somewhat ironic given my general apathy towards biology courses.  At the end of the year, I also took national entrance exams for the famous Indian Institutes of Technology (IITs) and for the Christian Medical College in Vellore, one of the finest medical schools in India, but which had a very small quota for males since it was founded to train female doctors. I did not do well enough to qualify for admission to either institution. However, as a result of doing well in my university exams, I was offered admission to study medicine in Baroda. In the meantime, however, I was offered the National Science Talent Scholarship. I had made an agreement with my father, who wanted me to study medicine, that if I was awarded this scholarship I could choose to study basic science. That decided, there was the further question of where to do my undergraduate studies. I briefly considered going to Madras, which would have reconnected me with my Tamil roots, but a faculty member in the physics department in Baroda, S.K. Shah, told me about a brand new curriculum they were introducing for their undergraduate course. It began with the Berkeley Physics Course, and was supplemented by the [Feynman](https://www.nobelprize.org/nobel_prizes/physics/laureates/1965/) Lectures on Physics before moving on to more specialized areas. I therefore decided to enroll in the B.Sc. course in physics in Baroda, my hometown. Since I was only 16 when I began this course, I sensed that my parents, especially my father, were relieved that I was not leaving home at an age when they felt I was not sufficiently mature emotionally.  My teachers in physics, especially S.K. Shah and H.S. Desai, were very excited to be teaching the new curriculum for the first time, and their enthusiasm was infectious. I also had several excellent mathematics teachers, including the scholarly S.D. Manerikar, who discarded our exam-oriented Indian textbooks and taught us from books like Hardy’s “A course of pure mathematics” and Courant’s textbooks of calculus. It was during this time that I first met Sudhir Trivedi, who has gone on to a successful career in applied physics in the U.S.A. and become a lifelong family friend. When we had a boring class, we would often skip it. Once he and I sat near an open window and decided to jump out of it as soon as attendance was taken to go off and have tea and snacks at a nearby restaurant. His jump created a loud thud so I could not follow because the professor was staring directly at me.  Towards the end of my undergraduate studies I had to decide where to go to graduate school. The normal route for science students was to do a master’s at some university in India before thinking of going abroad. As a Science Talent Scholar who was doing well, I would have been accepted almost anywhere. However, my parents were doing a short sabbatical at the University of Illinois in Urbana at this time, so it was tempting to spend the summer with them and go on to graduate school in the United States. By the time I applied, it was too late to take the GRE and without it almost no universities would consider my application. The University of Illinois accepted me into their graduate program in physics initially, but when they found out I was not yet 19 years old and had taken almost no non-science courses, they changed their minds and said I would have to enroll as an undergraduate! Needless to say, this was not an option I was prepared to consider, not least because it would have been impossible financially. At about this time, my chairman N.S. Pandya brought to my attention a letter from the physics department at Ohio University, which said they were looking for qualified students for their graduate program. I wrote them a letter of inquiry and soon afterwards was accepted with a fellowship. I was living alone when the acceptance arrived, and was absolutely thrilled to be going to graduate school in the U.S.A., a land I associated with many of the great scientists whose textbooks I had studied, including Feynman, Purcell and others. I arrived in America a month after my 19th birthday, and spent the summer in Champaign-Urbana with my parents. I sat in on a number of mathematics and physics courses there, which helped ensure that I did not have serious deficiencies in my readiness for graduate school.  **Graduate School in the U.S.A.** When I got to graduate school in Ohio, I was surprised to see that over half of our class consisted of foreigners, many of them from India. I passed the obligatory comprehensive exam after two years of coursework, and then chose to work in solid-state theory with Tomoyasu Tanaka. For my proposal, I had considered doing some theoretical work on biological systems, but since neither he nor I knew any biology, this did not go anywhere. The problem I took on was to look at ferroelectric phase transitions in potassium dihydrogen phosphate. This was a particularly difficult time for me, since I had no feel for the problem or even what the basic questions were. It was the first time in many years that I felt I had chosen the wrong field. At the same time, I found myself tremendously interested by the articles in biology in *Scientific American*, to which I have subscribed off and on through the years. It appeared that hardly a month went by without a major breakthrough in the life sciences, whereas physics was having a hard time making any fundamental progress. Certainly I felt that if I continued in physics, I would be doing boring and tedious calculations rather than making really interesting advances. The result was that I felt so frustrated that I withdrew from my thesis work and spent an inordinate amount of time on extracurricular activities. I went hiking and hopped on freight trains with my good friend and class mate Sudhir Kaicker, learned about western classical music from another friend, Anthony Grimaldi, played on the chess team, read literature, and went to concerts. In short, I did everything except make progress on my work. Tomoyasu was far too kind and patient, but even he would get worried every few months and ask how I was getting on. I was too embarrassed to tell him that I wasn’t getting on at all! I often joke that if I had graduate students like me, I’d fire them! In hindsight, I feel that given my aptitude and tendencies, I made a mistake in choosing theory over experiment for my thesis work, and I might have done better under someone like Ron Cappelletti (now at NIST), who was not only a fine experimentalist but also tougher and less likely to tolerate an irresponsible student. Interestingly, I later became good friends with Ron.  It was during this time that I met Vera Rosenberry, who was majoring in painting and was introduced to me by mutual friends because, unusually for the early 1970s in Ohio, we were both vegetarian. After an intermittent courtship that lasted only 11 months in total, we were married in 1975. She has been my companion and friend ever since, and has not only done most of the work of raising our children but uprooted herself many times to move with me all over the U.S.A. and to England. The emotional support and stable home environment she provided has been invaluable to me and my work. During that time, in addition to painting, she also became a children’s book writer and illustrator, and has published over 30 books.  After my marriage at the age of 23, I was suddenly no longer alone but had a wife and a five-year-old stepdaughter, Tanya Kapka. This sudden change in my responsibilities made me realize that I had to get on with my career. I produced a passable thesis in the next year and obtained a Ph.D. in physics in 1976 just a month before our son Raman was born. But by that time I had already decided I was going to switch to biology.  **Transition to Biology** Since I hardly knew any biology, I felt I needed formal training of some sort. I could go to graduate school again, with the option of getting a second Ph.D. or go to medical school, which was ironic since I had turned down the opportunity to do precisely that when I was younger. I took the MCAT (a nationwide medical college entrance exam) but despite scoring in the 99th percentile in all the subjects, I only got one interview (at Yale) because I was not a U.S. citizen or even a permanent resident at that point. During that interview, I said I was mainly interested in research and not interested in practicing medicine since I felt the U.S. medical system involved a fundamental conflict of interest between doctor and patient. Needless to say, I was not selected. However, I had also written to a number of graduate programs. Many of them said that they would not accept someone who already had a Ph.D. The chairman of the Molecular Biophysics and Biochemistry (MB&B) department at Yale, Franklin Hutchinson, wrote to me saying that while they could not take me as a graduate student, he would circulate my CV to faculty members for a potential postdoctoral position. Two of them responded: One was Don Engelman, and the other, ironically, was Tom Steitz, with whom I shared the Nobel Prize. Although I found their work very interesting, I thought doing a postdoc directly from a degree in physics would leave me with too narrow a background in biology to be an effective scientist. So when three schools accepted me into their graduate program, I chose to go to the University of California, San Diego (UCSD), partly because of its large and diverse faculty and partly because La Jolla seemed an easy place in which to bring up young children.  During the first year, I did several lab rotations in biology and took as many undergraduate courses as I could possibly manage, including genetics, taught by Dan Lindsley, a well-known *Drosophila* geneticist, and biochemistry, where I was inspired by the brilliant and enthusiastic lectures of Paul Price. During a rotation project in Milton Saier’s lab, which was studying sugar transporters in bacteria, I was asked to measure the rate of sugar uptake in various mutants. The idea was to pipette 20 μl of a stock of 14C glucose into the tubes containing cultures at time zero, and then withdraw aliquots at regular intervals and measure the amount of glucose uptake by filter binding. I asked how they measured such a small volume as 20 μl. The technician showed me a micropipettor and how to set the volume and use it. We started, but as soon as I had plunged the micropipettor into the radioactive glucose solution, she screamed at me, “What do you think you’re doing? You have to use TIPS!” This episode has always made me more tolerant when my students do something out of ignorance resulting from lack of complete communication.  My first year in UCSD was tremendously exciting. For the first time in my life, I was at a university that was at the forefront of international research. I also made some wonderful friends, including Robert Anholt, now a professor in North Carolina who works on olfaction, and Mark Troll, a brilliant physical chemist who many years later married my sister.  In my second year, I settled down to do research in Mauricio Montal’s lab. Mauricio had developed an ingenious method of incorporating conducting channels into lipid bilayers formed by bringing together two defined monolayers, and was thus doing single molecule biophysics at a time when nobody called it that. Around this time, however, I read an article in *Scientific American*by Don Engelman and Peter Moore about their ribosome work, and became interested in it. It also struck me that there was no longer any reason to continue on to obtain a second Ph.D. because I felt I had acquired the background I needed. I therefore wrote to Don Engelman, one of the two people from Yale who had responded to me earlier. Don was interested in membrane proteins, a subject I was already working on in Mauricio’s lab. Don wrote back and said that he and Peter had a position open on their ribosome project, and I could always work on membrane-related projects once I got there. Peter arranged to meet me in San Diego in early 1978 and offered me a postdoctoral position soon afterwards. Thus began my lifelong interest in ribosomes.  **Postdoctoral Work in Peter Moore’s Lab at Yale** Peter Moore ran a very small lab with generally no more than 4 or 5 people. Among them was Betty Rennie (now Freeborn), who taught all of the lab members how to purify ribosomes, reconstitute them and assay them. The specialized methods I learned in Peter’s lab were invaluable to me twenty years later when I started tackling the structure of the 30S subunit that led to the Nobel Prize. Peter has been a lifelong role model. He is brilliant, rigorous, fair, straightforward and honest with his opinions, and has been a supportive mentor all my life. In his lab I participated in the long term project of mapping the spatial location of the proteins in the 30S subunit, which involved reconstituting ribosomes in which a specific pair of proteins were replaced by their deuterated counterparts. This was followed by smallangle neutron scattering experiments at Brookhaven National Laboratory, which would yield the distance between the centers of mass of the two deuterated proteins. I managed to map about a third of the proteins during my stay there, as well as contribute to the use of Bayesian methods to obtain the best possible estimates from the data.  Postdoctoral work combined with a family with two young children did not leave me much time to socialize with fellow students or postdocs. But we did have a number of good friends because we lived in Yale housing. I also remember these years as being particularly happy, since I was finally making progress on a real research project and felt that my career was finally beginning to take shape. This feeling quickly ran into reality when I applied for a large number of faculty positions during my final year at Yale, and did not get a single interview. This was partly because of my rather unusual career path, the fact that my degrees were from less than first-rate institutions, and perhaps more importantly, universities did not know what to think of a physicist turned biologist using an esoteric technique like neutron scattering. I was beginning to get very discouraged when two openings finally materialized. One of these was a limited-term position at the National Bureau of Standards with Alex Wlodawer. The other was the result of a phone call by Don Engelman to Wally Koehler at Oak Ridge National Laboratory, who was looking for a biologist to hire for their new small-angle neutron facility. I chose the Oak Ridge position because it seemed more stable and permanent, and I was told that I could have a joint appointment in the Biology Division and be able to carry out my own research in addition to collaborative experiments using neutron scattering. I should have waited until the end of the school year to move, but instead chose to do so in February during an ice storm.  **An Interlude in Oak Ridge** Soon after I arrived in Oak Ridge, I realized that I had completely misunderstood my position. The Biology Division saw me entirely as an employee of the neutron scattering facility, and would not commit any resources to support me, although they gave me some space in an empty lab. I tried to remain positive and told my boss Wally Koehler that I could apply for NIH grants to fund my own research. He replied that it would look bad if I got external funding while senior scientists in the Biology Division were struggling, and moreover he had not hired me to be a biologist but to attract biologists to the use of neutrons. I found this attitude insulting and ignorant of both the way biology is done and the rather peripheral role that neutrons play in tackling important biological problems. As a result, I began looking for alternatives within a month after arriving in Oak Ridge, despite the fact that we had foolishly just bought a house.  While I was looking for a job, I talked to various people in the Biology Division and identified several projects where neutron scattering could provide some useful information. In the Division, I shared an office with Rose Feldman, a longstanding technician who worked for Salil Niyogi. Rose was my psychological support in what would otherwise have been a very difficult year. Moreover, I began collaborations with Mark Donnelly and Rick Wobbe, who both became lifelong family friends along with Mark’s wife Veta Bonnewell. I have never made so many longstanding friends in such a short time. One of the most useful collaborations was work on the nucleosome with Gerry Bunick, Ed Uberbacher and Don and Ada Olins. This sparked an interest in chromatin that continued until 1998, when I gave it up to concentrate entirely on the ribosome.  **Starting an Independent Career at Brookhaven** The Yale neutron effort on ribosomes was the direct result of instrumentation developed by Benno Schoenborn for the biological use of neutron crystallography and scattering at Brookhaven National Laboratory. When Benno learned of my situation in Oak Ridge, he told me to be patient and that a suitable staff scientist position would soon be available at Brookhaven that came with appropriate support and the freedom for independent research. I will always remain grateful to Benno for hiring me at Brookhaven and thereby rescuing me from scientific oblivion.  Personally, the move to Brookhaven was not easy. Vera and I liked Oak Ridge and the beautiful countryside around it. We were not enamored of the car-oriented commuting lifestyle of Long Island. But the job at Brookhaven was an excellent one in a department with fine colleagues, so we moved there in 1983. We sold our house in Oak Ridge for about 25% less than we had paid the year before and bought a house in East Patchogue, just outside the village of Bellport on the south shore of Long Island, about a 12-mile commute each way from the lab. There we became lifelong friends with Karen and Bruce Brunschwig. Bruce later played a crucial role in our ribosome effort by synthesizing a key derivative for us, osmium hexamine.  Unlike my experience in Oak Ridge, Brookhaven gave me exactly what they had promised. Benno said it would be nice if I did some experiments that used neutron scattering, but that they were broadminded and I could generally do what I wanted. They did advise me that if I wanted to get tenure, I could not simply continue what I had been doing in Peter’s lab as a postdoc, but had to show independence. Nevertheless, my first experiment was on ribosomes, in which I tried to settle an emerging controversy about whether the proteins and RNA in the 30S subunit were asymmetrically distributed. This resulted in my first independent paper being a single author paper in *Science.*Since this was a decade before the internet, I wrote a letter to my father in India when it was accepted, and about a month later received his reply saying that he was glad I had made a good start, and that if I continued to work hard, I might some day even have a paper in *Nature!*  I also continued working on chromatin. The linker histone H1 binds to nucleosomes and helps to organize nucleosomes into a higher order tructure, commonly known as the 30 nm filament. I wanted to try to use neutron scattering with deuterated histone H1 to determine its location in the intact filament. But it was not clear how one could go about getting deuterated histones, and I spent at least a year in a futile effort to grow *Euglena gracilis*in deuterated media to try to isolate histones from it.  At about this time, two crucial developments occurred. The first was that Steve White joined me on the staff at Brookhaven. He had moved from the Max Planck Institute for Molecular Genetics in Berlin, where in Wittmann’s department, he had been working on the crystal structures of several ribosomal proteins. Because of our shared interest in ribosomes, he very kindly offered to collaborate with me. Initially, I did not contribute much to the project because I was focused on getting my own projects under way and collaborating with Wally Mangel on the conformation of plasminogen in solution. I began working with Steve by helping to grow large amounts of bacteria in a Yale fermentation facility, but when I saw the low yields that were obtained by purifying proteins from native ribosomes from *Bacillus stearothermophilus,* I felt that there had to be a better way. Indeed there was, and I could not have been in a better place to find it.  The second development was that at about this time, my colleagues Bill Studier and John Dunn had sequenced the genome of the bacteriophage T7, and had begun cloning a number of its genes. Importantly, because T7 RNA polymerase had its own promoter, they and their co-workers realized that they could overexpress target genes in *E. coli*using the T7 promoter and a cloned copy of T7 RNA polymerase under inducible control. They could also use T7 RNA polymerase to transcribe target RNAs. Their work has revolutionized biochemistry, and today there is scarcely a lab in the world that has not at some point used their system to make large quantities of protein in *E. coli*. John and Bill, as well as their associate Alan Rosenberg, and two plant geneticists, Ben and Frances Burr, took me under their wing and taught me all about cloning, making libraries, doing Southern blots, and a then new technique called PCR. The result was that I was one of the few structural biologists who was familiar with these tools at the time. Luckily, I had two wonderful technicians, Sue Ellen Gerchman and Vito Graziano, who were quick to learn these techniques as well, and apply them to our work. They were later joined by the energetic Helen Kycia. These tools allowed me to think about cloning the genes *ab initio*for the various ribosomal proteins that had been crystallized from native sources. This idea worked very well and the result was that material was no longer limiting. Moreover, in our chromatin work, we expressed histone H1 in *E. coli*and used that as a route for deuteration.  When I had been at Brookhaven for a few years, I was asked by the departmental tenure committee what I would do if they gave me tenure. I said I would probably stop doing neutron scattering and go away on sabbatical to learn crystallography because that was how I could answer the really important questions in my field. To my relief, they were quite enthusiastic about the idea and awarded me tenure. My colleague and friend John Dunn brought a large stick covered in aluminum foil to my home and presented the symbolic staff to me, saying, “Welcome to the tenured staff.”  Steve had constantly been encouraging me to get interested in crystallography, saying that someone with my physics and small-angle scattering background would have no trouble learning it. He finally kick-started me into it by setting up, on my behalf, the first crystallization trials of the globular domain of a linker histone, GH5. Shortly afterwards, in the fall of 1988, I took the first Cold Spring Harbor Course in crystallography. In subsequent years, this course was attended by several well-known scientists including Rod Mackinnon and Art Horwich. During the following year, we obtained crystals of GH5 that diffracted well. By then, several of the ribosomal proteins that we had over-expressed had crystallized in previously identified conditions. So there were several crystallographic projects that needed to be carried out. I felt the best way to learn how to solve these structures was to go away on sabbatical and do nothing else but work on them. There was only one place I wanted to go for a sabbatical, the MRC Laboratory of Molecular Biology in Cambridge, England. There were several reasons for this: it was the birthplace of crystallography and many technical developments had occurred there; it had a huge reputation in molecular biology; the director at the time, Aaron Klug, was considered a giant in the field of chromatin structure; finally, Vera and I were both anglophiles and we liked the idea of spending a year in England. I therefore wrote a letter to Aaron Klug, pointing out that I had crystallized GH5 and would like to come for a year to learn enough crystallography to solve its structure. He wrote back an encouraging letter, and supported my application for a Guggenheim Fellowship, which covered half my salary while Brookhaven paid the other half.  At Brookhaven, Bob Sweet taught me a great deal about data collection and crystallography in general. As a result, shortly before I went to Cambridge, Steve White and I collected data on ribosomal protein S5 using a previously identified gold derivative, and with Bob’s encouragement and advice, Vito Graziano and I collected multiwavelength anomalous diffraction (MAD) data on crystals of selenomethionyl GH5. With the data in hand, I set off for Cambridge in late August, 1991, with Vera and our son Raman, who was then 15 years old, and our daughter Tanya, who had just graduated from Oberlin College and wanted to spend a couple of weeks touring England.  Arrival at the MRC Laboratory of Molecular Biology (LMB) was a surprise in many ways. We had rented a large car at the airport in which to carry all our luggage and our bicycles. Driving on the left side of the road after an overnight flight from New York was challenging. When we got to the Addenbrookes Hospital site, I was lost and asked someone where the famous MRC Laboratory of Molecular Biology was, and to my great surprise, the first few people I asked had no idea! This reminded me of the story in [Crick](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1962/index.html)‘s autobiography “What Mad Pursuit” in which his taxi driver had no idea where the Cavendish lab was.  I already knew that the LMB was a crowded laboratory with shakers and refrigerators in the hallways, but coming from Brookhaven, where my department building had originally been a bowling alley in an army base, this lack of poshness did not bother me. When I arrived, my host John Finch, a Fellow of the Royal Society and longstanding colleague of Aaron’s, told me that unfortunately they did not have a bench or desk for me to work at just yet. I rather naively told him that all I needed was a small corner in his lab. John politely smiled at this, and I found out a day later that he, a world-famous scientist, only had a desk and a small part of a lab bench! This was still a place where senior scientists did lab work and shared offices if they had one at all.  On my first full day there, I arrived around 9 am, and about an hour and a half later, John came by and asked me if I would like to go up to the canteen for coffee. I thought I had hardly done anything yet and declined, saying I didn’t drink coffee. Again, John gave me one of his enigmatic smiles and a colleague who watched this exchange said, “He hasn’t learned our ways yet.” As the days passed, I realized that these regular breaks from work to have meals or coffee or tea allowed scientists to talk informally together in the famous canteen on the top floor. It is also true that the human mind can only really concentrate for a couple of hours at a time, and these breaks re-energized people. The canteen was especially wonderful for a sabbatical visitor because I quickly got to know lots of scientists. Two of them, Daniela Rhodes and Kiyoshi Nagai, had labs adjacent to where I worked and were very welcoming and friendly. They have gone on to become lifelong friends and colleagues.  There were two other important lessons I learned at the LMB. I found that almost nobody there was working on routine problems just because they would lead to publishable results. Rather, they were trying to ask the most interesting questions in their field and then developing ways to address them. The other lesson was that even very famous scientists would ask questions at seminars that were often trivial to people in the field. It reinforced in me the feeling that ignorance is not something to be ashamed of, and that no question is too stupid to ask if you want to know the answer.  Although I had come with MAD data on GH5, Aaron thought that the structure of the protein by itself might not be interesting enough and wanted me to try to form and crystallize a complex of GH5 with DNA. The problem was that it was not a sequence-specific protein, and it wasn’t even clear whether a duplex of DNA was an appropriate target. But being in awe of his reputation, I started working on it, sharing a bench with his brilliant postdoc, Wes Sundquist. After about a month, I realized that this was not something that could be done on the time scale of my sabbatical, if ever. With some trepidation, I told Aaron why I thought this was not a useful approach and that I wanted to focus on solving the two structures using the data I had brought with me. Somewhat to my surprise, he readily agreed, and I think it increased his respect for me. When I stopped working on forming GH5-DNA complexes, I stopped doing any bench work for the rest of my sabbatical. My last gel was left unused on my bench, and it was with great amusement that Wes watched it slowly dry out over the next few months.  With the help of many people, including Phil Evans, Andrew Leslie and especially Paul McLaughlin, I learned the basic nuts and bolts of how to solve a structure. At a crucial point early in my stay, Alwyn Jones visited from Uppsala, and showed me how to start building a structure into maps using his program O. The result was that by the end of my sabbatical year, both structures were solved and eventually published in *Nature.*In the second of these, GH5, I had shown that one could treat MAD data as a special case of isomorphous replacement with anomalous scattering. This was the direct result of a suggestion by Eleanor Dodson, who conveyed it to me through Phil Evans. This worked extremely well, and helped to change the way that MAD structures are solved in practice. I was particularly proud when only a few years after having taken the first Cold Spring Harbor crystallography course, I was invited to give a lecture in it because of my contributions to methodology.  **Move to Utah** Upon my return to Brookhaven, apart from finishing our last neutron scattering experiment to locate H1 in the 30 nm chromatin filament, my lab focused almost entirely on the crystallography of ribosomal proteins and factors. However, my experience at the LMB made me unsatisfied with the environment at Brookhaven. Although I had excellent colleagues, the Department of Energy that ran the laboratory increasingly emphasized large projects over individual investigator-initiated research. It became very hard to recruit new staff scientists to the lab, particularly in new areas of biology. The support offered to principal investigators was not sufficient to run even a modest sized group of a few people, and grants, e.g. from the NIH, were not easy to get, partly because of the overhead costs charged by the lab, which were much higher than charged by many universities.  I wrote to Richard Henderson, the head of the Structural Studies Division at the LMB to ask if they had any openings for me. He wrote back a friendly letter saying they all liked me during my sabbatical but had no openings, so I should just stay in touch. Not knowing Richard, I simply took this to be a polite no. Meanwhile, my sabbatical bench mate, Wes Sundquist, was now an assistant professor in Utah and invited me to give a seminar. A few months later, his department asked if I would be interested in applying for a job there. I very much liked both the faculty at Utah and the spectacular location of Salt Lake City, nestled in a valley surrounded by beautiful mountains. There were a lot of people interested in ribosomes and RNA there, including Ray Gesteland, John Atkins, Brenda Bass, and Jim McCloskey. I also particularly liked Wes and the charismatic and ambitious crystallographer Chris Hill, who would be my immediate colleagues. When I was offered the job, I was staggered because they offered me a salary that was $20,000 (or 30%) more than I was making at the time, and felt they must be expecting something of me that I couldn’t possibly deliver. I accepted the job, but a week later, I panicked at the thought of having to be totally reliant on external funding once my start-up had run out, so I actually called up Dana Carroll, the chairman, and said I was sorry but I couldn’t come after all. They were understandably unhappy about this sudden waffling on my part, but fortunately kept the position open and allowed me some time to think about it. So after some agonizing, I decided to put aside my fears about funding and move to Utah.  The Biochemistry Department at the University of Utah was a small but dynamic department with a relatively young and ambitious faculty working on exciting problems. The department lived up to every promise it had made, and within a few months, I had settled in and got my lab running. Wes and Chris were wonderful and supportive colleagues, who occasionally acted as my psychiatrists whenever I would panic about failing. My chairman, Dana, became a close personal friend because we were similar in age and had common interests such as chamber music and hiking.  Bob Dutnall, who had done his Ph.D. at the LMB under Daniela Rhodes, joined me as a postdoc to work on chromatin modifying enzymes. We went on to solve the first structure of a histone acetyltransferase, Hat1, in collaboration with Rolf Sternglanz from Stony Brook. We were helped by a technician, Adrian Hahn. Except for Bob, and another postdoc, Mabel Ng, the lab was now focused on solving ribosomal protein structures. Bil Clemons joined the lab initially to work on ribosomal protein S15. Brian Wimberly had turned down a faculty position to do a second postdoc with me. He first solved a ribosomal protein structure, and then solved the structure of the first protein-RNA complex in the ribosome, that of L11 with a piece of RNA that binds to it. This part of the ribosome is also the target of antibiotics such as thiostrepton. The effort involved in this made me realize how much work it would take to solve all of the binary protein-RNA complexes in the ribosome, and how little we would learn about how the ribosome actually works from that effort. Even before coming to Utah, I had ideas of solving the structure of the ribosome, beginning with its small or 30S subunit. These ideas and their scientific consequences are outlined in my [Nobel lecture](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/2009/ramakrishnan-lecture.html) and will not be discussed here. But how it happened from a human point of view is perhaps interesting.  My first task was to convince someone in the lab that this was a worthwhile project. Brian was cautious. Perhaps he knew too much about the difficulties, and also because it was his second postdoc, felt he couldn’t take such a risk. So he decided to focus on solving the complex of protein S7 with its binding site on RNA. I made a friendly but wildly optimistic bet with him that we’d solve the entire 30S (including S7 of course) before he solved his complex. Another postdoc, Matt Firpo, worked on the problem for about a year, but had to leave when his funding ran out.  The project really took off when the two graduate students came on board. Bil Clemons was a smart and very ambitious student who fortunately was at a stage where he was willing to gamble on something potentially big. His eyes lit up at my suggestion and he immediately said he would take on the project. He worked on two small proteins to learn crystallography first before devoting his full attention to the 30S subunit. John McCutcheon also enthusiastically decided to devote full time to it. I knew I needed Brian Wimberly on board because of his encyclopedic knowledge of RNA structure and the literature on ribosomes, and as soon as we had made tangible progress, he too joined the team. With a capable technician to assist us, Joanna May, we were off and running.  As soon as we started, my insecurities about funding again set in. I could just imagine writing a grant application to NIH saying that we had no good crystals of the 30S subunit but had some ideas about how to get them, and that although a group had been working on good crystals of the 50S subunit for almost a decade, we had some ideas for how to solve our structure if we got good crystals. Having served on study sections myself, I could just imagine the peals of laughter that would go around the table as my application was considered. On the other hand, I knew that the LMB, where I had done my sabbatical, had a longstanding tradition of supporting exactly this kind of difficult but fundamentally important project. Apartment from funding issues, I felt I would have access to world leaders in crystallographic methodology who could help me if I ran into technical problems.  So I wrote again to Richard Henderson, who by that time had also become the director of the LMB, and we agreed that I would visit on my way to a ribosome meeting in Sweden. After my talk on ribosomal proteins, Richard and Tony Crowther (who was joint head of the division with Richard) chatted with me for a couple of hours on the “ribosome problem.” They were interested in my ideas, what the competition was likely to be, what approaches had failed, what resolution one would have to reach to achieve a significant breakthrough in understanding and how long that was likely to take. The conversation was unlike any other job interview. There was no discussion of space, salary or equipment, just about science and ideas. At the time, I had no crystals; nevertheless Richard wrote shortly after my visit saying they were interested in supporting me, and would let me know when they would have the additional space to accommodate me. Aaron, Daniela and Kiyoshi also expressed support for the idea of my move there. A few months later, Richard wrote again to say that indeed the space had materialized. I suddenly had to make what was one of the hardest decisions of my life: whether to gamble everything on going to the LMB and work exclusively on this project, which would involve taking a large salary cut and leaving our families (including our grown children) in the U.S.A., or to continue working in Utah, where I would probably have to hedge my bets by working on safer projects simultaneously. In the end, I decided that the structure of the ribosome was the most important goal in my field, the time was ripe for an attack on it, and it would be a mistake to be distracted from it by other projects because there was only a narrow window of opportunity before other groups entered the field that had so long been dominated by just one person, Ada Yonath.  Most people thought that it would be insane to move to England, staking all on this one risky project. Two people who encouraged me to go were Peter Moore and Steve Harrison. Both recognized from their own careers the ambition to solve a fundamental problem regardless of the challenges. While many in my family were ambivalent, my mother encouraged me to put aside my fears and go to Cambridge and give it a shot. Vera and I finally decided to leave Utah, where we were very happy, take a 40% salary cut and move to the LMB. It was a very difficult moment for me when I had to tell Dana, Wes and Chris of my decision. I had to stay there for another year to work out the logistics of moving. During this time, I came to realize how truly wonderful my Utah colleagues were. They put aside any disappointment at my leaving and were both understanding of my decision and supportive of my efforts during my last year, helping in every possible way in our work. In one last hiccup, I almost didn’t move to the LMB when I found I was going to lose John McCutcheon because he had personal reasons not to move, while during the student recruitment day in Cambridge I found myself unable to attract anyone to this effort. Fortunately, two people courageously agreed to join my lab at the LMB without ever having met me: Andrew Carter, who joined me from Oxford as a Ph.D. student, and Ditlev Brodersen, a postdoc who came highly recommended to me from Århus in Denmark, where I knew his supervisor Morten Kjeldgaard. Their joining me was a stroke of luck and meant we would have a viable team at the LMB.  With the decision to move to the LMB made, I decided to focus entirely on the 30S subunit. Within a few months we had crystals, and a few months later, we had cracked the problem of getting them to diffract well. This was largely due to John and Bil’s willingness to try completely new approaches to purifying the 30S subunit and to their sheer dedication and hard work. We were also helped by Malcolm Capel’s willingness to let us screen lots of our initial crystals at the NSLS at Brookhaven. Shortly before our move to the LMB, we collected data on several derivatives to 5–6 Å resolution.  **Work at the MRC Laboratory of Molecular Biology** I moved to Cambridge in April of 1999, while Brian, Bil and Joanna stayed behind. The result was that I was able to make use of the LMB’s computing resources to try several phasing runs in parallel, and send the maps to Utah where Brian and Bil would look at them. Because of the 7 hour time difference, we may have been the only group that actually speeded up to some extent as a result of a move. I suggested to Brian, who up to that point was focusing entirely on the RNA in the maps, that some of the tubes we were seeing were probably alpha helices of proteins. By the time I left that day, he told me he had identified a protein, S6, in the maps. The next morning, I was amazed when I came to the LMB to find out that he had identified all of the proteins of known structure in the maps! He said it was like eating potato chips: once he had identified one, he couldn’t stop. With his knowledge of the protein-RNA interaction data, and his feeling for RNA folds, he went on to trace the entire central domain of the 30S subunit, and also identify a protein of previously unknown structure, S20. So only a few months after my move to Cambridge, with the rest of my lab still in Utah, we had made a major breakthrough. When I revealed our findings at the triennial ribosome meeting in Denmark in June, I could sense the shock in the audience, especially since virtually none of them knew we were working on the problem. Soon afterwards, our work was published in *Nature*in August, 1999 with much fanfare.  Although Tony, Kiyoshi and Daniela were very welcoming to us, we had trouble settling into Cambridge. Vera and I were shocked by the rapidly increasing housing prices, and for a while despaired of ever finding a house we could actually buy since we kept being outbid on the many offers we made. When I was away on a synchrotron trip at Brookhaven, Vera found a house in Grantchester, a historic village just outside Cambridge that was within bicycling distance of both the city center and the LMB, and made a bid that was actually accepted. So we finally had a permanent home in Cambridge. By this time, Brian and Bil had moved from Utah, and we needed to focus on getting to high resolution.  **Solving the 30S Subunit Structure** Getting to the high-resolution structure of the 30S subunit was beset with problems, which are described in the Nobel lecture. This was a particularly stressful time for me and my lab members. The Yale group of Tom Steitz, Peter Moore and their colleagues was making steady progress with their structure of the 50S subunit. More significantly for us, soon after we had decided to focus on the 30S subunit in Utah, I had found out that Ada Yonath, who had first crystallized the 50S subunit and had been working on determining its structure for over a decade, had now essentially switched to determining the 30S subunit structure using crystals obtained by a slightly different route. So instead of having a quiet niche to myself, we were in a flat-out race. Our progress slowed down because the limitations of the crystals meant that we could not collect data to high resolution at Brookhaven. The one high intensity beam line where we could orient crystals about a mirror plane was at the new SBC 19ID beam line at the Advanced Photon Source (APS) in Argonne. We felt this orientation was necessary to eke out the best anomalous signal from our crystals. But the beam line was not yet open to the public, since it was just being commissioned. Our competitors had already collected data there but it was not clear that we would be able to get time on it. Fortunately, as a result of a request from Peter Moore on our behalf to Paul Sigler, who was on the advisory board for that beam line, we were awarded beam time 2–3 months hence, in late February. It was tragic that only days after he interceded on our behalf, Paul suddenly died of a heart attack.  Given the competition, we wanted to ensure that our data collection at the APS was a success, since it was not clear that we could avoid being scooped if that trip failed. Bil Clemons and Rob Morgan-Warren, a technician who joined us at the LMB, froze over a thousand crystals in the cold room while listening to Johnny Cash on a mini stereo system. We then would take the crystals to Daresbury to screen and group them into crystals that had similar cell dimensions and diffracted well. Not content with this, I sent Bil on a solo trip to Brookhaven where he collected low-resolution data on each of the derivatives to make sure they were bound. He was completely exhausted after having spent 48 hours without sleep.  During our crucial trip to the APS in late February 2000, four of us worked in 12 hour shifts using a large spreadsheet that told us which crystals we had to look at next. Ditlev used his computing skills to streamline our data collection and analysis procedures. We calculated an anomalous difference Fourier map while still at the beam line, and when I saw the large number of strong peaks for our best derivative, much to Rob’s amusement, I started dancing around the office saying, “We’re going to be famous!”  The maps from the improved data were stunning, and we were on our way to building the structure. With five of us working long hours, were able to build a complete atomic model for the subunit within weeks. Even before we had finished, Andrew Carter had crystallized the subunit with three different antibiotics, and seeing them directly in difference Fourier maps was another great highlight.  The structure of the 30S subunit led to a number of follow-up studies on antibiotics and ligand binding. The most important of these, largely carried out by James Ogle, led to understanding how the ribosome ensures the accuracy of translation during decoding of the genetic message. Our studies on decoding continue to this day in the context of the whole ribosome.  **The Whole Ribosome and Its States** It was always clear that we would need high-resolution structures of the entire ribosome in many states to understand the underlying mechanisms of translation. This problem turned out to be much harder than we had anticipated, given the speed with which our 30S work had been accomplished. A stream of dedicated postdocs and students wrestled with the problem for many years. Frank Murphy, assisted by Mike Tarry, worked out procedures for how to make ribosomes that were pure enough to crystallize. Tina Daviter and Ann Kelley introduced methods to purify large quantities of ribosomes. Maria Selmer and Christine Dunham collaborated on a project that led to high-resolution crystals of the whole ribosome with mRNA and tRNA bound, and they were joined by Frank, Sabine Petry and Albert Weixlbaumer to build the structure. This was another frantic effort that had echoes of the 30S race, because we had suddenly heard that Harry Noller, whose lab had solved the whole ribosome at low resolution, now had improved crystals of a ribosome complex and we did not want to be beaten to it after having spent so many years on the problem.  Of the current members of the lab, Martin Schmeing, Caj Neubauer, Rebecca Voorhees, Hong Jin and Yong-Gui Gao work on many different aspects of the translational pathway including elongation, termination and quality control. Two postdocs, Leong Ng and Israel Sanchez have boldly decided to tackle the eukaryotic ribosome, and Alexey Amunts is involved in a joint collaboration with John Walker on the mitochondrial ribosome. Throughout all this, Ann Kelley has become the senior member of the lab. As a longstanding research associate, she is the person who holds the lab together, training new people, making essential reagents, and becoming the general repository of knowledge for the lab. She does this in her usual matter-of-fact way without complaining, and given my other duties in the last few years, the lab would run into great difficulties without her.  **Life in Cambridge** Despite our having enjoyed Cambridge thoroughly during my sabbatical year, Vera and I were surprised to find our permanent move there in 1999 difficult. The pay cut and the increase in cost of living were less of a problem because we simplified our lives and never really noticed a difference in our standard of living. But we had left our families, especially our children, behind and there were just the two of us in England.  That isolation has been compensated for by life in Cambridge. Our simple car-free life style, coupled with the rich cultural life of Cambridge and the proximity of London has made our daily lives in Cambridge a pleasure. We have made many good friends who have enriched our lives. At the lab, Kiyoshi Nagai, Daniela Rhodes, Phil Evans, and Andrew Leslie are among many people with whom I have become friends over the years. Every Easter, Vera and I join Phil and his wife Carol, along with Guy and Eleanor Dodson, and Peter and Judith Murray-Rust, to go on a walking holiday. These trips have allowed me to see some of the beautiful countryside of England. We also take bike rides and walks with Alan Coulson (who was [Fred Sanger](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1958/)‘s long time associate and a coauthor on the dideoxy sequencing paper) and his wife Sue, and Ray and Judy Steward. So over the years, we have come to regard England as home.  Fortunately, our family has also survived the transatlantic separation. Tanya is a physician with a master’s in public health who works mainly with poor immigrants in Portland, Oregon. Raman, after graduating with a physics degree, obtained a master’s degree in music from the Juilliard School and is a cellist with the Daedalus Quartet. My sister Lalita is on the faculty at the University of Washington in Seattle where her work on TB using novel model organisms for both the bacterium and host is allowing her to make important discoveries. My parents lived near her in Seattle, but sadly, my mother, who first encouraged me to go into basic science and later to go to Cambridge, died two years before the Nobel Prize for the ribosome was awarded. My father, who is 84 years old, helped to raise my sister’s children and remains physically active and mentally alert, cleaning two houses, cooking and doing the laundry, in addition to trying to establish educational programs in India. Our geographical isolation from our family has been mitigated by the increasing ease of communications, including the use of programs such as Skype.  **Reconnecting with India** Since I left India at the age of 19, I had been back only three times in about 28 years. One by-product of my travels was that in early 2002, I was asked to give the first G.N. Ramachandran Memorial Lecture in Chennai. On this trip, I also visited the Indian Institute of Science in Bangalore for a day. This was my first visit to India in 13 years, and my first ever interaction with the Indian scientific community. It started a process by which I not only became more familiar with scientific research at a few institutions in India, but also got to know individual scientists well. In the last few years, I have had a G.N. Ramachandran visiting professorship at the Indian Institute of Science in Bangalore, and have used it to escape the dark and dreary late December – early January period in Cambridge and work in Bangalore on papers and reviews, give lectures and talk to colleagues and especially young scientists there. This reconnection with my Indian roots has given me great satisfaction, and I was touched when in 2008 the Indian National Science Academy elected me as a foreign fellow.  **The Politics of Scientific Recognition** People go into science out of curiosity, not to win an award. But scientists are human and have ambitions. Even the best scientists are often insecure and feel the need for recognition. Our ribosome work led to lots of invitations to give seminars and speak at conferences. It resulted in my election to the Royal Society and the U.S. National Academy of Sciences and also led me to receive a prestigious European prize, the 2007 Louis-Jeantet prize for medicine. Thus in both my scientific efforts and the recognition for it, I had succeeded beyond my wildest dreams.  Although few scientists are foolish enough to enter a field to win a Nobel Prize, ever since the 30S subunit had been solved, people would regularly bring up “the Prize” in conversations whenever I went to conferences or give seminars. It was clear to me that the ribosome was at least as important as other structures that had been awarded the Nobel Prize. But there were many more than three people who had contributed to the ribosome, even if one only counted principal investigators, which itself is a fictional view of the way modern science is done.  While we were solving the structure of the 30S subunit, I had mostly refused to be distracted by going to meetings to speak about our work. So it was something of a shock when only a couple of months after the atomic structures of the subunits came out, a prize in the U.S.A. was awarded to just one aspect of the ribosome, peptidyl transferase. It seemed to me that instead of waiting for the impact of the ribosome work to become clear and then thinking hard about what had really made a difference to the field, the committee had hurriedly decided on which three people they wanted to honor and then written a citation around them that would exclude the others. Richard Henderson, my director, suggested that I should accept more invitations to meetings and talks to get our story known if only to get proper recognition for our work, regardless of prizes.  Deep down, I felt that the scientific event that transformed the field more than anything else was the determination of the atomic structures of the ribosomal subunits and the functional studies that followed as a result, to which we had made a major contribution. However, international prizes for work on ribosomes always seemed to go to other people. So over the years, I had gradually come to accept that I would probably not get a major international prize for the ribosome, least of all the Nobel Prize. Once I had accepted that, I felt liberated and happier, but I have to confess that I felt some trepidation each October. Every time I learned the Nobel Prize was for something other than the ribosome, I would be relieved because it was a postponement of what I felt would be the inevitable disappointment. As the years went by, it seemed to me and many other scientists that there would never be a Nobel Prize for the ribosome because the problem of choosing three people out of all the contributors appeared insurmountable.  **The Nobel Prize and Its Immediate Aftermath** On October 5, 2009, the Nobel Prize for Physiology and Medicine went for work on telomerase. Since the Chemistry prize had been awarded for biological work the previous year, I was confident that it would not be awarded for the ribosome that year. On the morning of October 7, I was halfway to work when my bicycle developed a flat tire. As a result, I came in quite late and somewhat irritated, and had completely forgotten that it was the day the Chemistry Prize was going to be announced. So when the phone rang soon afterwards and a voice said it was an important call from the Royal Swedish Academy of Sciences, I immediately suspected it was a prank orchestrated by one of my friends like Rick Wobbe or Chris Hill, who like practical jokes. When Gunnar Öquist came on the line and started talking to me, at first I simply refused to believe him and even complimented him on his Swedish accent. Finally, after he was done, I asked if I could speak to one of the committee members, Måns Ehrenberg, whom I knew personally. When I heard his voice, it was with a shock that I realized it was true, a feeling that was reinforced when Anders Liljas and Gunnar von Heijne also came on the line to congratulate me. Two members of my lab, Martin Schmeing and Rebecca Voorhees, had desks just outside the open door to my office and had overheard my end of the entire conversation. They did not share my skepticism and could hardly contain themselves. By the time I got off the phone, they were jumping up and down, and Martin popped open a bottle of champagne he had been saving to celebrate the publication of a paper that had just been accepted in *Science.*In the intervening minutes between the phone call and the public announcement, I was unable to get hold of Vera, because she was taking a walk with Tanya and does not use a mobile phone. It was 2 am in Seattle and 5 am in New York, so I did not want to wake up my father, sister or Raman. Unfortunately, the press was not so considerate.  It was not until I saw the public announcement on the Nobel web site that it fully sank in. Within a few minutes, the phone rang and did not stop ringing for two days. My colleagues at the LMB, many of whom had supported me when I had nothing but an idea, were delighted. They organized the customary drinks celebration in the canteen, for which Mike Fuller bought and served the champagne as he had for all the previous Nobel Prizes awarded to scientists here. After the celebration, Vera and I walked my bicycle home in the rain. It was touching to get congratulatory messages from old friends and scientific colleagues around the world. I was especially moved by messages from colleagues in the ribosome community including my mentor Peter Moore and Joachim Frank, both great scientists who had made major contributions to the field and were justifiably contenders for the prize themselves. Peter was particularly (and typically) gracious, and seemed proud that his protégé had done so well. Much was made of my prize in India, and I found myself the subject of an entire nation’s celebration. I was taken aback by the flood of emails from complete strangers in India, and when they continued unabated for several days, I overreacted to what I felt was an intrusion on my ability to carry out my work. This angered many people there and a clarification I made only partly mollified them.  The Nobel week in Stockholm in December was surreal and memorable. After Sweden, I went on my usual annual visit to India, but this time with some trepidation because I did not know what the reaction to me would be given the email controversy. I need not have worried, because I was overwhelmed by the warmth and affection from both members of the public and my scientific colleagues there. I was honored that the Government of India decided to bestow upon me their second highest civilian award, the Padma Vibhushan. I have come to realize that I have inadvertently become a source of inspiration and hope for people in India simply by the fact that I grew up there and went to my local university, but could nevertheless go on to do well internationally. On my return to Cambridge in early January, things slowly began returning to normal after the euphoria of the autumn. I began to realize that the Nobel Prize could be seen not just as an affirmation of my past work but also as an encouragement to continue to work on interesting problems. Certainly, it seems to have fired up people in my laboratory, and I look forward to the struggles ahead as we try to answer some of the hard questions in our field and beyond. Looking back on my life so far, I feel a deep sense of gratitude for having been able to lead such a rich life, both intellectually and personally. |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** | [VR]  [Venkatraman Ramakrishnan] Hello?  [Adam Smith] Hello. Professor Ramakrishnan?  [VR] Yes.  [AS] Hello, my name’s Adam Smith. I’m calling from the official web site of the Nobel Foundation in Stockholm.  [VR] Yes.  [AS] We have a tradition of recording very short interviews with new Laureates. May I offer you my congratulations and speak to you for a few minutes?  [VR] Yes. Thank you.  [AS] You started out as a physicist, and I just wanted to ask what attracted you to biology in the first place?  [VR] Well, I’ll be honest with you. I was a theoretical physicist but my Ph.D. work was on a problem that was not particularly interesting to me at the time. And I used to subscribe to *Scientific American* and I found that there were all these wonderful discoveries happening in biology and I also knew that a number of physicists had gone into biology and been successful. So, I decided to switch.  [AS] Well so many, like Francis Crick, and so many others who moved into molecular biology for instance …  [VR] Yes, exactly. In fact many from my own lab, you know, where I work.  [AS] That’s right. And you do work at the LMB in Cambridge, this marvelous place where so many great ideas have come from. What is it that makes it so special?  [VR] I think it’s the ability to tackle difficult problems in a sort of stable and supportive environment. I think that’s the real key to it.  [AS] So one is challenged, always, to address the most difficult problem one can think of?  [VR] That’s right. And I think, you know, the history of the place means that you don’t waste your time doing sort of mundane or routine things.  [AS] And in particular, the problem of the ribosome, this extraordinarily complicated structure. It perhaps seems like a mountain that’s too high to climb, but that itself attracted you?  [VR] No, because I started working on ribosomes when I was a post doc, in 1978, when it would have been impossible, really, to solve it. But, it was just a fundamental problem in biology. And we felt, no matter, anything we do to chip away at the problem would be useful. So it was more that that attracted me. And I think the fact that it was large and kind of difficult to come to grips with, yes, it was attractive. Really what was attractive was that it was a fundamental problem.  [AS] And Francis Crick had made this proposal in the 60s, that it might perhaps be the link between the pre-DNA world and life now as we know it.  [VR] Yes. And the structures have definitely shown, or confirmed, earlier biochemical work, mainly by people like Harry Noller, that the key elements of the ribosome that are involved in function are made of RNA. And so a primordial ribosome could very well have consisted entirely of RNA. And, so, yes it does … But Crick was amazingly, I think, prescient to have thought about it.  [AS] There’s a marvelous video on your web site showing the ribosome in action, which indicates that really we understand its workings pretty well.  [VR] Well, only if you don’t think of it as chemistry. Because we understand in a sort of fuzzy way that something has to come in, and something has to move, and so on. But, if you really want to understand the detailed molecular interactions that make it go in a particular direction, make certain contacts, break other contacts, hydrolyze GTP, you know, form bonds, etcetera, and do it all amazingly accurately, then you do need a high resolution picture of those states. But, that’s not going to be enough. It’s going to take a lot of work by biochemists, by computational people who do molecular dynamics and things like that to really, eventually, understand it in the sense that we would understand, say, a more typical reaction.  [AS] And, the three of you who’ve been rewarded with the Nobel Prize today, have all worked on bacterial ribosomes. Is it the case that bacterial ribosomes are a good model for our ribosomes?  [VR] They are good for certain things, but they’re not good for initiation where it’s very, very difficult so … But there are people working on trying to get eukaryotic ribosomes crystallized and trying to study it, but I think that will be a difficult problem for quite a while.  [AS] And just as a last topic, one thing that the committee have emphasized is all three of your work on antibiotics and ribosomes and the structural work on antibiotics interacting with ribosomes. Do you have high hopes that this structural biology will lead to new antibiotics to treat resistant strains of bacteria.  [VR] Yes. So the fact is that … You know, having a high resolution structure in hand, one of the first things that those of us who were working on it did was to try and determine the structure with antibiotics, with known antibiotics that bind to the ribosome. And those gave us a very good idea of how they interacted with the ribosome. And it also gave us an idea of why certain mutations would cause resistance and how you might design better antibiotics. And, indeed, one of my co-winners, Tom Steitz, founded a company in New Haven and that company is devoted to making new antibiotics based on the structure of the ribosome and they have, actually, new potential drugs in clinical trials. So that’s one of the more satisfying things to come out of it.  [AS] OK, well thank you very much. I can hear behind you what sounds like a celebrating lab. What do you think is about to happen?  [VR] It looks like, from the way the phone’s ringing, that today’s going to be written-off. But I haven’t even told my wife yet. I couldn’t reach her. She’s probably gone for a walk, and she doesn’t use a mobile phone, so it will be interesting. And my father lives in Seattle and I don’t want to wake him up because it’s three in the morning, so …  [AS] So, you’ll be held on the phone for a while more before you can speak to the family. Well, good luck good luck with the rest of today and we look forward to meeting you when you come to Stockholm in December.  [VR] Thank you, bye, bye.  [AS] Bye, bye. |
| **Interview** |  |

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| **Biographical** | I was born in Milwaukee, Wisconsin in 1940, and my family lived in an apartment above a paint store in the downtown area until 1949. Although my father had obtained a law degree from Marquette University in Milwaukee, he became the administrator in charge of personnel at the Milwaukee County Hospital. My mother grew up on a farm in Waukesha county outside of Milwaukee and graduated from Carol College, a small college in Waukesha. My mother devoted her time to all of the domestic chores required for raising a family which eventually grew to five children – two younger brothers and two younger sisters. My father’s parents lived about 20 blocks away and my mother’s parents and her brother’s family lived on the family farm in Waukesha county.  I attended elementary school at the Elm Street School, an old brick building with an asphalt playground located a few blocks from our apartment. I did not like the school much and often got beaten up by a bunch of slightly older guys on my way home from school. My report card, which I brought home for my parents’ signatures at the end of second grade, showed grades that were just above failure. My parents were upset and asked what I was going to do to change, and I said that I did not really care about the grades. My mother (I think) then applied the “board of education” to the “seat of knowledge” – my first and last spanking. This was definitely the low point of my academic career.  In the middle of my third grade school year we moved from 27th Street to a new house on 75th Street in the Milwaukee suburb of Wauwatosa and my life was transformed, academically and in all other ways. My teachers, schools and classmates were all marvelous in grade school, junior high and high school. The Roosevelt grade school playground had tennis courts and a grass playing field, on which a large skating rink was made every winter with a warming hut and outside lights added. Almost every evening in the winter I would go skating for hours with friends playing team skating games.  Visits to my grandfather’s farm during the 1940s and 50s played an important role in my life in that period. His farm was what is referred to as a “truck farm” where he grew vegetables, mostly radishes, carrots and onions. In the WWII years, however, he had a cow for milk, cream and cheese and a picture from about 1941 shows me with my grandfather and his cow (Fig. 1). My family made frequent visits to the farm, which was only about a 30 minutes drive from Wauwatosa. A picture of my parents and their five children standing in front of my grandfather’s green Hudson car, taken in about 1952, shows a harvested wheat field and one of my grandmother’s gardens (Fig. 2).  During my early teenage years I spent most of my summer school vacation working in the fields on my grandfather’s and uncle’s farm. I worked with many other kids, bunching radishes and weeding 20 acres of onions. Work would start just after sunrise at about 5:00 a.m. and continue to late afternoon every day, except Saturday. (The market was closed on Sunday.) I received 5 cents per dozen bunches of radishes and often tied as many as 100 dozen. I used the money to buy myself a new saxophone, a bicycle and a tennis racquet and save money for college.  The junior and senior high schools were about a 20 minute walk away and introduced me to an additional set of classmates and importantly to music, art and shop besides the academic courses. The shop courses in junior high included electricity and magnetism, where I made an electric motor from scratch, winding the wire coils and making all of the connections. In the woodworking shop I made a coffee table for the family. In the plastics shop I made letter openers and light stands. I do not remember what I did in metal working. I have found that the basic skills in working with tools and materials that I learned in the shop courses have proven invaluable for me in subsequent years, at home and in the laboratory, including constructing models of proteins. I think it is unfortunate that such courses have been eliminated in many schools today as being unnecessary or too expensive.  I developed a serious interest in music in junior high school, where I joined the band and the choir. On the first day of band practice I brought my father’s C melody saxophone to the band leader, who told me it would not work in the band but lent me the school’s E flat alto-saxophone. I became a very serious saxophone player and in high school played solos, duets, quartets as well as organizing a big band style dance band in addition to playing in the school band. I practiced one to two hours a day at home and won a number of “gold” medals at state contests when I was in high school. I seriously considered becoming a musician, but then concluded I could do music as a hobby if I went into science, but could not do science as a hobby if I went into music.  My grades in Longfellow Junior High School were mostly B’s during my first two years – good but not great. Then, my younger brother Dick entered junior high during the middle of my second year, and he got straight A’s. This was a wake up call for me and the competition was on. I believe I got mostly A’s the next year. I did much better in high school, graduating 8th in a class of over 300. Competition can be motivating in the classroom as well as on the tennis court.  Fortunately, the students in all of my courses in high school were separated according to their academic ability in a particular field. Thus, the very best 25–30 students of the 300 total were in my math, science and English classes. This, of course, meant that the teacher could instruct us at a much higher level than if the students in the classroom were a random selection from the whole class, and we learned from and were challenged by our fellow students. I particularly remember how extraordinarily good the girls were in my math classes – only two or three of the top ten were boys. I have never had any doubt that women are as good at or better than men in math, contrary to the impressions of a former president of Harvard. I think it is very unfortunate that many, if not most, high schools (like the one in my home town of Branford, CT) no longer separate students by ability; this does not motivate or properly educate the very best students.  **Lawrence College** My choice of what college to attend was heavily influenced by my best high school friend, Alex Wilde, and most importantly, by his mother. My father wanted me to attend Marquette University or the University of Wisconsin, Milwaukee, neither of which appealed to me. I had gotten to know the Wilde family very well, particularly Alex’s mother whose father was the then Senator Wiley from Wisconsin. She suggested that I apply to Lawrence College where Alex was intending to go, and since I could not afford the tuition, that I should apply for a scholarship, which I did. I received a full tuition scholarship for four years and upon visiting Lawrence College I knew where I wanted to go to college – an important choice.  My four years at Lawrence College changed my life, my view of the world and my professional direction. Since Lawrence is a liberal arts school, I was required to take many humanities courses to supplement what turned out to be my major in chemistry. These courses began with what was called a Freshman Studies course which was a broad based reading, discussion and writing course on many classical books. We learned to ask as well as answer questions. Importantly, we were also required to take a philosophy course, a scholarly based (e.g., Niebuhr, etc.) religion course, and an anthropology course, as well as English, History and language courses. I entered Lawrence with a heavy religious background and left it with an entirely different understanding of the origins of religious beliefs, their veracity and their roles in cultures. Lawrence also has a music school so that I was able to continue my love of music by participating in the band, orchestra and choir.  While I had many wonderful, inspiring teachers at Lawrence, the person who had by far the greatest influence in inspiring me to pursue a career in science, and in particular chemistry, was Professor Robert Rosenberg, or Bob as I can now call him (Fig. 3a). I still recall the early lectures in his introductory chemistry course where he introduced to us the concepts of atomic orbitals and bonding and how studying chemistry at the physical chemical atomic level allowed us to understand the properties of chemicals, such as their color. It was a wonderful revelation to me about how the world around me could be understood.  I had several opportunities to work on research projects in laboratories outside Lawrence. The first opportunity, which was arranged by Bob Rosenberg, was to spend the summer between my junior and senior years doing research in the biochemistry laboratory of Lorazo Lorand at Northwestern University. My project was a kinetic study (determine kcat and Km) of the hydrolysis of a variety of para-nitrophenyl ester substrate analogues by chymotrypsin, trypsin and thrombin. After making the measurements, I started the calculations, which seemed tedious. I then decided to write a computer program (my first) to process the data on the university IBM 650. The process went so quickly that I finished my summer project two weeks early and asked what I should do next. I was told to do some organic synthesis of a new substrate compound, which I began. While working in the hood with some organic solvents, in the presence of a lit Bunsen burner, the solvents, not surprisingly in retrospect, exploded (fortunately without any injury), and that ended the organic chemistry phase of my research career.  The end of summer before my senior year in 1961, I was invited to participate in a two week conference at MIT for selected science students from small colleges. This unique meeting was organized and paid for by the American Biophysical Society in order to encourage students to consider the field of biophysics (of which I had never heard). Four students each from about two dozen top small colleges were invited to participate, all expenses paid. It was my first trip on an airplane and my first trip outside of Wisconsin, except for Chicago. The venue consisted of lectures on a broad range of biophysical topics by faculty, mostly, but not exclusively, from Harvard and MIT. I remember one of the organizers, J. Oncley, sitting in the audience with the most wrinkled plaid sport coat I had ever seen. Most memorable, not only for its exciting content, was a lecture by Alex Rich. His lecture was truly inspiring and in an area of research I pursued years later. He was dressed in a fine dark suit (not today’s lecture garb) with a white shirt and tie. Another important lecture for me was given by Paul Doty from Harvard on biophysical studies of nucleic acids, which was one of the reasons for my later wanting to attend Harvard. Students at the conference also had a great opportunity to interact with each other and go out to dinner together in various parts of Boston and Cambridge. I particularly remember dining with three Reed College students, who included Don Engelman and Mark Ptashne, as well as a few others who subsequently became fellow graduate students at Harvard. This two-week meeting was possibly inspired in part by the Kennedy call to respond to Sputnik. It was a truly important event for influencing the career choices of many of us, but unfortunately was not repeated.  In the fall of my senior year I participated in a research program for selected students sponsored by the Midwestern small colleges at Argonne National Laboratory. I lived on the lab grounds and worked on a chemistry project that I neither liked nor remember. All I remember of the dull semester was my first opportunity to see the Moscow Bolshoi Ballet and marvel at the ability of the male dancers to leap across the stage. During the summer between Lawrence and starting studies at Harvard I worked for Dupont on another forgettable project, measuring the dynamic stretching modulus of various synthetic cloth materials being considered for use in making bras. Unfortunately, I was not invited to join the group that evaluated the final product being modeled.  **Harvard University** I went to Harvard as a graduate student to work on biophysical studies of nucleic acids, but fortunately, chose a different pathway. In the spring of my first year in 1963, I attended three Dunham lectures given by [Max Perutz](https://www.nobelprize.org/prizes/chemistry/1962/perutz/facts/) (Fig. 3E) in which he presented the first atomic resolution protein crystal structure, that of myoglobin. He showed stereo slides, and I was stunned to see the atomic structure of myoglobin pop out in three dimensions over Max’s head; this was clearly the way to understand how macromolecules carry out their biological functions. Shortly thereafter, while playing tennis with a Lipscomb graduate student (Peter Boer), I mentioned how unfortunate it was that no one was doing protein crystallography at Harvard. He said on the contrary, the “Colonel”, as [Bill Lipscomb](https://www.nobelprize.org/prizes/chemistry/1976/lipscomb/facts/) (Fig. 3B) was referred to by his students and postdocs since he was from Kentucky, had a group who were working on the crystal structure of bovine carboxypeptidase A (CPA). Shortly thereafter I made my way to the Colonel’s office, a little nervous because I had already been turned down (fortunately) by another faculty member, in order to make an appointment to see him. He was standing in the office of his secretary, who was not there, and when I asked if I could make an appointment to see him, he invited me right in. After he described the CPA project, I excitedly asked if I could join the project, and he said yes. So, I had just received the wonderful opportunity to join the Colonel’s army, and the rest is history.  The CPA team consisted of five postdocs at that time, of whom Martha Ludwig was the most important for my training. I worked with her on structural studies of substrate and inhibitor complexes of CPA as well as with the whole group on the determination of the crystal structure of the apo protein. I remember being excited at one time when we succeeded in collecting 5,000 reflections in one week using the Hilger-Watts linear diffractometer. Now, of course, we can collect 5,000,000 reflections from ribosome crystals of the ribosome in an hour (about a factor of 105 faster for an assembly that is about 80 times larger). All computer programs were written in Fortran for an IBM 7094 computer that had 32 K of memory, had no discs and used computer cards. The advantage of the latter was that we could save the used cards and sell them as used paper in order to support lab parties every few months. (I always thought we should have written a program called GENCARD to increase the party frequency.)  Because of the superb team that the Colonel assembled and his encouraging management style, the project moved on well. In 1966 we published a 6 Å resolution map, including a model of the polypeptide backbone that I had over-optimistically built, but showing many of its structural features. Martha and I, with postdoc Flo Quiocho, published a low resolution map of an inhibitor complex that showed the first example of a substrate induced conformational change. In 1967 we obtained what I realize in retrospect was a superb 2.0 Å resolution electron density map of the apo-CPA that allowed us to correctly position every residue of the polypeptide backbone, even in the absence of an amino acid sequence. CPA tied in 1967 with three other proteins, RNase A, RNase S and chymotrypsin, for being the third highresolution protein structure determined after myoglobin and lysozyme.  Unlike PIs today, the Colonel was almost never absent from the lab to attend meetings and present seminars. He did, however, take a sabbatical in England, and while he was gone, I came up with the idea of using direct methods to phase the Fderivative-Fnative difference coefficients in order to calculate a projection difference Fourier map, which clearly showed the heavy atom positions. When I showed him the paper I had written on the work upon his return, he allowed me to publish the paper in *Acta Cryst*. without his being a co-author, also not a common practice among PIs today.  The Colonel provided me with what turned out to be a great opportunity that had an important impact on my future faculty job opportunities when he arranged for me to give a talk at the Protein Gordon Conference, which was chaired by Fred Richards in the summer of 1966. I talked about the CPA structure and the conformational change produced by substrate or inhibitor binding, the concept of induced fit. Dan Koshland was a participant and greatly appreciated this new experimental evidence for his hypothesis of substrate-induced conformational changes. I assume that my talk and opportunity to meet him partly motivated his advocating that the Berkeley Biochemistry Department interview me and offer me a faculty position, which they did, and I accepted in the late spring of 1967. Due to the reluctance of the Department to consider hiring a woman for a faculty position (Joan) in 1970, I resigned my Berkeley position after two months on the faculty and accepted a position at Yale offered by Fred Richards.  **The Laboratory of Molecular Biology, Cambridge** After Harvard and before going to Berkeley I spent 3 years at the MRC laboratory of Molecular Biology in Cambridge from 1967 to 1970 in the group of David Blow. He was recommended to me by Hilary Muirhead, who was a postdoc with the Colonel and a former student with Max Perutz. In David’s lab I worked with Richard Henderson on determining the structure of chymotrypsin complexes with substrates.  The Cambridge Laboratory of Molecular Biology was a completely unique and outstanding laboratory. It inspired and trained a very large group of postdocs from the U.S. in molecular and structural biology who then returned and transformed these fields in the U.S. Perhaps the most remarkable and unique feature of the laboratory was the canteen located on the top floor which provided coffee in the morning, lunch after mid-day and tea in the afternoon. The attraction was definitely not the “bangers” or, the “toad in the hole” or other culinary opportunities, but sitting down with a random collection of lab directors, postdocs and graduate students and talking about science. The canteen was set up by Max and run by his wife, Gisela. When I first arrived, it was so small that whenever I got through the food line, there were only a few empty seats. Consequently, I would have to sit at a table that might include Max, [Francis Crick](https://www.nobelprize.org/prizes/medicine/1962/crick/facts/) and [Sydney Brenner](https://www.nobelprize.org/prizes/medicine/2002/brenner/facts/) (Fig. 3E) at it as well as postdocs and students. Within about two months I had met nearly everyone in the whole laboratory. The conversations were always about science and about experiments, never about the movie someone saw the previous night. Everyone contributed suggestions and/or criticisms. Initially I wondered how anyone got any experiments done since they were spending so much time in the canteen, and then I realized that the many discussions reduced the number of unwise or unnecessary experiments that were done and enhanced the good ones.  There were no weekly group meetings, but there was an annual one-week meeting for essentially everyone in the LMB which was generally known as “Crick week”. Francis would sit in the front row and frequently ask many questions. On one occasion I remember [Fred Sanger](https://www.nobelprize.org/prizes/chemistry/1958/sanger/facts/) presenting a talk on his recent research and in the middle Francis jumped up and said “Fred, if you did (this) and (this) and (this), then you would be able to find out (that) and (that)”. Fred, without taking his hand off the chalkboard turned toward Francis and said, “That’s it, Francis, that’s it; you’ve got it”, and then carried on. Since Crick week included a broad range of molecular and structural biology topics, it was very useful that directors in the front row would ask questions that many of us were reluctant to ask. During one lecture that involved a comparison of a process that occurs both in eucaryotes and procaryotes, Max asked, “What is a eucaryote and what is a procaryote?”, terms that were just beginning to be used. I was glad that Max asked the questions, since I had no idea what the terms meant. Sydney Brenner would have coffee available in his lab dishwashing kitchen on Saturday morning about 10:30 or so and would always be there with the postdocs and students from the molecular biology floor directed by himself and Francis, plus others of us who wanted to drop by. Sydney would invariably hold forth on some interesting topic with lots of funny stories and “one-liners”.  I learned about all of the major research problems being pursued at the LMB from Crick week, the canteen, Saturday coffee and the random conversations in the hall, as well as the quick evening trip to the pub for “last call”, which the American postdocs did. (The Brits were mostly not there at night.) It was at this time that I developed my interests in trying to understand the structural bases of the mechanisms by which the many proteins and nucleic acids that are involved in “Crick’s Central Dogma” carry out their functions: how DNA is copied into DNA, DNA transcribed into RNA and finally the RNA translated to protein.  Access to computing facilities was extremely limited at Cambridge. The LMB used the computer owned by the Cambridge University astronomy department, and we were allowed to make only two submissions a day for the five working days, and the morning run could not take more than two minutes. I would check and recheck the computer cards I was submitting to eliminate as many mistakes as possible, because otherwise one of 10 opportunities would be lost to me for the week. In retrospect, it is amazing that we were able to accomplish anything. Certainly, the timescale was longer.  At some point in my second year Brian Hartley (Fig. 3C), who was collaborating with David Blow on chymotrypsin studies, came up to me and asked what research project I planned to pursue when I left the LMB and went to Berkeley. I said I wanted to solve the structure of an aminoacyl-tRNA synthetase, ultimately complexed with substrates including tRNA. This is the step where a specific amino acid is attached to the tRNA containing the correct anticodon. Brian patted me on the back and said “There, there, my boy. That is an interesting problem, but you must work on something you can actually do successfully. I suggest that you study the structure of hexokinase”. I thanked him for the advice and ran down to the library to find out what hexokinase was. I subsequently learned by reading papers from Dan Koshland (Fig. 3D) that the hexokinase reaction was his primary example of why some enzymes must undergo a substrate-induced fit conformational change. He reasoned that if the enzyme was rigid with all of its catalytic groups properly oriented to catalyze the nucleophilic attack of the six-hydroxyl group of glucose on the alpha phosphate of ATP, then why would water not hydrolyze ATP in the absence of glucose? The six-hydroxyl group is after all a water molecule with some carbons attached. He hypothesized that the binding of glucose must cause a conformational change in the enzyme that is necessary for catalysis. I consequently started growing crystals of hexokinase at Cambridge and spent the next 10 years studying this enzyme. Mentorship is always essential, and not only from your direct supervisor.  I submitted my first grant application to the NIH in 1969, I believe, in which I proposed to determine the structures of yeast hexokinase, of which I had managed to produce crystallographically suitable crystals. I had to go to Berkeley for a site visit by an NIH panel and was asked by a panel member how I was going to collect the x-ray data. I said by using a diffractometer, whereupon I was told that data collection with a diffractometer would not work because the unit cell dimensions of my hexokinase crystals were too big (one dimension was 200 Å). This, of course, was a ridiculous comment, since one just moves the detector further away from the crystal, but the reviewer was firm and ultimately my first application was turned down. (A few decades later this reviewer asked me in an elevator while being escorted to my next faculty visit how we had solved the structure of hexokinase, and I said “by using a diffractometer to collect data”.)  Sometime at the end of 1969 or early 1970, Fred Richards (Fig. 4D) was visiting the LMB, and I had an opportunity to talk to him. Since I had become worried about my funding at Berkeley, I asked him whether a faculty position for me was possible at Yale, and he said he would look into it and get back to me. Years later I learned from Sydney Brenner, while dining with him at King’s College, that Fred had run up to his office after talking to me and asked him if he could encourage another American postdoc in Sydney’s lab to either accept or reject the offer that he had received from Yale. Sydney immediately called the postdoc into his office, closed the door, put a piece of paper on the table and told the postdoc that he would not be allowed to leave the room until he had written and signed a letter to Fred either accepting or rejecting Yale’s offer. Sydney then took the letter rejecting Yale’s offer to Fred, who left Cambridge with two faculty slots in his pocket. Fred had wanted to have two positions available, since there were faculty in the department who wanted to hire Joan, and perhaps Fred thought Yale might have an advantage over Berkeley if they offered both of us jobs. Indeed, that turned out to be true.  **Yale** I arrived at Yale in the late fall of 1970 and began our structural studies of yeast hexokinase captured with and without the substrate glucose bound, a project that occupied the efforts of most of my lab during the 1970s. I was extremely fortunate to have Robert Fletterick join my lab to work on hexokinase as my first postdoc during my first year at Yale. Bob had come to Yale to do a postdoc with Hal Wyckoff and had a fellowship. He decided he wanted to switch labs, and Hal was very accommodating. Our structures of hexokinase with and without glucose bound showed the largest conformational change in a single subunit that had been observed at that time and clearly established that Koshland’s induced fit hypothesis was correct for explaining the specificity of hexokinase. The pictures of our hexokinase structures with and without glucose bound have been published in far more textbooks than any other work from my lab. Brian Hartley had certainly made a good suggestion for what research direction I should pursue, and I can only wonder what I would have accomplished in the 1970s had I not had the hallway hexokinase discussion with Hartley.  A very important factor in making the quality of structural biology so excellent at Yale beginning in the 1970s was the shared computation and x-ray facility, the “core” laboratory, and the many interactions it facilitated. When I arrived in 1970, Fred Richards and Hal Wyckoff, who solved the structure of RNase S in 1967, had a shared x-ray and computation lab that I joined and added some equipment. In 1975 I suggested to Fred that we should consider applying for an NIH program project grant, which I had just learned about, to support our structural biology efforts, and Fred took the lead in organizing five of us, the WERMS group (Wyckoff, Engelman, Richards, Moore and Steitz), to apply which we did successfully in 1976. The “WERMS” grant, as we referred to it, is now in year 34, but I am the only WERM left on it. In the late 1980s, funding from HHMI provided additional support for the core x-ray and computational lab, including two technical staff positions and additional equipment. They also provided an investigator position for me as well as additional faculty/investigator positions for the MB&B department, and in the mid-1990s the WERMS group also included Paul Sigler, Axel Brünger and [Jennifer Doudna](https://www.nobelprize.org/prizes/chemistry/2020/doudna/facts/) (Fig. 4).  This group of seven laboratories constituted the Yale Center for Structural Biology (CSB) and Fred Richards was appointed by the Yale president to be the first director of the CSB. The shared core computation and diffraction laboratory was always abuzz with the activity of students, postdocs and technical staff who interacted and helped each other solve problems. In the mid-1990s there were six technical staff in the core lab to help users with problems they encountered, and about 100 postdocs, students and technical staff in the CSB laboratories. All of the seven faculty members of the CSB in 1995 (when our work on the ribosome began) are or were in the U.S. National Academy of Sciences. In the mid-90s, these seven labs and their extensive and collegial interactions provided perhaps the best environment in the world for doing structural biology in general and determining the structure of the ribosome in particular.  **Son Jon** Our son Jon was born in 1980 and met his first Nobel Prize winner, Fred Sanger, at the age of 4 weeks during an MRC LMB celebration on the day of Fred’s being awarded his second Nobel Prize in chemistry. We happened to be in Cambridge on that day, after attending meetings in Switzerland, Germany and London. Jon got to go to many meetings around the world for the next fifteen years until baseball took over his world.  I started playing tennis and baseball with Jon when he was in grade school and installed a basketball hoop on the garage for him. Every weekend in the summer we would go to a baseball field in our home village of Stony Creek to practice his throwing, catching and batting skills. That lasted until he started hitting the ball out of the park into the salt marsh grass. In high school he was quarterback on the football team, guard on the basketball team and pitcher on the baseball team for four years. At the end of his senior year he was drafted in the 44th round of the baseball draft, but wisely chose to go to Yale. At Yale he majored in molecular biophysics and biochemistry, and baseball, as did two of his classmates and teammates, Craig Breslow and Matt McCarthy. At the end of his junior year, Jon was drafted by the Milwaukee Brewers (ironically) in the third round and received a signing bonus that was slightly larger than my share of the 2009 Nobel Prize. After a shoulder injury caused him to leave baseball, he went to Yale Law School and is now working in consulting with McKinsey Corporation. Breslow, who worked in Joan’s lab as an undergraduate and intended to go to medical school, had also been drafted by the Brewers and is now pitching for the Oakland Athletics team.  Jon learned to ski by coming on what we now refer to as “Riboski” trips. Starting in the late 80s, a group of RNA-centric friends and their kids started going on annual ski trips together: Tom and Carol [Cech](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1989/) (+2); Jim and Elsbet Dahlberg (+2); John Abelson (+1) and Olke and Lori Uhlenbeck. Since we sent the kids to take ski lessons while the adults skied together, Jon quickly improved, and by the age of 12 he could ski circles around me. Perhaps my most memorable ski trips were my two 4-day trips with Jon to Snowbird in Utah over Thanksgiving break during his junior and senior years in high school (Fig. 5). He would ski the double black diamond runs while I would ski the double blue or black diamond trails and we would meet at the bottom of the ski lift.  **The Structural Basis of Crick’s Central Dogma of** **Molecular Biology** Our decades’ long quest to obtain a structural understanding of the mechanisms by which the macromolecules that carry out the process of DNA makes DNA makes RNA makes protein – Crick’s central dogma – began with our establishing the structure of the catabolite gene activator protein (CAP) with only cAMP bound in 1981. This was the first structure of a DNA binding protein, a transcription activator. Our subsequent structure of CAP bound to DNA in 1991 showed a remarkable bending of the DNA backbone, and our recent structure of the unliganded CAP exhibited a very large conformational rearrangement of the DNA binding domains which explains how the binding of cAMP activates the ability of CAP to bind to DNA.  In the 1980s we also determined the first structure of a DNA polymerase, the Klenow fragment of DNA polymerase I (whose discovery by [Arthur Kornberg](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1959/) led to his receiving the Nobel Prize) and its complex with a DNA substrate in the 3′-5′ exonuclease active site. The structure of the substrate complex led to our discovery of the two-metal-ion mechanism of a phosphoryl transfer reaction and our later proposal that this mechanism is employed by many ribozymes, which has recently shown to be the case for several of them. We also published our first structure of a fragment of the site specific recombination enzyme, gamma delta resolvase, that lacked its sequence specific DNA binding domain. Perhaps the most exciting (to me) leap forward in the late 80s was our obtaining the structure of glutaminyl-tRNA synthetase complexed with tRNAGln and ATP. This was the problem I had wanted to work on 20 years earlier when Brian Hartley wisely advised me that it was too early. Obviously, he was correct. This first structure of a synthetasetRNA complex showed how the synthetase recognizes the correct tRNA containing the glutamine anticodon and discriminates against all of the other tRNAs. This is the first critical step in the translation of the genetic code into proteins.  We had many exciting advances in our central dogma quest in the first half of the 1990s. We obtained the first structure of HIV reverse transcriptase complexed with a non-nucleotide inhibitor, which was then one of the few drugs used to treat patients with AIDS. We also determined the first of the many structures of T7 RNA polymerase that we have obtained over the last 15 years captured in many of its functional states. This was the beginning of our exploring how DNA is transcribed into RNA starting with an initiation state with T7 RNA polymerase bound to its promoter and going on to the elongation and termination states. Significant progress was also made in our studies of DNA recombination. We obtained the first structure of an enzyme involved in homologous recombination, recA, and the structure of the site specific recombinase, gamma delta resolvase, bound to its specific DNA target. While this latter structure illuminated how resolvase recognizes its DNA target, it did not reveal how the protein brings the two DNA duplexes together to form a synaptic complex or how strand exchange is accomplished; that would take us another 10 years. We also obtained the structure of the first binary complex of a DNA polymerase (Klenow fragment) with its duplex DNA substrate bound to the polymerase active site, but without the incoming dNTP.  By 1995, then, we had made significant progress on obtaining structural insights into the mechanisms of all of the steps of the central dogma except the last one – protein synthesis by the ribosome. It was at this time in the fall of 1995 that Nenad Ban joined by lab and said he wanted to work on the structure of the ribosome – the right person at the right time. As discussed in more detail in the [Nobel lecture](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/2009/steitz-lecture.html), we collaborated with Peter Moore and Ban was joined later by Poul Nissen and Jeff Hansen. Between 1995 and 2000 our goal of obtaining the structure of the 50S ribosomal subunit and a complex with a transition state intermediate was attacked successfully by the swat team of these three postdocs (Fig. 6). Jeff Hansen also determined the structures of many complexes between the *Haloarcula marismortui*50S subunit and antibiotics bound to the peptidyl transferase center, which formed the basis for our founding of Rib-X Pharmaceuticals, Inc. Subsequently, substrate complex structures were pursued by a graduate student, Martin Schmeing, in the early 2000s (Fig. 6). During the 1990s our small ribosome group had daily conversations and regular meetings around a lunch table to discuss progress and ideas for moving forward. The calculation of the 2.4 Å resolution electron density map in early 2000 and our months of building a model of the ribosome were the most exciting research times I had ever experienced. We had no idea what the ribosome structure, particularly the RNA, would look like and peering into its emerging interior was simply amazing  Looking back over the development and progress of my career in science, I am reminded how vitally important good mentorship is in the early stages of one’s career development and constant face-to-face conversations, debate and discussions with colleagues at all stages of research. Outstanding discoveries, insights and developments do not happen in a vacuum. Our research accomplishments on the structures of the large ribosomal subunit and its many complexes were greatly enhanced and accelerated by the structural biology environment at Yale in the 1990s as well as the long term support of risky projects by the Howard Hughes Medical Research Institute. As I watch increasing numbers of my faculty colleagues, students and postdocs communicate with each other almost exclusively by email rather than discussing ideas over the lunch table (as I experienced in Cambridge and the first decades at Yale), I wonder whether they will be as creative and have as much fun doing science as they could with more face-to-face contact. |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** | [TS]  [Thomas Steitz] Hello?  [Adam Smith] Good morning, may I speak to Professor Thomas Steitz please?  [TS] Speaking.  [AS] Hello, this is Adam Smith from the official web site of the Nobel Foundation in Stockholm. Congratulations on the award. And, we have a tradition of recording very brief telephone interviews with all new laureates. Would it be possible to record a brief conversation?  [TS] Ah, OK.  [AS] Thank you. So for a starter, I’m right in thinking, I believe, that you and your wife are both biology professors at Yale?  [TS] We’re both professors of molecular biophysics and biochemistry at Yale, yes.  [AS] And when you got the call this morning, were you asleep?  [TS] Yes.  [AS] Nice way to be woken up, I imagine?  [TS] Oh, it is indeed!  [AS] And what for you is the particular joy of trying to unravel these large macromolecular structures?  [TS] Well, I found the most exciting thing about the ribosome was seeing a structure, seeing a large macromolecular assembly that I had no idea what it would look like. And I have to say it was the most exciting time in science that I’ve had, by a lot. Just, you know, it’s like getting to the top of Mt. Everest and seeing the view, it’s terrific.  [AS] There seems to have been this magical year of 2000, when the high resolution structures began to come out.  [TS] That’s correct. Yeah, we… it started coming out in the earlier stages in ‘98 and then of course there’s always communication back and forth about how to do things and it all happened at once after many, many years of not happening. It was great!  [AS] And, it’s all about images, it’s all about building images of the various subunits and putting that together to get a picture of how the ribosome functions. Do you feel that we now have a good picture of the way the ribosome works?  [TS] Oh, I think that it’s an extraordinarily good picture. I mean there’s always more that one can do, of course. And it’s led to insights in a variety of things and most … I think one that will have the most profound effect on the public at large is the ability to use this structural information to design new antibiotics that are effective against disease resistant strains.  [AS] Indeed, you founded a company, Rib-X Pharmaceutical, to pursue that. And it sounds, from what you’re saying, that you’re very hopeful that there will be new classes of antibiotics that result from this?  [TS] Yes, they have one that’s completed Phase II clinical trial successfully and is now ready for Phase III. And they have several others that are coming along in earlier stages, so it’s a rich environment for designing antibiotics and it’s the major target of antibiotics in general anyhow, so … And the structure has been very, very illuminating. Now that wasn’t our original goal in solving the structure. I wanted to understand how it worked! But this was sort of a little, side benefit of learning the structure. This is why I think basic research is very important because it can have applied consequences that you didn’t even think about.  [AS] And it’s an enormously important problem because antibiotic resistance is increasing at a very alarming rate, yes.  [TS] And there was an article in the *New York Times* about a year ago, two years ago, that said that there were twenty thousand people a year who died of MRSA infections in US hospitals alone. That’s a lot of people.  [AS] One of the things that you contributed was the solution of the phase problem for the larger subunit of the ribosome, which reminds one of [Max Perutz](https://www.nobelprize.org/prizes/chemistry/1962/perutz/facts/) who had solved the phase problem for smaller proteins in the 1950s.  [TS] Yes, my idol.  [AS] Because you were a post doc at the LMB in Cambridge for a while?  [TS] I was indeed.  [AS] So, did you encounter him there?  [TS] Oh yes. I knew Max Perutz very, very well. Actually it was Max Perutz who inspired me to go into structural biology when he gave a lecture at Harvard in 1963. As soon as I heard him talk, I decided that this is what I want to do.  [AS] That’s nice to be able to pinpoint it to a single moment.  [TS] Yes.  [AS] Well, thank you very much indeed. I’d just like to finish by asking; would you describe yourself and Ada Yonath and Venki Ramakrishnan as being collaborators or are you friendly competitors?  [TS] Ah, well, we’re not collaborators in the sense that we’ve all worked completely independently. And I’ve known Venki Ramakrishnan much better because he was a post doc at Yale in the ‘80s and so I knew him them and I’ve known him subsequently. So we’ve interacted much more than I have with Ada Yonath.  [AS] OK, thank you. OK, well, I better leave you to get on with this day. Do you know what’s going to happen next?  [TS] Ah, no.  [AS] Well, I leave you to discover.  [TS] OK!  [AS] And when you come to Stockholm in December to receive the award we have a chance to speak at greater length.  [TS] OK, good.  [AS] OK, thank you and congratulations again.  [TS] Thank you.  [AS] Thank you, bye, bye,  [TS] Bye. |
| **Interview** |  |

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| **Chemistry\_2024-2000** | |
| **ID** | 0342 |
| **Biographical** | I was born in Jerusalem in 1939 to a poor family that shared a rented fourroom apartment with two additional families and their children. My memories from my childhood are centered on my father’s medical conditions alongside my constant desire to understand the principles of the nature around me. The hard conditions didn’t dampen my enormous curiosity. Already at five, I was actively investigating the world. In one of my experiments I tried to measure the height of our tiny balcony using the furniture from inside the apartment. I put a table on another table, and then a chair and a stool on top, but did not reach the ceiling. Hence, I climbed up on my construct, fell down to the back yard on the ground floor and broke my arm … Incidentally, the results of this experiment are still unknown, since the current tenants in the apartment have remodeled the ceiling.  My parents were raised in religious families, being educated mainly in Judaism (my father) and women household skills (my mother). All of the schools in my immediate neighborhood were based on the same principles as those of my parents. However, despite the poverty of my parents and the lack of formal education, they went out of their way so that I could obtain a proper education in a very prestigious secular grammar school, called “Beit Hakerem”.  My father was frequently hospitalized and operated on, and when I was 11 years old he died. My mother barely coped, and I started to help her at that age. I had all types of jobs, cleaning, babysitting and providing private tuition to younger children. But both of us could not earn enough to support our little family, and consequently a year later my mother decided to move to another city, Tel Aviv, in order to be closer to her sisters. There I completed my high school education, and my mother, despite her tough life, supported my desire to keep on learning.  Indeed, after I spent my compulsory army service in the “top secret office” of the Medical Forces, where I was fortunate to be exposed to clinical and medical issues, I enrolled to the Hebrew University of Jerusalem. There I completed my undergraduate and M.Sc. studies in chemistry, biochemistry and biophysics. My doctoral work was carried out at the Weizmann Institute. I tried to reveal the high resolution structure of collagen. I continued to work on fibrous proteins (muscle) in my first postdoctoral year at the Mellon Institute in Pittsburg, Pennsylvania and then moved to the Massachusetts Institute of Technology (MIT) to study the structure of a globur protein staphylococcus nuclease. After completing my postdoctoral research, at the end of 1970, I returned to the Weizmann Institute. There, I initiated and established the first biological crystallography laboratory in Israel, which for almost a decade was the only laboratory for such studies.  At the end of the 1970s, I was a young researcher at the Weizmann Institute with an ambitious plan to shed light on one of the major outstanding questions concerning living cells: the process of protein biosynthesis. For this aim I wanted to determine the three-dimensional structure of the ribosome – the cells’ factory for translating the instructions written in the genetic code into proteins – and thus reveal the mechanics guiding the process. This was the beginning of a long quest that took over two decades, in which I was met with reactions of disbelief and even ridicule in the international scientific community. I can compare this journey to climbing Mt. Everest only to discover that a higher Everest stood in front of us.  I began these studies in collaboration with Prof. H.G. Wittmann of the Max Planck Institute for Molecular Genetics in Berlin, who supported these studies academically and financially. In parallel I maintained my laboratory at the Weizmann Institute, initially with a very modest budget and a grant given by the USA National Institute of Health (NIH). Over the years, a center for macromolecular assemblies was established by Mrs. Helen Kimmel at the Weizmann Institute, and consequently I came to lead a large team of researchers from all corners of the globe. Though my research began as an attempt to understand one of the fundamental components of life, it has led to a detailed understanding of the actions of some of the most widely prescribed antibiotics. My findings may not only aid in the development of more efficient antibacterial drugs, but could give scientists new weapons in the fight against antibiotic resistant bacteria – a problem that has been called one of the most pressing medical challenges of the 21st century.  Because the ribosome is so central to life, scientists around the world had been trying for many years to figure out how it works, but without an understanding of its spatial structure there was little hope of forming a comprehensive picture. To reveal the three-dimensional structure at the molecular level, crystals are required, but when dealing with ribosomes, there are added challenges. The ribosome is a complex of proteins and RNA chains; its structure is extraordinarily intricate; it is unusually flexible, unstable and lacks internal symmetry, all making crystallization an extremely formidable task.  At the start of the 1980s, working at both the Weizmann Institute in Israel and the Max Planck Institute in Germany, we created the first ribosome micro crystals. The procedure, which I developed especially for this aim, included a method for the preparation of the crystallizable ribosome that had been developed at the Weizmann Institute by Prof. Ada Zamir, Ruth Miskin and David Ellison. My inspiration came from an article on hibernating bears that pack their ribosomes in an orderly way in their cells just before hibernation, and these stay intact and potentially functional for months. Assuming that this is a natural strategy to maintain ribosomal activity for long time, I searched for ribosomes from organisms that live under harsh conditions, first of semi thermophiles, given by Dr. V. Erdmann and later I developed a unique experimental system based on ribosomes taken from the hardy bacteria living the extreme environments of the Dead Sea, thermal springs and atomic piles. In this way we managed to produce the initial micro crystals of ribosome in a fairly short time. However, even after obtaining preliminary diffraction indications, when I described my plans to determine the ribosome structure many distinguished scientists responded with sarcasm and disbelief. Consequently I became the World’s dreamer, the village fool, the so-called scientist, and the person driven by fantasies.  In the mid-1980s we visualized a tunnel spanning the large ribosomal subunit and assumed, based on previous biochemical works (Malkin & Rich, 1967, Blobel & Sabatini, 1970) that this is the path through which the nascent protein progresses as it is being formed – until it emerges out of the ribosome. In the course of my research, I developed a number of new techniques that are today widely used in structural biology labs around the world. One of these is cryo-bio-crystallography, which involves exposing the crystal to extremely low temperatures, –185°C, to minimize the crystalline structure’s disintegration under the X-ray bombardment. The day we conducted this experiment was special and unique. One of the rare “Eureka!” events. In retrospect, it was second only to the great pleasure I had when seeing our first high resolution structure a dozen years later. In fact the “Eureka type” of an experiment was not common, although we frequently had a great pleasure of overcoming complicated challenges.  In the mid-1990s, once we proved the feasibility of ribosome crystallography, several groups from leading universities or research institutions initiated parallel efforts. As they could repeat our procedures, I was no more alone in this field. At the end of the 1990s, we as well as those who used our experimental systems succeeded in breaking the resolution barrier, thanks to improvements in the crystals, in the facilities for detecting the X-ray diffraction and in ways to determine the diffraction phases. The first electron density map of the ribosome’s small subunit was a real breakthrough, and for me, a tremendous excitement. Then, in 2000 and 2001, we published the first complete three-dimensional structures of both subunits of the bacterial ribosome.  These discoveries are clearly a high point in 20 years of research, but my quest to understand the ribosome is still far from complete. Armed with new insight into ribosomal structure, I can afford moving on to revealing what else these structures can tell us about the ribosome actions, and how antibiotic drugs block those actions in bacterial ribosomes. Because ribosomes are so essential to life, many antibiotic drugs work by targeting their actions. The advances we made in our long quest to solve the structure and function of the ribosome may also pave the way toward improving existing antibiotic drugs or designing novel ones. We therefore crystallized bacterial ribosomes that can serve as pathogen models, complexed with each of over two dozens antibiotic compound. We found that the drugs bind in specific “pockets” in the structure, located at or close to functional centers, thus can block them and prevent the ribosomes from manufacturing proteins. Since these findings were published in *Nature,*in 2001, we have revealed the means of action of almost all of the antibiotics that target the ribosome, and our research in this area is ongoing.  For all scientists, the true scientific discovery is the top. In my case I can recall saying things like: ‘why work on ribosomes, they are dead … we know all what can be known about them’, or: ‘this is a dead end road’, or: ‘you will be dead before you get there’. Indeed, to my satisfaction, these predictions were proven wrong, the ribosomes are alive and kicking (so am I) and their high resolution structures stimulated many advanced studies.  And in the future? We plan on looking to the distant past. Ribosomes are found in every living being – from yeast and bacteria to mammals – and the structures of their active sites have been extraordinarily well-preserved throughout evolution. We have identified a region within the contemporary ribosome that seems to be the vestige of the primordial apparatus for producing peptide bonds and essentially giving rise to life. How did these first ribosomes come into being? How did they begin to produce proteins? How did they evolve into the sophisticated protein factories we see today in living cells? We plan on answering these and related questions in our future work.  Awarding the Nobel Prize exposed the ribosome to the public. It stimulated true scientific interest and turned on the imagination of many youngsters. As I have curly hair, there is a new saying in Israel: “Curly hair means a head full of ribosomes”. Furthermore, our studies added to the buzz around the lovely North Pole Bears, which inspired my own research and are now endangered by the changing climate.  These studies could not be performed without the help and/or active participation of many individuals. Thanks are due to the Weizmann Institute, particularly its presidents Michael Sela and Haim Harari, for keeping up with me for over two decades and for allowing me to work; to the Max Planck Society, especially the late Prof H.G. Wittmann for co-initiating this project, for producing the ribosome and their crystals and for financing my dream; to Ms. Helen Kimmel for establishing and maintaining the Kimmelman Center, thus paving the road for us from the early stages of our studies; to my colleagues in Hamburg (e.g. Frank Schluenzen, Heike Bartels, Joerg Harms and Ante Tocilj) and in Israel (especially Anat Bashan, Ilana Agmon, Tamar Awerbach, Ziva Berkovitch-Yellin, Raz Zarivach and Shulamit Weinstein), as well as my collaborators in Berlin (especially Francois Franceschi) for their devotion and enthusiasm in good and bad periods.  Above all, to my family who supported me with no questions or complaints despite my frequent disappearances and although at times my mind was not solely with them. These include my parents, who were brought up far away from science, especially my mother, who experienced enormous difficulties in raising and educating me after my dad’s death when I was still a child; my young sister Nurit, and my daughter Hagith, who had to tolerated me in my presence as well as in my absence; and to my granddaughter Noa, who at the age of five invited me to her kindergarten to talk about the ribosome! |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** | [AY]  [Ada Yonath] Hello?  [Adam Smith] Professor Yonath?  [AY] Yes.  [AS] Oh hello, my name is Adam Smith and I’m calling from the Nobel Foundation website and we record very short interviews with new Laureates. So, congratulations on the award.  [AY] Thank you.  [AS] And, you are the first woman to be awarded the Nobel Prize in Chemistry since [Dorothy Hodgkin](https://www.nobelprize.org/prizes/chemistry/1964/hodgkin/facts/) in 1964.  [AY] I think I’m the fourth. There was [Marie Curie](https://www.nobelprize.org/prizes/chemistry/1911/marie-curie/facts/), and her daughter …  [AS] That’s right.  [AY] … Dorothy Hodgkin and now it’s me.  [AS] That’s right, exactly. You’re the fourth ever. And Dorothy Hodgkin’s was also of course for crystallography, so perhaps there’s something about …  [AY] That’s correct. She was a crystallographer and I admire her.  [AS] So, when you famously started working on the ribosome when others said it couldn’t be done, what do you think gave you the courage to try?  [AY] Ah. This was a sequence of events for which – and I’m not sure that you want it for this interview, the whole story – but because of a bicycle accident, I had some free time and I had to recover and I read a lot. And in this time, I read that the bears from the north pole … you know the bears that hibernate? That go to sleep in the winter? …  [AS] Yes?  [AY] … Take their ribosomes almost regularly, almost periodically, from the membranes of themselves and that’s the way they pass the winter. And this gave me the idea that ribosomes can be packed orderly, which was not believed at that time. And, I thought, “why do they do this?” And, the logical way to explain what the bears are doing was that, in the end of the winter, they need lots of active ribosomes – ribosomes deteriorate very quickly otherwise – and if they slept all the winter, hibernate all the winter, and the ribosomes would be gone, what will you do when they get up? So, I thought that this is the way that they preserve active ribosomes, by the close-packing. And because of it, I thought maybe this type of attitude should be given also for solving the structure of the ribosomes. So, I used ribosomes from very, very robust bacteria under very, very active conditions and found a way – I actually took advantage of research done before me at the Weizmann, the same institute I am now – how to preserve their activity and their integrity while they crystallized. And, they crystallized! So, this is what gave me the courage, the north pole bears.  [AS] It’s a marvelous story and shows the advantage of reading more widely than one would think one needs to.  [AY] Yes, and first of all have … you know in the bicycle accident I had a brain concussion. It was relatively serious when it happened but when I recovered people asked me why did you, why the hell did you start with such a project. I said I had a brain concussion! This is correct but not the whole truth.  [AS] Well thank you for the story, it’s marvelous. And, along the way, did you ever doubt that you would succeed or were you certain that you could get there in the end?  [AY] Oh ya, I doubted more than expected. I had doubts all the time. The way was extremely, extremely difficult. And the crystallization, or the interaction I had with the bears, or with the journal about the bears, was just one small problem – afterwards I thought. Maybe it was the main problem in the beginning. But there were lots of them. At one point I had to describe what I am doing to a person who is a great intellectual but not a scientist, and I told him what we felt is that we are climbing mountains in order to reach the climax – and these mountains are like the Everest, the biggest most difficult to climb – only to find out that there is another mountain waiting behind it to be climbed afterwards. So every climbing was an achievement but there was a bigger problem behind it or above it. I had lots of minutes that I didn’t expect, but I thought science in general and this science particularly is worth the effort – even if we would never get the ultimate result.  [AS] Yes. It’s all to do with images your work, so can you describe how you see the ribosome when you think of it? Is it a machine?  [AY] I think that I understood the question. The ribosome is a machine that gets instructions from the genetic code and operates chemically in order to produce the product. During the work – they work very fast and very well and very accurately – and during their work they have to proof read the results and to protect the product until the product is capable of protecting itself. The product is a protein and if you think about the kangaroo in a pocket, the product goes first into a pocket which is actually in the ribosomal tunnel And this way you can look at it as a machine and we call it the cellular machine.  [AS] That’s a very nice image to hold in one’s head of the protective pocket of the kangaroo’s pouch, yes.  [AY] There is a tunnel for that, inside the ribosome, through which the newly-born protein progresses until it emerges out of the ribosome.  [AS] And, one of the aspects of the work that has been highlighted by the committee is the ribosome’s interaction with antibiotics and the hope that understanding the structural nature of those interactions will …  [AY] The ribosome is so important that it is a target for many antibiotics. Try to understand how this happens, how the antibiotics, they interact with the ribosome: what is the secret for their inhibition and how to reduce resistance to antibiotics and how to increase the possibility of the antibiotic to distinguish between the patient, that has to recover, and the pathogen, that has to die.  [AS] Yes, yes of course. So may I end by simply asking you what the award of the Nobel Prize means to you?  [AY] Oh, a lot! I think it’s the highest recognition, and although I can’t see myself working everyday for recognition, and if I thought about recognition I won’t go with the pathway that I did. I appreciate it very much. I think that there is something special with this prize.  [AS] Yes. And perhaps particularly special to be a woman who receives it?  [AY] I’m sorry that I can’t, I can’t think this is because of my gender. And, I don’t think that I did something that is specially for women, or the opposite. During my time I had some very difficult years and I had very pronounced competition, all by men. But I don’t think that this is because I was a woman. I’m pretty sure that if I was a man too they would compete, if the men would get to where I was at that time. I think that it doesn’t help to be a woman in science. Maybe now, but not when I was progressing. But I don’t think that it disturbs, in my opinion. I may be wrong. I may be wrong: women try to explain me all types of things. And I think that women can make … women need, actually, they’re fortunate because if they don’t want to do science they can say, “I want to be with my kids.” And this is understandable, whereas a man cannot do this. So if we look at it from the other point, but this means also stopping science.  [AS] OK, well, when you come to Stockholm, in December, we have a chance to speak at greater length and perhaps we can explore these things more then.  [AY] I’m looking forward to it.  [AS] We are very much looking forward to seeing you here and I just wish to offer my congratulations again.  [AY] Thank you.  [AS] OK, thank you very much for speaking with us.  [AY] Bye, bye.  [AS] Thank you, bye, bye. |
| **Interview** |  |

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| **Biographical** | I was born on August 27, 1928, in the town of Fukuchiyama, Kyoto-Fu, Japan. My father Chikara was an army captain of the Fukuchiyama regiment. In the spring of 1933, my father took a post in Manchuria, which was under Japanese occupation. Because there were some insurgents in the Manchurian area, my mother Yukie, my younger brother Sadamu, and I chose to stay in Japan and moved to Sasebo, Nagasaki Prefecture, where we lived with my grandmother, Tsuki Shimomura. After the insurgents were wiped out, we moved to Renzankan, Manchuria in March 1935. A sister, Toshiko, was born there, but she died of pneumonia one year after her birth. I remember my mother’s deep sorrow after Toshiko’s death.  In early 1938, my father was transferred to an army position near the Soviet border. The rest of my family moved back to Sasebo. Mother soon departed to Manchuria again to live with my father, and Sadamu and I were in the custody of grandmother Tsuki for about one year. Because I was the elder son, Tsuki raised me carefully and strictly as the heir of the Shimomura family. Since I was physically not very strong, she tried to feed me various nutritious foods like omelet with ground beef and soybean milk. Grandmother was very strict about manners and etiquette. I always had to keep a good posture in her presence. She often said, “the samurai betrays no weakness when starving.” After I bathed, she would check behind my ears and neck for dirt. If she found any, she would say it would be ignominious to be dirty when I was beheaded (it is sometimes honorable for a samurai to commit hara-kiri and then be beheaded). I knew she was talking about the importance of readiness, but it was a little scary. A year later, father took mother back home and stayed only briefly (Fig. 1).  In April 1941, I entered the seventh grade at Sasebo middle school. Japanese militarism was maximal at the time. We had to perform military exercises once or twice a week under the direction of the officers attached to the school. Later that year, my father was transferred to Osaka, and after the Pacific War began on December 8, we joined my father there. At school in Osaka, my teacher happened to be Shizuo Ito, a well-known poet from Isahaya. I contracted tuberculosis and was often tired; though I studied hard, my class rank was poor. I was interested in making model airplanes at the time. Once I built a plane based on an article in a scientific magazine, and I exhibited it at a large department store. My sister, Setsuko, was born, and I had to babysit occasionally.  When I was in the ninth grade, the war became clearly unfavorable to Japan, and my father was sent to Thailand. At school, missing lectures became common and military exercises increased. Once, on an overnight march to Mt. Ikoma, I saw many tiny irregular spots of light on the road. Now I think they were probably luminous earthworms crushed by shoes. In the summer of 1944, my father wrote us to move to the countryside to avoid American bombings. My mother chose to move us to her parents Fujiyama’s house in Isayaha near Nagasaki. That September, on my first day of school (tenth grade), the teacher told us, “This class is mobilized to the Omura Naval Aircraft Arsenal immediately. Other classes are mobilized to Mitsubishi shipyard and arms factory in Nagasaki.” Because the National General Mobilization Law had been activated earlier, I expected to be mobilized sooner or later, but I didn’t think it would be on the first day of school. From that day on, we did not listen to lectures or study at school; we worked.  Two months after I started working at the Omura Naval Aircraft Arsenal, the arsenal was destroyed by bombing. That day, when the air-raid siren sounded, some students took shelter in an underground bunker and the rest of us ran to the edge of the airfield, then waited in a ditch. Soon I saw a formation of more than 20 B-29s coming from the west, and the bombing started. A stray bomb fell nearby and showered us with sand and gravel. The bombing destroyed most of the facilities, but I saw that one hangar was still standing and some people were trying to pull a fighter plane out of it. We rushed there to help them. However, an enemy plane was ahead in the smoke-covered sky. At the moment we reached the hangar, we were showered with numerous incendiary bombs. I heard someone shouting an order to take refuge. We ran between bombs burning with white flame; I saw a person who had been hit on the shoulder running with one arm dangling.  After the air raid, we learned some of the students had died in the underground bunker, and that our dormitory had burned down. Within a month, several wooden factory buildings were built between the hills near Isahaya, and we were ordered to work there. I attended the factory every day even before it was completed; if I found nothing to do I would often lie down in a sweet-potato field nearby and watch large formations of B-29s going east high above Mt. Tara-dake. It was beautiful to see the shining silver B-29s against the background of blue sky. Then, in about 10 minutes, I would see black smoke in the Ohmuta industrial area on the opposite shore of the Ariake Sea, and I could only imagine the scene of carnage over there.  The new factory was for the repair of fighter engines. My job was to smooth the face joining the crank case to the cylinder. My class graduated in March, 1945, at the factory, without a graduation ceremony or diplomas. I was 16 years old. After graduation, the student mobilization continued.  **The Nagasaki atomic bomb and the end of the war**  On August 6, 1945, news reports informed us that the city of Hiroshima had been completely destroyed by a new type of bomb; we didn’t know what kind. Three days later, shortly before 11 AM, a siren sounded at the Isahaya factory, notifying us of an air raid. As usual, rather than going into a bunker, I went to the top of a nearby hill with a couple of friends and looked at the sky. We saw a single B-29 going from north to south towards Nagasaki, about 15 km away. I thought that its course was unusual. The B-29 dropped two or three parachutes and I heard sporadic gunshots. Watching carefully, I saw no people attached to the parachutes. Within a few minutes, another B-29 followed the first one, and a siren sounded the “all clear” signal. We returned to our factory building.  At the moment I sat down on my work stool, a powerful flash of light came through the small windows. We were blinded for about 30 seconds. Then, about 40 seconds after the flash, a loud sound and sudden change of air pressure followed. We were sure there was a huge explosion somewhere, but we didn’t know where. The sky was rapidly filling with dark clouds, and when I left the factory to walk home, about three miles away, a drizzling rain started. It was black rain. By the time I arrived home, my white shirt had turned gray. My grandmother quickly readied a bath for me. That bath might have saved me from the ill effects of the strong radiation that presumably existed in the black rain.  The next morning, a technical officer told us that the parachutes we had seen the day before contained measurement instruments and a transmitter. He also mentioned that there was serious damage in Nagasaki, but the details were unknown. The chief of the factory organized a rescue party. We tried to enter Nagasaki, but could not because the roads and the railroad were impassable. Later that afternoon, the railroad was opened to Michinoo, near Nagasaki station, and rescuers began to transport injured people to Isahaya and other cities.  On August 15, in a radio broadcast, Emperor Hirohito declared unconditional surrender. This was the first time that most Japanese citizens had heard the emperor’s voice. I think there was a widespread feeling of relief, and also fear for an uncertain future.  Many years passed before we had detailed information about the atomic bombs that were dropped on Hiroshima and Nagasaki. The Nagasaki bomb was a different type and far more powerful than the Hiroshima bomb. Even if the use of the Hiroshima bomb was justifiable in order to precipitate an end to the war, the bomb dropped on Nagasaki three days later was clearly a test of new arms. It cannot be justified.  The student mobilization ended, but I was not sure if my school record would allow me to enter a college. To receive some guidance, I visited my Isahaya school a week after the end of the war. Attached to the main gate were several sheets of large paper, on which numerous names were written. About half of the names were crossed off. Apparently the school was being used to accommodate the injured people of Nagasaki, who were listed on the papers. In the exercise field, several men were slowly strolling under the strong summer sun amid the noisy shrill of cicada. All were half-naked. When I looked closer, I saw that their skin was covered with something black with white specks. I thought it was a black medicine (I later found out it was dried blood). The white specks were maggots that had hatched on the human flesh. But that was not the most shocking sight. At the front of the gate, bodies covered with straw mats were stacked on a cart, probably to be taken to a crematory. Two people with a stretcher, a body on it, were coming from the school building. At that moment I noticed two half-naked people standing near the fence. They had been watching the loading of the bodies, a process that might happen to them in a few days. I felt as if I were seeing ghosts. My brain froze, the shrill of cicada faded, and my senses vanished. I think the mental shock I had at that sight, when I was 16 years old, had a certain permanent effect on me. I have regretted for a long time that I did not speak to these people; probably I didn’t have the courage at that time.  **Nagasaki Pharmacy College**  I tried to enter three different colleges in 1946 and 1947, but all rejected me. I didn’t have a strong school record to assist me, because I hadn’t studied even one day at the Isahaya school from which I graduated. I then heard that the Nagasaki Pharmacy College, a part of Nagasaki Medical College, was readying a temporary campus at a vacated military barrack near my home. (Both colleges had been completely destroyed by the atomic bomb.) I was admitted to the pharmacy college in April 1948. Although I was not planning to be a pharmacist, I didn’t have any other choice, under the circumstances. My grandmother presented me with a suit of silk clothes upon my entrance to college. There was no cloth to buy at the time, but she had a mulberry field. So she raised silkworms, reeled silk thread off the cocoons, dyed the thread, hand-wove the thread into cloth by herself, and then tailored the clothes.  Most of the pharmacy students lived in the dormitory, and they were always hungry due to an extreme shortage of food. I lived at home, and we owned farm land, so I was very lucky concerning food. Despite great effort by the professors, the resources and equipment at the pharmaceutical college were poor. We had a lot of difficulty carrying out experiments. Instruction in analytical chemistry and physical chemistry seemed fine, but I learned very little organic chemistry. In experiments on organic synthesis, we often set fire to solvents, due to poor technique and poor glassware. But many of us were experienced firefighters due to growing up in wartime, and we had no problem putting the fires out.  My interest in chemical experiments developed, but due to equipment limitations, the only experiments I could carry out were inorganic ionic reactions. With the permission of Professor Shungo Yasunaga (Fig. 2, left) of the Pharmaceutical Analysis Lab, I prepared many glass capillaries 1 mm in diameter, and packed them with alumina powder. When a small amount of a mixed solution of metallic ions was applied to the tip of the capillary and then it was dipped in a developing reagent, the reagent quickly rose up by capillary action. In the process, metallic ions were separated and colored bands appeared corresponding to the ions separated. It was a kind of chromatography. With Prof. Yasunaga’s permission, I brought back a small amount of various chemicals to my home and studied the conditions of separation in detail. The results were reported in the Journal of the Pharmaceutical Society of Japan a few years later, as my first paper (Yasunaga and Shimomura, 1953).  In March 1951, I graduated from Nagasaki Pharmacy School, at the top of my class. The school was reorganized as the Department of Pharmacy, Nagasaki University. Professor Yasunaga offered me a job there as an assistant in the analytical chemistry laboratory for students, and I took it. When I had spare time, I continued the chromatography experiments I had started when I was a student. I became interested in classical music after I heard an LP record somewhere. However, one LP cost nearly a month of my salary. Somehow, probably with my parents’ financial help, I managed to buy a record player and speakers, and I assembled an amplifier out of glass vacuum tubes, condensers and resistors.  Professor Yasunaga was a gentle and very kind person, trusted by people. After I had worked for him for four years, he obtained a leave of absence with pay for me, to study for one year. Moreover, he offered to introduce me to Professor Fujio Egami of Nagoya University, a well-known molecular biologist. We took the train to Nagoya, but unfortunately we found Professor Egami wasn’t at the university that day. Professor Yasunaga visited another person, Professor Yoshimasa Hirata (Fig. 2, center), an organic chemist. We chatted a few minutes. As we were leaving, Professor Hirata said to me, “Come to my lab. You may start at any time.” This was surprising, because we had just met. I didn’t know much about molecular biology or organic chemistry, so it didn’t matter to me which specialty I would study. I thought Professor Hirata’s words might be the direction given by heaven, and I decided to go to his lab. It seems that this decision determined my future, directing me to the studies of bioluminescence, aequorin and green fluorescent protein (GFP).  **The Hirata lab and *Cypridina*luciferin**  I enrolled in the Hirata laboratory, Department of Science, Nagoya University, as a research student in April, 1955. The Hirata lab was a wonderful place with a splendid atmosphere. Nobody taught me anything, but I learned much by watching other people and by independent study.  On my first day, Professor Hirata brought out a large vacuum desiccator and said, “This contains dried *Cypridina*.” He explained to me that *Cypridina*, a small crustacean common in shallow coastal waters of Japan, emits light with an organic compound called luciferin and an enzyme, luciferase. He told me that luciferin is extremely unstable and rapidly decomposes in the presence of oxygen, and also that Professor Newton Harvey of Princeton University had been trying to purify luciferin for the past 20 years but had been unsuccessful. Professor Hirata asked, “Could you purify and crystallize *Cypridina*luciferin for the purpose of structure determination?” At the time, crystallization was the only practical way to prove the purity of a substance. Professor Hirata also told me that he could not give this project to a student pursuing a degree, because the outcome was so uncertain. I clearly understood the difficulty of the work. Since I was there for study, not for a degree, I replied, “I would like to do my best.”  This did, indeed, turn out to be a very difficult crystallization. It took me ten months of extremely hard work to extract, purify, and crystallize the luciferin. When I finally succeeded, I was so happy I couldn’t sleep for three days. Since the end of the war, my life had been dark, but this gave me hope for my future. Probably the greatest reward I gained was self-confidence; I learned that any difficult problem can be solved by great effort. With the crystallization accomplished, my stay in Nagoya was extended one year to study the structure of *Cypridina*luciferin (Fig. 3). Our first paper on *Cypridina*luciferin was published in 1957, although the chromophore structure of luciferin remained to be elucidated.  **To America**  In the spring of 1959, I received a letter from Dr. Frank Johnson (Fig. 2, right) of Princeton University inviting me to work at his laboratory. When Professor Hirata heard about my plan to go to Princeton, he awarded me a doctoral degree for my *Cypridina*work, even though I wasn’t enrolled as a doctoral student. Prof. Hirata knew having a doctorate would double my salary at Princeton. I was completely surprised, and I accepted his offer with thanks. I applied for and received a Fulbright travel grant, which provided me with various experiences unavailable otherwise.  On August 4, 1960, Akemi Okubo and I got married in a traditional way, arranged by a match-maker. Akemi was a graduate of the Pharmacy Department where I worked. On August 27, I left Yokohama on a ship bound for Seattle, along with more than 200 other Fulbright fellows and students, but Akemi could not accompany me due to a visa problem. The day was my 32nd birthday. Since that voyage was the last Pacific cruise of the ship Hikawa-maru, the pier was filled with people (Fig. 4). Thousands of colored tapes connected people on the boat with well-wishers on the pier. I will never forget the scene when the ship started to move, and the tapes broke and then fell. After traveling by rail across the United States, I arrived at Princeton on September 17, 1960, and stayed at Dr. Johnson’s house that night. The next morning, Dr. Johnson offered to help me find an apartment. We saw a newspaper advertisement for a room for rent, and we stopped at the house. A man responded to the doorbell, but he quickly shut the door when he saw my face. It was a clear case of racial discrimination that I rarely encountered.  On my first visit to Dr. Johnson’s office, he took out a small vial containing white powder, and said “This is the freeze-dried light organs of the luminous jellyfish *Aequorea*, and it should emit light when mixed with water.” We went into a dark room and tested it, but we could not see any light. However, he enthusiastically explained to me that *Aequorea* were very abundant in Friday Harbor, Washington State, and that they were brilliantly luminous. Then he asked if I would like to study the bioluminescence of this jellyfish. I answered, “I will be glad to do it.” Thus, we decided to go to Friday Harbor the following summer.  During my first few months in Princeton, I extracted and purified luciferase from dried *Cypridina*. I was surprised at the large quantity of dried *Cypridina*that was stocked in the Princeton biology department, which included sealed bottles dated 1928 and a sealed tin can bearing the name of Sakyo Kanda, a pioneer in the study of bioluminescence. There was also a large amount that had been collected for intended military use by the Japanese army during the war, seized by the U.S. Navy at the end of war and then donated to Professor Harvey’s lab. Dried *Cypridina*, even if it is many decades old, luminesces when crushed and mixed with water.  Miss Yo Saiga arrived in December 1960 to work as our research assistant, and my wife, Akemi, arrived the next month just after the inauguration of President John F. Kennedy, after a delay of four months due to her visa problem.  On June 23, 1961, Dr. Johnson, my wife, Miss Saiga and I departed for Friday Harbor. Dr. Johnson had purchased a new Plymouth station wagon for the trip. We loaded it with a large photometer, other instruments and chemicals needed for research, and suitcases for four people on the roof. It took us seven days to cross the continent, with Dr. Johnson driving the whole way. Upon arrival, we met our host, Dr. Robert Fernald, at the Friday Harbor Laboratories, University of Washington.  Friday Harbor is on San Juan Island, which lies east of the city of Victoria on Vancouver Island. The scenery of San Juan Island was splendid. The sea was clean and beautiful. At low tide, there were colorful sea urchins and starfish in various sizes scattered on rocks, and some abalones. There were also abundant fish. We could easily get rock fish of about 30 cm long using simple lures from a boat or rocky shore. We often ate them as sashimi. Indeed, Friday Harbor at the time was a kind of paradise for us.  For research space, Dr. Fernald assigned us part of a large laboratory. There were three other scientists in the room, and one of them was Dr. Dixy Lee Ray, a professor at the University of Washington at the time, and later chairperson of the U.S. Atomic Energy Commission and governor of Washington State. She was always accompanied by her dog, even though dogs were prohibited in Friday Harbor Laboratory by a state law. She declared that the animal was her assistant.  Our research material, *Aequorea*, was really abundant. A constant stream of floating jellyfish passed along the side of the lab dock every morning and evening, riding with the tidal current. I describe our methods for collecting and extracting the luminescent material from *Aequorea*in my [Nobel lecture](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/2008/shimomura-lecture.html).  We brought the crude extract back to Princeton in September 1961, where we began the process to purify it. In February 1962, we obtained about 5 mg of nearly pure luminescent substance. It was a protein, and we named it aequorin. Aequorin attracted wide attention as a unique protein that emits light in the presence of calcium ions, even in the absence of oxygen. Aequorin was the first photoprotein ever discovered. During the column chromatography of aequorin, we found a trace of protein that showed green fluorescence, which eluted sooner than aequorin. We also purified that protein, which is now called green fluorescent protein (GFP).  In August 1962, I visited Bermuda to study the famous fireworm *Odontosyllis enopla* at the Bermuda Biological Station. The fireworms are very small but they show a spectacular bioluminescence display that is correlated with the lunar cycle. The luminescence display takes place during a period of several days following a full moon. It begins about one hour after sunset and lasts only for 10 minutes. It begins with the sudden appearance of a swarm of brilliantly luminescent females (about 2 cm long) at the surface of the water, each worm quickly moving in a tight circle. Within a few seconds, numerous brightly luminescent males (about 1 cm long) appear, and they dart toward the females from all directions, attracted to the light. I collected the fire-worm and studied the properties of its luciferin.  Due to my U.S. visa expiring in 1963, I was expected to return to my position in the Pharmacy Department at Nagasaki University, from which I was on leave. However, I received through Professor Hirata an offer of the position of associate professor at the Water Science Institute, Nagoya University, with the understanding that I could continue my research on bioluminescence. I took the offer. In September 1963, I began working under Professor Tadashiro Koyama at the Water Science Institute. A few months later, Professor Hirata asked me to assist his graduate student, Yoshito Kishi (later a professor at Harvard University) to determine the structure of *Cypridina*luciferin. In the summer of 1964, Kishi and I went to Setoda in the Inland Sea to do mass collection of *Cypridina,* taking some 10 students with us. From frozen *Cypridina*, we extracted luciferin and then purified and crystallized the luciferin. With that material, Kishi successfully determined the structure of the luciferin the next year.  In February 1965, I went to New Zealand to study two kinds of bioluminescent organisms: the cave worm *Arachnocampa* and the freshwater limpet *Latia*. Soon afterwards, I decided to go back to Dr. Johnson’s lab at Princeton University, because I realized I did not have sufficient ability to do top-level work in two unrelated fields, earth science and bioluminescence. I wanted to study and clarify the chemical mechanism of aequorin bioluminescence, since some people doubted the existence of a photoprotein like aequorin. In December 1965, I returned to Princeton with my wife and our one-year-old son, Tsutomu.  Since the early 1950s, it had been believed that calcium ions play important roles in living bodies, but there had been no way to demonstrate this experimentally. In 1967, however, Ellis Ridgway and Christopher Ashley, University of Oregon, experimentally proved the involvement of calcium ions in the contraction of muscles using aequorin as an indicator. As the usefulness of aequorin as a calcium probe increased in the fields of biology and physiology, I wanted to clarify the mechanism of aequorin luminescence to assist in its use.  I already knew that the aequorin luminescence was caused by an intramolecular reaction that takes place in the protein molecule, which would be difficult to study. But I decided to do my best. It turned out to be an unexpectedly large undertaking. It took about 12 years to obtain a structural model of aequorin, as detailed in my [Nobel lecture](https://www.nobelprize.org/prizes/chemistry/2008/shimomura/lecture/). We needed a large amount of aequorin to carry out this study, so we returned to Friday Harbor every summer for more than 10 years, where we collected and processed about 3,000 jellyfish a day. My staff, my wife, my children, and some local students that we hired were of great assistance in the collection and processing of *Aequorea*. Dr. Johnson devised a “jellyfish-cutting machine” to speed up the process of cutting the ring from the animals. In 1972, back at Princeton, we succeeded in determining the structure of AF350, a part of the aequorin chromophore. By 1978, we had achieved a general understanding of the aequorin luminescence reaction.  Between 1965 and 1978, in addition to my work with aequorin, I also did research on the bioluminescence of various luminous organisms including the limpet *Latia*; the krill *Meganyctiphanes*; the worm *Chaetopterus*; the firefly squid *Watasenia*, various coelenterates, and luminous bacteria. I also studied the properties of GFP and resolved a controversy regarding the role of a dioxetane intermediate in the luminescence reaction of firefly luciferin. Those matters are detailed in my book (Shimomura, 2006).  **To the Marine Biological Laboratory, Woods Hole**  Dr. Johnson retired from Princeton in 1977, and I decided to move to a marine laboratory. Before leaving Princeton, I elucidated the chromophore of GFP (Shimomura, 1979). I also performed research on dinoflagellate luciferin and luminous scale worms. In 1981, with the kind arrangement made by Dr. Woodland Hastings of Harvard University and Dr. Benjamin Kaminer of Boston University, I moved to the Marine Biological Laboratory (MBL) in Woods Hole, Massachusetts, where I was a Senior Scientist. My wife, Akemi, worked at the MBL as my research assistant. I also accepted an adjunct professorship at Boston University Medical School.  Established in 1888, the MBL is the oldest marine laboratory in the western hemisphere. Over the years, many Japanese scientists have performed research at the MBL, including historic names such as Shosaburo Watase, Umeko Tsuda, Hideyo Noguchi, Sakyo Kanda, Katsuma Dan, Sachio Hiramoto, and Shinya Inoué. At the MBL, I continued my work to extract, purify and study the luminescent substance of many organisms, including the millipede *Luminodesmus*; the brittle star *Ophiopsila*; and several types of luminous mushrooms.  Since 1975, aequorin had become widely used among cell biologists and physiologists as an excellent calcium probe, and its applications peaked around 1985. Since I was practically the only source of aequorin in this time period, I sent out several hundred aequorin samples in response to requests from investigators all over the world. The cDNA of aequorin was cloned and recombinant aequorin was made in 1985, but the patent owners of recombinant aequorin, the University of Georgia and Chisso Corporation of Japan, were not sure about expanding the use of aequorin, thus the general use of recombinant aequorin was delayed. In 1988, in collaboration with Professor Yoshito Kishi of Harvard, we succeeded in making various aequorins that had different calcium sensitivities and properties. Those aequorins contained various derivatives of coelenterazin instead of coelenterazine in their molecules, and were called semi-synthetic aequorins. In 1995, I undertook work on the X-ray structure of aequorin, and the three-dimensional structure of aequorin was obtained in 2000 (Head*et al*., 2000).  In 1992, the cDNA of GFP was cloned by Dr. Douglas Prasher, who was then at Woods Hole Oceanographic Institution. At that time, however, it was commonly believed that expressing the cDNA in living organisms would not produce fluorescent GFP, because the formation of its chromophore requires the reactions of condensation and dehydrogenation that are not expected to occur spontaneously. In 1994, however, Dr. Martin Chalfie of Columbia University tried to express the cDNA in *E. coli* and a nematode worm, and he and his colleagues unexpectedly observed the fluorescence of the expressed GFP. The results suggested GFP, and other proteins linked to GFP, could be expressed in living organisms to observe their behavior. Dr. Chalfie’s work attracted the interest of many people, triggering rapid progress in the applications of GFP. Dr. Roger Tsien of University of California, San Diego, engineered GFP by modifying the amino acid residues surrounding the chromophore, producing many different fluorescent proteins that emit various colors, from blue to red. Today, GFP is widely used as a fluorescent marker of protein molecules and cells, and it is an essential tool in the study of biology, physiology, and medicine. GFP has been used also in other fields, such as the detection of cadmium, zinc, and explosive TNT and fumes (Zimmer, 2005). The range of applications of the fluorescent proteins is beyond imagination.  **After my retirement**  I retired from the Marine Biological Laboratory in 2001. Because I wanted to do some more experiments and also I was still supplying aequorin samples to people upon request, I moved all my laboratory equipment and chemicals to my home, where I set up my Photoprotein Laboratory. My retirement symposium, “GFP and Aequorin,” was held at the MBL’s Lillie Auditorium on July 27, 2002, through the kind arrangement of Dr. Shinya Inoué, a world authority on microscopy. Among the attendees were Martin Chalfie and Roger Tsien. I started to write a book for the next generation students who want to explore the chemistry of bioluminescence. The book *Bioluminescence: Chemical Principles and Methods* was published by World Scientific Press in 2006. The book contains a comprehensive overview and chemical information on all known bioluminescence systems, comprising 35 different types of bioluminescent organisms.  The summer of 2004 was splendid. In July, I received the Pearse Prize from the Royal Microscopical Society for the discovery of GFP. In early August, I gave an invited lecture at the International Bioluminescence and Chemiluminescence Symposium. In the end of August, I attended the symposium, “Calcium-Regulated Photoproteins and Green Fluorescent Protein”, which was held in my honor at the Friday Harbor Laboratories as part of the lab’s centennial celebration. At this symposium, almost all the well-known researchers in bioluminescence and related fields gathered from all over the world, including Martin Chalfie, Roger Tsien, Shimya Inoué and Atsushi Miyawaki. I was happy to see many of my old friends, though I was a little sad to observe that the sea at Friday Harbor was steadily being polluted. In 2006, I received the Asahi prize, one of the most prestigious prizes in Japan.  I would like to add a note on the jellyfish *Aequorea* at Friday Harbor. Between 1961 and 1988, we traveled to Friday Harbor and back to the East Coast 19 times (13 of which were road trips) and collected a total of about 850,000 *Aequorea*specimens to obtain aequorin for my research. The jellyfish were always abundant during that period. Mysteriously, however, they suddenly decreased in number after 1990, and it became very difficult to collect even a few. The cause of this drastic decrease could be pollution of the sea bed by crude oil spilled from the tanker Exxon Valdez in 1989, or it could be a natural cause. If the disappearance of the jellyfish had occurred 20 years earlier, we wouldn’t have been able to learn the mechanism of the aequorin bioluminescence reaction, as well as the chromophore of GFP. |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** | [OS]  [Osamu Shimomura] Hello.  [Adam Smith] Oh, hello. Professor Shimomura?  [OS] Yes.  [AS] Hello, this is Adam Smith from the Nobel Foundation web site in Stockholm. Congratulations on the award of the Nobel Prize.  [OS] Thank you.  [AS] First off, where were you when you heard the news? I imagine it was quite early when you received the phone call.  [OS] Yes, at 5:00 AM when I was in deep sleep!  [AS] Did you wake up when they phoned?  [OS] Well, my wife woke up, and she told me, this is a phone from Stockholm.  [AS] Yes?  [OS] Then I knew, something wrong!  [AS] I imagine that you have had some idea that this might be on the way before?  [OS] Well, well, only thing with a call from Stockholm is possibly Nobel Prize.  [AS] Yes, yes.  [OS] No other business I guess.  [AS] Yes, yes.  [OS] At least, to me.  [AS] Exactly. So, your interest in bioluminescence began …  [OS] Yes, I purified a bioluminescent protein from a jellyfish. In 1961.  [AS] Exactly. So this was the isolation of green fluorescent protein.  [OS] No, no, no, no, no. Just luminescent protein; bioluminescent protein. I think people confuse luminescence and fluorescence. There are two kinds of protein in the jellyfish. One is a luminescent protein just we talked, that name is aequorin. Another one is a separate protein which emits green fluorescence. That is the subject protein in this Award.  [AS] Yes.  [OS] And I didn’t know any use of that protein, of that fluorescent protein, at that time, until Chalfie discovered in 1994 that it can be expressed in living cells. So I had no idea of the applications of green fluorescent protein for a long time.  [AS] So, first you isolated the bioluminescent protein.  [OS] Yes, that was my objective. My purpose.  [AS] And you had remarkable collecting expeditions when you were doing that project, because you had …  [OS] Yes, there were many difficulties and trouble. But anyway, somehow I found how to extract that protein. And after finding that, what we needed to do to study that protein is we have to get large amounts of that protein. So, we collected huge numbers of jellyfish by going to Friday Harbor, Washington, every summer.  [AS] And how many jellyfish were you having to collect?  [OS] Well, our … schedule was 50,000 per summer, in one or two months.  [AS] That’s an extraordinary collection!  [OS] And only for one year.  [AS] Yes, and then you did this every year?  [OS] Yes, we have been 19 years. Nineteen summers. And we collected a total of 850,000.  [AS] Good grief! This is *classical* biochemistry.  [OS] Yes, of course that’s classical biochemistry, not genetics or something like that.  [AS] Yes. Do you think that there are still many undiscovered molecules in nature which emit light?  [OS] Yes, there are many, many. Interesting, at least to me. But the problem is that … I talked many times since this morning … young people try to avoid this kind of subject.  [AS] Why do you think that is so? Why do they stay away from …?  [OS] Because it’s difficult.  [AS] Uh-huh, uh-huh.  [OS] They prefer easier research. And they prefer research subjects that you can see the results; that you are sure to get the results. If, you see good results often, and important results often come out from unknown research.  [AS] Yes, this Nobel Prize is a classic example of research in one field yielding results in another field in a completely unexpected way.  [OS] Yes, but the point is that I don’t study, I don’t do my research for application or any benefit. I just do my research to understand why jellyfish luminesce, and why that protein fluoresce?  [AS] So, how would you appeal to young people, or what advice would you give to young people who wanted to enter the field?  [OS] Young people, study whatever if they are interested in that subject. But don’t give up on the way until they finish the subject. Also, good subjects have a lot of difficulty. If one gives up, on the way; that’s it, that’s finished. To get success, everybody has to overcome any difficulty on the way.  [AS] I gather you are now retired from Wood’s Hole, but you still have a laboratory in your basement in your house?  [OS] We call it a basement.  [AS] Right. And what are you working on now?  [OS] At this moment, I’m too busy for doing experiments. I don’t have much time. And this time, I think it’s hopeless to work out of the laboratory for the next several months, I guess.  [AS] I’m afraid, yes, your life has taken a new turn, yes.  [OS] Hopeless, yes. But anyway, for the past two or three months I was just working on writing papers, and also helping other people.  [AS] One last question, please.  [OS] Yes, yes.  [AS] I have read that, as a child, as a teenager, you temporarily lost your vision after the bomb fell on Nagasaki.  [OS] No, I understand what you mean. When you encounter a very strong flash, you don’t see anything for 30 seconds or so. That’s not a real loss of vision. The temporary loss of sight. I was about 12 kilometres away from Nagasaki. Of course I had seen the flash of light, and the strong pressure wave, and also I had black rain.  [AS] Yes.  [OS] I was soaked by black rain.  [AS] Yes.  [OS] So, I was contaminated by the radioactivity, a lot of strong radioactivity. But fortunately still I’m alive.  [AS] Yes. So, do you have any plan for how you might celebrate the award when you finally …?  [OS] [Celebrate? I’d like to have a good sleep tonight, but that may be impossible!  [AS] I fear so. I think that people will be hounding you for days and days to come, yes.  [OS] Oh.  [AS] Anyway, I hope you do find time to celebrate at some point. Thank you very much indeed.  [OS] Okay.  [AS] Thank you for speaking to us.  [OS] You are welcome. Bye.  [AS] Bye, bye. |
| **Interview** |  |

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| **Biographical** | I was born on January 15, 1947 in Chicago, Illinois, the oldest of three sons of Vivian and Eli Chalfie (Figure 1). In trying to reconstruct the events that led me to this opportunity to write an autobiographical essay, I realize how much chance, luck, the influence of others, and, in some cases, my own pigheadedness influenced my life. I have tried to show how unexpected this journey has been and, where possible, to find links to Chemistry (one of the ironies of this Prize).  Three of my grandparents were immigrants. My father’s parents had immigrated to the United States from the town of Brest-Litovsk on the Russian-Polish border and settled in Cincinnati. My paternal grandmother, Esther, died before I was born and all that I know of her is that she was the cook in the Manischewitz Company executive dinner room in Cincinnati and that my father was devoted to her. I have a picture of him standing proudly beside her, but I do not have any of her recipes. I have only a faint memory of my paternal grandfather, Benjamin, who died when I was five. I remember going for a rowboat ride with him and his giving me the paper ring from the cigar he was smoking. He came to the United States to avoid being recalled for duty by the Russian Army during the Russo-Japanese war. He had trained to be a cabinet maker (I have a few of his tools), but in Cincinnati he worked as a tailor.  My father was born in 1910, a year or so after my grandparents settled in Cincinnati. I do not know much about my father’s early life except that he clearly had an aptitude for music, teaching himself how to play mandolin and then banjo and guitar when he was quite young. He went to a two-year trade school instead of high school, but I always thought of him as very worldly-wise and intelligent. He wrote wonderfully crafted and humorous letters and had a handwriting that I still wish I could imitate. He was nineteen when the Great Depression began and already a professional musician. In fact his income as a musician supported his family and allowed his younger brother, Sam, to stay in school and eventually go to law school. He became the staff guitarist at one of the country’s largest radio stations, WLW in Cincinnati, and later the guitarist with the Russ Morgan Orchestra. Throughout his life he had a great intuitive feel and love for music. While at WLW he invented a radio quiz program called Tunecode, which he patented. As he envisioned the program, contestants would be asked to name a series of popular songs after hearing short excerpts from them. They then needed to take the first initials of all the songs and rearrange them into the name of a famous person. As far as I can tell, my father was one of the few people in the world who could actually do this. I do not think that the show was ever produced.  My mother and her mother, Madeline Friedlen (Figure 1), were born and raised in Chicago, Illinois. My maternal grandfather, Meyer Friedlen, was born in Moscow, but his parents emigrated when he was a month old. I know little about him because he died well before I was born. My mother adored and revered her mother. Both women were brilliant, hard-working, and very independent. During the Depression Madeline started her own business, a dress-manufacturing company named Mountain Home Smart Apparel (the name allowed her to use up a set of labels left over from a failed sweater-making venture of my grandfather’s). I remember her as someone who was always loving and always interesting, whether she was telling me about how much she admired Eleanor Roosevelt, trying to get me interested in studying metallurgy (which she thought would be the science of the future), or giving me a copy of [Herman Hesse](https://www.nobelprize.org/nobel_prizes/literature/laureates/1946/)‘s *Siddhartha*. I also remember coming out of Temple during the High Holy Days and hearing her say that the entire story about Abraham’s willingness to sacrifice Isaac was ridiculous. She thought that any person that would give up their child for any reason was just nuts. This was my first introduction to questioning religious belief, and it stuck with me.  My mother was born in 1913, and I think she had probably been an excellent student, although she never told me. She was very proud of having graduated from Senn High School in Chicago. She enrolled in the University of Chicago, which she attended for a year and a half. At the start of the second semester of her sophomore year, however, her parents told her that they could no longer afford the $100 tuition. Without hesitation or complaint, she put away her books and joined her parents that day at work. My mother and grandmother worked together until my grandmother became ill in the 1960s. For most of the time that I was growing up my mother was the head of the business. She was one of the most organized people I have ever known, and I regret that I did not inherit this ability. I do, however, have her love of learning and her independence.  It was my father’s chronically bad teeth that led to my parents’ meeting. My father had enlisted in the Navy during World War II, where he was a musician second class; some mischief he was involved in or insubordination that he never explained to me lost him his first class ranking. He would play his guitar and banjo at officers’ club and a few times march in the Navy band (I think he had to carry a drum), but ended up on a battleship in the Pacific. For a while he was stationed at the Great Lakes Naval Station near Chicago. Problems with his teeth caused him to go to a dentist in Chicago, who invited him to a USO breakfast for Jewish service men and women in Chicago called the Lox and Bagel Club. At the breakfast the dentist introduced him to my mother and grandmother who were USO volunteers. My father shipped out soon after this on the USS Missouri, witnessed the signing of the Japanese surrender, and returned to marry my mother. He did not know what he wanted to do at the time, only that he no longer wanted to travel with the orchestra. After a few years he joined Mountain Home and helped run the factory and sold the line on the road.  I would often go with my parents to the office, make fabric swatch cards, and print out the tickets that would accompany the dresses as they were being made. I really got a chance to see my parents’ style of business, however, in 1970, when my father had surgery for colon cancer and I, having finished college, took the line on the road for him. My parents believed in building up long term relationships with the shops they sold, so all I had to do was walk in with the samples, show the latest dresses, and fill out the order form. The buyers already knew what to expect and what they liked. I was grateful that I did not have to do any selling (I would not have been able to in any event). More importantly, I got a chance to see the trust and respect all the buyers had for my parents.  My upbringing and that of my brothers Ed and Alan was comfortable, ordinary, and from the age of eight, when my parents moved from Chicago to Skokie, Illinois, suburban. My parents had moved to the suburbs to find better schools for their children. My brothers and I rode our bikes all over the place, played baseball (poorly), and swam at the local swimming pool. We also mowed and edged the lawn in the summer, raked the leaves in the fall, and shoveled snow in the winter. I now live in an apartment to avoid these chores. In general, life was enjoyable and uneventful.  And we were loved and always had our parents’ support. My brother Ed has reminded me that my mother predicted, when we were very young, that I would go to Harvard and that he would go to MIT, which we did. This attitude was not one of pushiness on my mother’s part, but an extreme pride in her children. Although out of chronological order, a good example of my parents’ different styles of affection is seen in an event that occurred when I was in graduate school. During a visit home for the Thanksgiving holiday, my mother asked me if I wanted a tennis racket. The racket was part of a promotion recently started by their bank. I told her that I wasn’t interested in learning tennis, I didn’t want a racket, I had much too much lab work to do, and I didn’t really need to learn how to play tennis to get a girl friend (the real reason for her offer). I thought that the issue was closed, but soon after I returned to the lab I received a package with the tennis racket, t-shirts, shorts, and socks. The package also contained a note that I regret I no longer have. On the note my mother had written: “Marty, we really loved your visit and hope that you love your new tennis racket. We love you, love you, love you, love you, love you [or something like that]. Love, Mom.” Under this my father had written: “Get your own balls. Dad.”  When I was growing up I became proficient at two activities that have given me much enjoyment throughout my life, as well as a feeling of uniqueness. The first was swimming. I had learned to swim at day camp and turned out to be good at it (I was fairly hopeless at other sports). I remember being eager to go to high school because the school had a swimming team, and I could finally participate in a sport that I could do well in. I also remember thinking after a particularly long practice of unbroken swimming in the high school’s bromine-containing pool that Hell had to be a place where you swam laps forever. Nonetheless, I swam (usually butterfly) throughout high school and college. I have swum off-and-on ever since.  My second activity was playing classical guitar. When I was twelve, my father gave me a Gibson C1 Classical Guitar, and taught me how to play for about a year (Figure 2). He was an amazingly good teacher, who never got impatient with my ineptitude. I wish I had his teaching skills. Although I went on to take more formal lessons (with Richard Pick, a well-known teacher at the time), I cherish the fact that my father was my first teacher and all the hours we spent playing duets together. I still play and get immense enjoyment from the guitar, though I do not have his skills. And I wish I had talked with him more about playing. My father suffered from dementia in the last years of his life, but continued to play guitar. On a visit home I gave him some guitar versions of the Bach cello suites, which he would play for hours a day. On a return visit, he told me that he thought this guy Bach was terrific. I realized that with his memory going, he was rediscovering Bach every day, which was the one consoling consequence of such a horrible condition.  I was interested in science or at least nature from an early age, learning the names of planets, cutting cartoons with facts about animals out of the newspaper and gluing them into a scrapbook, and, with a friend when I was five or six, trying to design a submarine. I know I had a child’s microscope and a chemistry set. When I was a postdoc, however, I finally realized how deficient my early experiences had been. I, alone of my colleagues (or so it seemed), could not boast of that ultimate young scientific achievement of almost blowing up my home trying to make fulminate of mercury or gunpowder. I do remember, however, sneaking into the chemistry supply area in high school to get ammonium dichromate to make flaming “volcanoes,” so maybe I do qualify.  What I did do a lot as a child was read, and I particularly remember reading all the “Hardy Boys” books, a set of history books call the “Landmark Books,” and a series of science books called the “All About Books.” My mother saved many of these books, which I now have: *All About the Planets*, *All About Insects*, *All About Rocks*, and *All About Dinosaurs,*among others. The last must have made the biggest impression on me because it was the only book whose author (Roy Chapman Andrews) I remember. Unfortunately, I no longer have a copy of the volume entitled *All About The Changing World of Chemistry* that I praised in a book report I wrote in fifth grade. Either my spelling was quite horrible at this time or I thought the subject strange and deadly because I referred to Chemistry as “Chemistery” and “Chemitery” in the report.  None of the standard high school science courses made much of an impression on me, but I did enjoy the Advanced Placement Chemistry course I took in my senior year. This course had only eleven students and was taught by a rarity for our school, an exchange teacher from England, Mr. Leslie Sturges. Mr. Sturges taught a very relaxed but rigorous course and gave us a lot of freedom. I remember we would take a break in the middle of our two-period long exams where the eleven of us would attempt to sing Tchaikovsky’s *1812 Overture* (cannons included) and our own version of a song from the movie *Mary Poppins*, which had been released that year: “Just a Spoonful of C12H22O11 Helps the Medicine Go Down.” We were nerds before it was fashionable. Recently, a member of that class sent me a picture from our senior yearbook showing that I was a member of a student club called the Chemistry Advisory Board (Figure 3). When I first looked at the picture, I had no idea I had been in any club like that. Then I realized that all the people in the picture had been members of the AP Chemistry class, and I remembered that one of my classmates had complained to the yearbook editor that he was not in enough pictures. He found that a club was considered official, and hence eligible for a picture in the yearbook, if it had met for at least one hour during the school year. We probably sat around for an hour, sang our chemistry-related songs, told jokes, and then had the picture taken to be published with an impressive caption for posterity.  I entered Harvard in 1965 not really knowing what I wanted to do. This confusion seems to have lost me a fellowship. G. D. Searle and Company, the pharmaceutical firm, had their home office in Skokie, and they gave a fellowship each year to a graduate from my high school that was going to major in science in college. My brother Ed reminded me that I was interviewed for this fellowship, but felt compelled to say that I was not sure what my major would be and could not even guarantee that I would major in a science. I was disqualified. Apparently, when I got back from the interview and told my mother what I had said, she remarked that total honesty might not be the best policy.  In any case, when I started at Harvard, I took second and third year calculus in my first year, mainly because I was very impressed by a wonderful professor (Jerry Kazdan). I flirted with the idea of majoring in Math, but soon discovered that I did not have the intuitive grasp of the material that I thought I needed. I then decided to become a Biochemistry major because the subject matter felt more exciting than a Biology major and because it required a broad range of courses, and I could satisfy some of the requirements with the math courses I had already taken.  I realized that if I was going to major in Biochemistry, I needed to have some laboratory experience. My first research experience was in the lab of Dr. Paul Kohn in the Biochemistry Department at the University of Illinois at Chicago during the summer between my sophomore and junior years. He was interested in synthesizing furanosyl nucleosides (purines and pyrimidines linked to six carbon sugars with five member rings) as potential antitumor drugs. I do not recollect whether I was successful in the lab, but I suspect I was not. In fact, I have only a few memories from that time. Paul insisted that everyone take a break at three in the afternoon. I remember all of us going dutifully as a group to the cafeteria, but I also remember being disappointed that the usual topic of conversation during these breaks was not science, but property taxes. I also remember trying to enliven the lab by putting a quote of the day on the lab blackboard (most were fairly silly).  My first real research project came during the next summer, and that led to my dropping out of science. I wanted to do research for a senior thesis and had arranged to work for Klaus Weber at Harvard. Klaus wanted me to analyze the active site of the enzyme aspartate transcarbamylase by chemically modifying different amino acids within it, and gave me a bench in a student lab. I was alone in this lab and had no idea what I was doing. Looking back on this period in my life, I believe that I was too afraid to ask for help, thinking that I should be able to do everything by myself. I should have asked more questions and sought more guidance. In any case I tried doing experiments all summer, but nothing worked. At the end of August I went to Klaus and asked him what I should do next. He said I should try the experiment one more time and if it did not work, I should abandon the project. I tried one more time and still failed. I did not enjoy failing and decided that a career in science was not for me. I spent my senior year taking non-science courses (except for one remaining Physics course that I needed for my major) and loving them.  My undergraduate education was both good and bad. On the one hand I felt intimidated by the many astonishingly smart people that I met at Harvard, and this made me less confident. I suspect that many people entering Harvard have a hard time living up to what they imagine is expected of them. I did reasonably well in my classes, but not great (my worst grades were in chemistry and physics). More importantly, I felt that I had to do everything on my own, because asking for help was a sign that I was not intelligent enough. I now see how destructive this attitude was, but then I assumed that this was what I had to do. On the other hand, the courses I took were challenging and stimulating, and they taught me to think about and draw conclusions from data. Useful skills for what I do now.  And Harvard provided the spark that eventually led me back into a career in biology. During my junior year, I took Cell Physiology from Woody Hastings. Woody, a pioneer in bioluminescence research and one of the early researchers studying GFP, who was a new and especially kind faculty member. One day I went to his office and asked if I could have a key to the biology library so I could study late at night. He immediately got up from his desk and walked down four flights of stairs to the main office and instructed the people there to give me a key. No one had gone out of his or her way like that for me before. I was very impressed.  I had entered the Cell Physiology course a week late and so could not take the lab. I wrote a term paper instead. The paper was on the role of cyclic AMP in the activation of sodium transport in the toad bladder, the transport being measured with Ussing chambers. I received a B– (I still have a copy of the paper) and didn’t think about the subject until three years later.  My college years (1965–1969) were a time of considerable student activism and experimentation. I was not immune to the changes that were going on around me. I was strongly for civil rights, against the Vietnam War, and owned a pair of black and red striped pants. I was not, however, much of an activist (I would have been classified as a liberal). Nonetheless, during my last semester at Harvard, I and virtually all of my friends went on strike after the University had allowed the Cambridge police to come onto campus and beat the student protestors. The initial confrontation had made the national news, so when I decided to boycott my classes, I called my parents to tell them my reasons. My parents were sympathetic, but did not want me to get in trouble (the fears of what had happened during the Red Scare of the 1950s made them caution me against joining any political organizations). Our conversation lasted more than an hour. At the end, my parents reluctantly agreed with my actions. Not willing to end our conversation at that point and trying to get a rise out of my parents, I said, “Mom, Dad. Be sure to watch the news tomorrow night, because if there is another confrontation, I’m going to be right there on the front lines” (something that I would not have done). My mother replied, “Marty. If I ever find out that you were anywhere where there was violence, I’ll murder you.” Our mutual laughter finished the conversation (Figure 4).  After college I had no idea what I was going to do with myself. At first I had the horribly naïve, arrogant, and totally wrong view that if I could not do well in science, then a social science would be a snap. As a result I had taken an introductory social science class during my senior year and intended to enroll in Harvard as a special student to study sociology. I soon learned that scholarship in sociology was not as easy as I imagined. I left the program after one semester with a much healthier respect for other academic disciplines. Still unsure what I should do, I had a series of short-term jobs: I interviewed people in hospitals to find out how they repaired their electronic equipment for a Department of Education study, substituted for my father selling dresses, did some draft counseling, and set up summer rock concerts in the parks of Cambridge, Massachusetts.  One year out of college I was hired to teach high school at Hamden Hall Country Day School in Hamden, Connecticut. I taught a broad range of classes in the two years I was at the school: chemistry, first-year algebra, and an introductory social science course. When the first school year ended, one of my fellow teachers, Barbara Beitch, who had a biology Ph.D., suggested that I talk with a friend of hers who had a lab at Yale Medical School about a summer job. I went to her friend, José Zadunaisky, and heard about his work. He explained that he was interested in active chloride transport in the frog retina and that he was studying the transport with a Ussing chamber. Remembering the Ussing chamber from the paper I had written for Woody Hasting’s class (but forgetting all the other details – which, of course, did not correspond), I asked if cyclic AMP was involved. He didn’t know, but remarked that someone else had asked him the same question the day before. He hired me, assigned me a different project, and then left for the summer to do his own research in France. With him gone, and enamored by my own idea, I hunted down the other person who had asked José about cyclic AMP, Arthur Neufeld, asked him how I could test for the involvement of cyclic AMP, and proceeded to do that experiment and not the one that I had been assigned. He suggested adding epinephrine (adrenaline) to the preparation to raise cyclic AMP levels. I set up the apparatus with a great deal of help from Stephen Klyce and Maurico Lande, two postdocs in the lab, added epinephrine, and the short-circuit current (a measure of the chloride transport) took off (Figure 5). I was elated. The experiment had worked. To me, the big difference between this experience and my disastrous summer at Harvard was that I had finally learned to ask for help. I continued to do experiments over the summer and also found considerable satisfaction in finding pertinent references in the library (the one skill I thought I could bring to these studies). José returned at the end of the summer and asked for the results of my experiments (we had not corresponded over the summer). I told him that I had not done the assigned work (much to his surprise), but I was able to show him what I had done. Fortunately, he liked the results, and this research led to my first scientific publications.  Having an experiment succeed really increased my confidence and my enjoyment of science. At the same time I was becoming disillusioned with teaching, not because I did not enjoy working with students, which I did, but because I felt I was ignored and dismissed by the school administration. I remember being told by a school administrator at a faculty meeting, “That is a good idea Marty, but we are not going to do that here.” I also found ironic that, contrary to common expectations, the scientists I knew were much more communicative and interactive than the teachers. The teachers were friendly people, but, perhaps because they talked all day in their classes, they were silent in the faculty room during their breaks. In contrast, the scientists in José’s lab, perhaps because they had spent long hours quietly working on their experiments, always seemed to be willing to take time to chat when someone came by. Perhaps I had just found a supportive home. In any event, these considerations and the naïve feeling that having a Ph.D. would be prestigious, led me to apply to graduate school. I was accepted into the Physiology Department at Harvard (I had applied to the Biology Department but they had transferred my application).  As a beginning graduate student, I was assigned a desk in a faculty member’s lab. Fortunately for me that faculty member was Bob Perlman (Figure 6). Bob had recently come from the National Institutes of Health, where he and Ira Pastan had discovered the role of cyclic AMP in catabolite repression in *E. coli*. At Harvard he was interested in catecholamine biosynthesis and secretion, particularly from the adrenal gland. My work on the effect of epinephrine on the cornea probably resulted in my assignment to his lab. I was given a desk right outside his office, and his door was almost always open. During my first year, when I was taking classes and had not yet started working in the lab, I spent a lot of time in the library reading reviews and other articles. Whenever I got an idea for an experiment, I would barge in on Bob to tell him about what I hoped would be a thesis project. Several times Bob would say that the idea was a good one and that coincidently he had just read an article in which the authors had already done the experiment. I was greatly discouraged by this turn of events, but Bob would tell me that I should be happy to have thought of a reasonable experiment. Somehow that was never quite as satisfying.  When it came time to choose a laboratory for my research, I rotated in two other labs, those of Tom Wilson and Sue Leeman. I learned much from both of them because both took a real enjoyment in their research, but Bob’s support was very important to me and I decided to do my thesis in his lab. Bob had learned that another Harvard researcher, Shields Warren, had generated an adrenal tumor (pheochromocytoma) in rats that only made norepinephrine. My project was to test a hypothesis of Richard Wurtman at MIT that cells of the adrenal medulla made epinephrine because they were bathed in high levels of glucocorticoids from the adrenal cortex and this induced the production of the enzyme that converted norepinephrine into epinephrine. I obtained a rat with the tumor from Warren’s technician, Rosanna Chute (who, because of her red hair, liked to be called Rusty Chute), transferred the tumor into new rats, and injected the rats with dexamethasone. The rats wasted away, but the tumors never made epinephrine. Another failed experiment. Fortunately for me, Bob suggested that I make cell suspensions from the tumors and study norepinephrine synthesis and secretion. Making the cell suspensions turned out to be quite easy (the tumors fell apart when pushed through a mesh), and the experiments proceeded fairly well.  Bob was constantly interested in our experiments and insisted that all his students and postdocs call him in the evening to tell him our results. I always enjoyed these conversations; Bob made me feel more like a collaborator than his student. This companionship extended to the writing of our papers. Every time we sent off a manuscript or had a manuscript accepted for publication, I would go into Bob’s office and we would each have a small beaker (5 or 10 ml) of Scotch whiskey in celebration. I learned much about writing from Bob, but when he wanted me to begin writing my thesis, he clearly thought that I had more to learn. To let me know it was time to start writing, he gave me a copy of Strunk and White’s *Elements of Style* and told me to read it from cover to cover. I still have the book above my desk.  My time in graduate school confirmed my opinion that the lab is a haven. I had many friends in the lab, especially Buddy Ullman, Jay Slater, Michele Carvotta, Debbie Hoadley, Jacqui Kitabgi, Lorna Role, and Karen Vaccaro. I also became friendly with a terrific group of faculty, students, technicians, and animal caretakers that got together almost every Tuesday afternoon when the weather was nice to play a very relaxed game of softball. This was really an excuse to have a beer; almost everyone had a can of beer at his or her position. Because most of these people worked in the Sex Lab (our name for the building called the Laboratory of Reproduction and Reproductive Biology), Bill Moyle and Jack Senier, the leaders of this group, insisted that the team be called the Nads so that we could cheer on our teammates by yelling, “Go Nads.” They even made a team t-shirt, which I still have.  Despite the fun and games of graduate school, I had to think about what I wanted to do for my postdoc. At first I considered going to another lab working on catecholamines, but I was not sure that I would learn much more in the area and I had no pressing ideas for experiments I wanted to do. Fortunately, I had a visit from [Bob Horvitz](https://www.nobelprize.org/nobel_prizes/medicine/laureates/2002/), who at the time was doing a postdoc with [Sydney Brenner](https://www.nobelprize.org/nobel_prizes/medicine/laureates/2002/) at the MRC Laboratory of Molecular Biology (LMB) in Cambridge, England. Bob and I had been friends in high school in Skokie and remained in touch through college and grad school. During this visit he wanted to talk with me about dopamine because he was interested in studying its action in the nematode *Caenorhabditis elegans*. I knew something about *C. elegans* because one of my roommates, Paul St. John, was a technician with Sam Ward, a former Brenner postdoc who established one of the first *C. elegans* labs in the United States. I liked hearing about Bob’s work with [John Sulston](https://www.nobelprize.org/nobel_prizes/medicine/laureates/2002/) elucidating the postembryonic lineage of the animal and the idea of spending some time in England, so I asked Bob if he thought Sydney would take me on as a postdoc. He suggested that I write Sydney. I was also encouraged by Bob Perlman, who said that he liked the idea that I would be working on a completely new system and that I would be working for Sydney, someone he himself had wanted to work with. Although Sydney’s brief reply said something about my working with John White, another staff member at the lab, I assumed that I was accepted and proceeded to apply for fellowships. I was fortunate to get a British American Research Fellowship given jointly by the American Heart Association and the British Heart Foundation, and I was particularly delighted with its acronym.  Since I had a few months free before I was to go to the LMB, Sam Ward kindly offered me a temporary place in his lab, which he referred to as the farm team. I looked at *C. elegans* for the first time at a tall biochemistry bench at which people usually stood to do their experiments. I sat rather unsteadily on an elevated chair, staring down a microscope for hours as I looked at the tiny worms moving on their Petri dishes. I was somewhat tense, because I wanted to do well. I worked intently, so much so that at night before falling to sleep I would close my eyes and see plates of moving worms. After a few days of this, I woke in the middle of the night from a dream in which I was writhing about saying, “Help – I’m a mutant,” to find myself with a debilitating muscle cramp that extended across my shoulders and down my arms to the elbows. I was unable to return to the lab for a couple of weeks, but finally came back and learned to grow *C. elegans*. (I now lecture everyone in my lab on the importance of how to properly view the animals.)  I had intended to work on neurotransmitters in *C. elegans*, but before I left the United States I went to the first international *C. elegans* meeting at Woods Hole and I acquired a new research project. I drove to the meeting with Bob Horvitz, and on the way he encouraged me to look at the work that John Sulston was doing on touch-insensitive mutants and to think about continuing that project. John had come to the meeting expecting to give a slide presentation about this work, but found on his arrival that he had been scheduled to present a poster. As a result the first picture I saw of John’s mutants was the 35 mm slide that he had taped to the window at Swope Hall. He was not going to continue the project, and it was too good to be abandoned. I was grateful to have the chance to continue the work.  Before I left Harvard another member of the faculty, excited about my going to Sydney’s lab, told me I was going to have a wonderful time. He also told me, however, that Sydney judged people very quickly and if he decided you were not worth talking with, you were finished. I arrived in Cambridge and went to see Sydney. I told him that I was interested in working on the genetics of touch and he thought that this was a good project. When he asked me if I had any questions, I asked him for an explanation of some part of his 1974 paper describing the genetics of *C. elegans* (something I always did with Bob Perlman). He looked a bit annoyed and didn’t really answer the question. I thought over what I heard at Harvard, suspected that I had done the unthinkable, and decided that my career in science was over. Fortunately, my initial fears were unfounded.  The LMB was an amazing place to do science, and, as many people have remarked before me, a postdoc is the very best time to do science. The lab was organized so as to optimize people’s research. In fact, the facilities were so good that you knew that the only limitation on research was your own imagination. I remember once going to the stock room to get an ultraviolet lamp that I needed for a chemical conversion and being asked by Mike Fuller, who ran the stock room, “Which wavelength?” In addition, postdocs were expected to find their own projects; their postdoctoral advisors never assigned a project. We talked a lot about experiments and made suggestions (as Bob had to me), but everyone was on their own to design what they did. As a consequence Sydney never put his name on any paper that did not contain experimental work he had done. As a result, Sydney is a coauthor on only one of the seven research papers that came from my time in his lab.  The most astonishing aspect of the LMB to me, however, was how everyone was deeply concerned about science. People talked about experiments at coffee, lunch, and tea and in our coffee room at all hours. And although molecular biology was considered the most important part of biology, people’s interests were more general. One day someone mentioned at morning coffee that the Cambridge astronomy department was going to show pictures taken by one of the *Voyager*probes, and about 35 people left to go see the film. People also made a point of reading and discussing scientific books (I particularly remember conversations about Stephen Jay Gould’s *Ontogeny and Phylogeny*and *The Mismeasure of Man*). I would often see friends from the lab Saturday afternoon at Heffers, the great Cambridge bookstore, looking for the latest books (although I should admit that our tastes were rather broad and not restricted to science).  Despite the terrific atmosphere at the LMB, it did lack one commodity: space. When I arrived at the LMB, I was given three feet of bench space next to a cubbyhole that contained our Nomarski microscope (later, when Bob Horvitz left for his faculty job at MIT, I was able to move to the slightly larger desk he used next to the window). I began by familiarizing myself with various mutant phenotypes using a demonstration collection that Bob had prepared for me. In the course of this introduction I actually found that a strain with a muscle mutation that caused twitching was also touch insensitive (presumably because it had habituated). I also started my first mutagenesis and began looking for touch-insensitive mutants.  One of the remarkable projects taking place in the lab at that time was the complete reconstruction of the *C. elegans* nervous system. Sydney had hired a spectacularly gifted electron microscopist, Nichol Thomson, who could cut and collect the thousands of serial section needed to trace the wiring of the nervous system, which was done by John White and Eileen Southgate. A separate room one floor below us housed this mammoth collection of serial electron micrographs. One day, thinking that I should see what the touch sensing cells looked like in these micrographs, I announced to everyone in the lab that I was going to look at “my cells” and would be down in the anatomy room. John Sulston had already found that these cells had unique bundles of very prominent microtubules (the cells were originally called the microtubule cells), so they were very easy to see in the micrographs. Having made this announcement, however, I had a problem, because once I looked at the pictures for a couple of minutes, I realized that I did not know what I should do with them. Too embarrassed to go back to my bench so quickly, I did the only thing I could think of: I counted the microtubules in each section and recorded the number. Then I graphed the number versus the position along the neuronal process. The graph was a jagged line that had many peaks and valleys. Having decided that I had spent enough time in the anatomy room, I returned upstairs to the lab where Jonathan Hodgkin, a new staff member, asked what I had been doing. I showed him the graph and he asked, “Is that what the microtubules are supposed to do?” I had no idea, but I soon found out that they were not supposed to act in this way. The common view was that microtubules all began at the cell body; the graph should have simply shown a decrease in microtubule number as one looked further from the cell body. Since the number of microtubules in the touch-sensing cells repeatedly increased and decreased along the process length, all were not likely to start in the cell body. Working with Nichol Thomson, who cut several new series of sections for me, I was able to show that microtubules did begin and end within the process, and was able to submit my first *C. elegans*paper. I was quite proud of the fact that the one skill I brought to this work was the ability to count to fifty.  When I was a graduate student Bob Perlman had ordered at least one hundred reprints of every paper, so when my microtubule paper was accepted, I asked Jonathan how many reprints I should order. He told me that at the LMB no one ordered reprints, but since I wanted some for future fellowship applications, I ordered the minimal number. Jonathan apparently thought that my action was hilarious, and began to make arrangements with Mariana Wolfner, a friend of his who was a graduate student at Stanford. Suddenly I started getting reprint requests for my paper, with a surprising number of them coming from Stanford. I even got a request card from [Linus Pauling](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1954/). I eventually learned that Mariana was the source of all these requests and had stolen the reprint request postcards from various professors. Unfortunately, Jonathan did not tell me about his prank until I had sent out many of the reprints. I imagine that Linus Pauling and the others were quite surprised to be getting reprints about worm microtubules.  I thrived at the LMB, and the experiments went well. Ironically, I had entered the *C. elegans* world just as Sydney was leaving it (he had several other interests he wanted to pursue). As a result, I had very few conversations with him about my work, but I always felt that he was supportive. The person I learned most from was John Sulston, who at that time was elucidating the lineage of male larvae and the embryo. John was an astonishing experimentalist, who always seemed to work out scientific ideas from first principles, all those ideas that are taught in introductory chemistry and physics classes. John is also one of the most moral and fairest people I have ever met. For example, I believe his later success in the *C. elegans* genome project stems directly from his desire to engage the entire worm community in an enterprise that emphasized sharing and openness. In addition to John, I collaborated with John White (who also taught me English slang, although I think he made up some of the terms), Nichol Thomson, Bob Horvitz, and Peter Evans (a friend from graduate school who had move to the Zoology Department in Cambridge). Together we worked on a wide range of problems. I isolated touch mutants, worked on microtubule structure, studied lineage mutants, investigated neural circuitry, and even did some work on neurotransmitters. I found the freedom to wander off into any direction very stimulating.  I made many friends at the LMB (Figure 7). In addition to the two Johns, Nichol, and Jonathan, who were staff members, we had a remarkable group of postdocs, many of whom still work on *C. elegans*. This group included Donna Albertson, Phil Anderson, Ed Hedgecock, Bob Horvitz (for six months), Jon Karn, Judith Kimble, Cynthia Kenyon, Sandy McLeod, Barbara Meyer, Tony Otsuka, Bill Sharrock, Kevin Struhl (for a short time), and, eventually, Andy Fire and Jim Priess. These people were brilliant, and I often felt that I had to play catch up to understand their conversations. I learned a lot from each of them.  I do not want to give the impression that all we did was work. The Frank Lee Center (with its pub, swimming pool, and squash courts) near the LMB, the Cambridge Arts Theatre and Arts Cinema, and several pubs (the Green Man in Grantchester and the de Freville Arms in Great Shelford – where I learned to play bar billiards) all helped make my five years in Cambridge very enjoyable. I swam at the Frank Lee with Jon Karn and Sandy McLeod and then much later with Bob Holmgren, a postdoc working on *Drosophila.*Jon, Sandy, and I realized we were one person short of a medley relay, and Jon tried to convince Sydney to make sure that the next worm postdoc was a backstoker, but that never happened. In my last years at the LMB, Bill Sharrock and I used to play our guitars in various folk clubs (all in pubs) around Cambridge. Folk clubs were still popular in England in the early 1980s, and we could play several times a week if we wanted. A typical session at a folk club would include a performance by an invited guest performer and then the rest of us would play. Having a voice that was capable of clearing the club, I usually played instrumental pieces.  During my last year in Cambridge, when I no longer had a postdoctoral fellowship, Sydney kindly made me a staff member. I really loved being in Cambridge and felt that I was working on exciting projects. Nonetheless, I realized that I could not stay there forever, and applied for faculty jobs, mainly in the United States. I was amazed when two visitors to the lab, Joel Rosenbaum from Yale and Ron Morris from Rutgers, offered to write letters on my behalf. They taught me a valuable lesson: that faculty members have an obligation to help their younger colleagues, not just the people from their labs. I am still grateful for their generosity and friendship.  Their letters and Sydney’s recommendation clearly worked because I was offered a position at Columbia University. I joined the faculty in 1982 and have remained there. Cy Levinthal was chair when I was hired, but I suspect that several members of the neurogroup (John Hildebrand, Darcy Kelley, Steve Schuetze, and, particularly, Eduardo Macagno) were helpful in getting me hired. At first I was a bit reluctant about living in New York, and during the first months as a faculty member, I complained to friends that I had made a horrible mistake. By six months, however, I told these same people that I could not imagine living anywhere else.  I continued to work on the *C. elegans* touch system, initially by amassing a much larger collection of touch-insensitive mutants. I was well funded and several people joined the lab. These talented students and postdocs and all the ones that followed were the real reason for the lab’s success. I find it difficult not to acknowledge all the contributions the people in my lab have made, but this biography is already too long. I hope they accept my apology for not naming them and my gratitude for all that they have done.  Unfortunately, I had acquired the habit, common to worm researchers in Cambridge, of not publishing partial stories, a habit that meshed well with my strong inclination to procrastinate. Since I was characterizing a very large collection of mutants, I did a great deal of research but did not publish my results for six years. My lack of publications was a great concern for the senior faculty, because they were worried about my chances for tenure. Eventually, I submitted manuscripts for most of the work, and the publications were considered sufficient for tenure in 1989. I remember with amusement a conversation I had with Cy during this time. He had gotten quite ill and was confined to his home. One day I visited him to tell him about a series of lectures that Sydney had just given in the department. Cy interrupted my recounting of the lectures to tell me that the letters had arrived for my tenure review and that he was “surprised, but delighted, that they were so good.”  By 1989 we were well on our way toward cloning the genes needed for touch sensitivity. Of course, as I have related in my [Nobel lecture](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/2008/chalfie-lecture.html), this was also the time that I first heard about GFP. The story of our GFP experiments is told there. That work was very exciting, but actually took up a relatively small amount of our time. Over the subsequent years, we continued to work on touch, and I was fortunate to have several more people push the work forward, especially the identification of the mechanosensory transducer.  The year 1989 was also the beginning of the best part of my life: my marriage with Tulle Hazelrigg and the eventual birth of our daughter Sarah. Since this is supposed to be a scientific biography, I will let this part of my life remain private. I do want to say, however, that I am grateful for all the love, humor, and music that have filled our lives. Well, maybe not always the humor; April Fool’s Day remains the most important holiday of the year and sometimes things get rough.  Writing an autobiography seems to call for a summing up of the lessons of one’s life. Other than saying that, so far, my life has been a rather undirected and surprising trip, I don’t feel I have much to say. As to the future, there are more experiments to do, music to play, people to enjoy, and surprises to catch me unaware. |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** | [MC]  [Martin Chalfie] Hi.  [Adam Smith] Hello, this is Adam Smith.  [MC] Hi Adam.  [AS] Hi. Thank you very much indeed for making time for this. It must be a very busy day. I’ve read on the news wires that you didn’t actually receive a call from Stockholm this morning?  [MC] I did not. Well, I did. I didn’t answer it because I slept through it.  [AS] Reasonable enough – I guess it was early in the morning.  [MC] Well, it also has to do with the fact that the normal ring on my home phone had been changed inadvertently a couple of days ago and I never took the time to change it back to the regular ring, so it was actually quite faint. So when I actually did finally wake up I actually heard something ringing, and I thought, “Ah, that must be somewhere else.” Another apartment!  [AS] Well I guess that in itself says that you weren’t expecting the news, so there you go.  [MC] Well, I … you know. You know that when October runs around that there are people that are considered for things, and you wonder, and especially when people come to you and say “Oh, you know, do you think this might happen?” So, it’s not that it comes out as a bolt from the blue, but it certainly is, you know, it’s not something you expect but it’s also, you know, you don’t really anticipate it’s going to happen so it’s always a surprise. But, on the other hand, it’s also not something completely new either.  [AS] How did you actually found out that you had …?  [MC] Ah. This is a sort of ridiculous situation, but sort of funny. I woke up at ten after six, and I realised that they must have given the Prize in Chemistry, so I simply said, “Okay, who’s the schnook that got the Prize this time?” And so I opened up my laptop, and I got to the Nobel Prize site and I found out I was the schnook! This was very funny to find. Now the other two guys are really terrific scientists, but I … so this is a very big and very nice surprise.  [AS] What a lovely way to hear. And, yes, I imagine you’re pretty much losing control of your life now as everybody’s …  [MC] For the day I think, yes.  [AS] Yes, yes.  [MC] So, how are you connected with the Nobel Prize organization?  [AS] So, we are the web site that you looked up. We are Nobelprize.org.  [MC] Ah, okay. Terrific.  [AS] If we just turn to the work for which you were awarded, you had the idea of using green fluorescent protein in species other than the jellyfish in which it was found, to label the expression of specific proteins, or indeed label specific cell types.  [MC] That’s correct.  [AS] And it was Doug Prasher who cloned it, and then you had the idea of taking it from him and expressing it in your systems, in *C. elegans*?  [MC] Yeah, I would put it slightly … I would use the wording slightly differently. I had heard about GFP in a seminar that I was listening to in about early 1989. I can’t remember the exact date. But I … and I tried to find out who was studying this and whether we could work on it, and I talked to Doug, and he had ideas that this would work as well, and he was wondering about it, and that was certainly the motivation he had in cloning this gene. And so we worked, we had a very excited, about a one-hour, conversation on the phone, and the upshot of that was that we were going to collaborate, and see if this would work in *C. elegans*. And through a couple of mishaps, it took us a couple of years to actually get back in touch with one another, but in 2002 we did. Not 2002, 1992 we did. And we got the clones from Douglas, and a very good graduate student, Ghia Euskirchen, put this in *E. coli*, and we had green fluorescent *E. coli* within a month.  [AS] Yes, yes. So, you mentioned that there was a couple of years delay in there, and given how incredibly powerful this technique has become, on reflection was it quite lucky that nobody else picked up on the idea while that was taking time?  [MC] You know, some people did. This is an interesting thing. I’ve subsequently found that at least three different people tried to get GFP to work, and had actually … See, Douglas … I’ll tell you a little bit about the intervening time. The intervening time after Douglas and I talked, I got married, and the woman I married was a Professor at the University of Utah. Her name is Tulle Hazelrigg. Now she’s here at Columbia. And, when I married Tulle, I decided to take my sabbatical working with her, so we could be together. And it was during the 9 months that I had of my sabbatical, in Utah, that Douglas finished the cloning. When he finished the cloning, he got in touch with me, or he tried to. He called my lab here at Columbia University and they said I wasn’t here, but I think they gave him the phone number for the University of Utah lab. But someone must have answered the phone at the University of Utah and said something to the effect of “Marty Chalfie, never heard of him.” And so Douglas Prasher got the idea that I had dropped out of science. And so, he didn’t tell me because he didn’t think I was interested anymore. So, it wasn’t until 2002, that …  [AS] Or 1992?  [MC] I’m sorry, I keep saying 2002, you’re right, thank you. It’s been an interesting day! … In 1992, that in September I had a new graduate student come and join my lab, Ghia Euskirchen. And Ghia and I talked; she had had some previous Masters degree work in which she had looked at fluorescence. And I said, “Well, I have this wonderful idea, or I hope it’s a wonderful idea, about using a fluorescent protein in cells. But the person I was supposed to collaborate with never got back to me, never called me back. So maybe we’ll have to look at something else. But the University now has just put Medline, the Medline database, on our computers. Let’s go look and see if they have anything about fluorescent proteins.” And what came up was Douglas Prasher’s paper about the cloning of the cDNA for green fluorescent protein.  [AS] Perfect timing.  [MC] And I said, “I wonder why he didn’t get in touch with me?” I subsequently learned he thought I was out of science. Anyway, we immediately ran downstairs to the library, got the article that he had published, and got in touch with him, and that’s what started our work. But other people also saw that article, and were also … You know, this is an idea that I’m sure has occurred to many people. And so, when these other people got it, there was one other thing that needed to be done, and no one would have really predicted this ahead of time. It was a stroke of luck on our part. And that is, that people in the field that were studying fluorescent proteins, particularly GFP, had the knowledge that the GFP fluorescence was made because of a rearrangement of the backbone of the protein; the peptide backbone. And they didn’t know how that peptide rearrangement – the peptide backbone rearrangement – took place. And so they said, “We don’t know, it might take one more enzyme to do this, or two or four, or 100. We don’t know how this is made.” But the thought was, that it would not work on its own. Well that was the bet that we were hoping to … So if you have sort of the weight of the field saying to you, “This should not work on its own”, and you do an experiment, and it doesn’t work, you, I think could be allowed to say “Hmm, maybe it doesn’t work. Maybe it does need something else.” And so, the three other cases of people that I know that tried this, tried it, and it did not work. And we …  [AS] So they thought they were missing some auxiliary factor.  [MC] They could have interpreted it like that. But what it turned out is the way they made the construct. And what they did is they had taken Doug Prasher’s clone, and cut out the appropriate-sized fragment from the DNA. But that fragment had extra little bits of sequence on either end. And apparently, it’s those sequences that were poison, so it never got made. So the extra DNA interfered with the protein production.  [AS] And you couldn’t have known that really.  [MC] And you couldn’t have known that. But we did it a different way. We simply amplified exactly the coding sequence from the clone, and didn’t have any of the extra DNA. So when we put our things in bacteria, it worked.  [AS] Right. It fluoresced.  [MC] So it was just great good fortune that we, that the procedure that I chose us to follow, was the one that happened to allow it to work. And the other three that I know of found it going in the other direction, or not being expressed.  [AS] A classic case of lucky experimental hands, but …  [MC] Yes.  [AS] … some people have them. And, it’s such a powerful technology. Are there any particular favourite applications that spring to mind?  [MC] You know, I have, there have been many wonderful applications, and there continue to be other applications. I, what I can tell you is not so much what are my favourites, but certainly the things that we have used in my lab that have been really of great help in the studies that we’ve done. Mainly I study the sense of touch, and what the molecules are that transduce touch. And I use mutants in the nematode *Caenorhabditis elegans* to look at that problem. And so, we have used GFP to ask in which cells genes are turned on. We’ve asked the question of, when we have a gene turned on and a protein is made, where does the protein go in the cell, and we’ve found some interesting patterns. We’ve used GFP to label the cell so we could then mutate the animals and look for defects in the development or growth of the nerve cells, whether they branch inappropriately. And other people have used it to ask questions of whether they make synapses inappropriately or not. We’ve also used GFP to label cells for electrophysiology. This animal is extremely tiny, and so it’s very hard to get an electrode to record electrically from a nerve cell. But there are methods that have been worked out, that one can look at this, one can be able to record from the cells, but only if you know what the cell is, and you can see it. And the way we see it is through GFP.  [AS] Right, and …  [MC] And then finally, we’ve been able to use GFP to label the cells, so that we could then take apart the embryo, and isolate the fluorescent cells away from all the other ones, so you can have just a pure collection of the cells we’re interested in to ask something about the nature of these cells and what they’re doing.  [AS] All quite amazing. And the worm you study is actually transparent, so that you can label cells and then see them in the living world.  [MC] Oh, absolutely. And in fact, I have said for many years now that the only reason that I worked on GFP is that for several years before I worked on GFP, I said that one of the great things about working on *C. elegans* was the fact that it was transparent, and so when I first heard that seminar describing GFP, and realised, “I work on this transparent animal, this is going to be terrific! I’ll be able to see the cells within the living animal.” That was really great. That really was the motivation.  [AS] Right, right. And so, given the explosion of interest in the field, for those who were now thinking of coming into it, what advice would you give?  [MC] Which field do you mean? The field of fluorescent proteins, or …?  [AS] I mean the field of using fluorescent proteins to label cells and proteins.  [MC] So GFP has now become an almost universally used tool. So, as … But I believe that there’s probably – and I’m not really the best person to talk about the future of the chemistry of this molecule and manipulations of it. But I’m always astonished that just about every year someone has come up with a new variant or a new idea where they use GFP. So people’s ingenuity always outstrips mine in terms of what can be done. And people have made remarkable discoveries about it. I think that the important thing is people should know is that it’s a tool that has been manipulated in a variety of ways to be an even more useful tool, and then to think about how that works, and what they want to do with it. I think that, as people see the examples of work, for example, that Roger Tsien has done, to make these really wonderful derivatives of GFP, or that use GFP. These tools he has made like the chameleons, for example. These are wonderful tools, and it’s by the ingenuity of using a fluorescent protein, coupled with another idea. And several people have had these wonderful ideas that have enlarged the usefulness of the molecule. So people, if they get interested in it, I think it’s up to their imagination of what they want to do, as it is in any aspect of biology, chemistry or physics.  [AS] That’s a nice thought. Okay, well, when you come to Stockholm in December, we get the chance to record a video interview with you, and so hopefully we’ll be able to speak for longer then.  [MC] That’s wonderful. I look forward to it.  [AS] I look forward to it too. And just one last question. Do you have any thought about how you might celebrate once you get off the phone with people like me?  [MC] Well, we had a nice reception here already in the department, and we’re going to have some friends over this evening, and I’ll try to wake up tomorrow and say that it wasn’t a dream! I think that’ll be the celebration. I think, I guess I could say that the real celebration I’m going to do is I have to write a grant by the end of the month, so I think I’m going to have to start getting to work on that grant application.  [AS] Yes, I’ve heard from previous Laureates that they’ve sometimes asked for delays given what’s just happened to them, and the authorities have said “No way!” So…  [MC] Yes, I’m not even anticipating asking, I know I just have to get the thing written. I don’t think they care!  [AS] Okay, best of luck.  [MC] Thank you very much. Nice talking with you.  [AS] Thank you so much. Bye.  [MC] Bye. |
| **Interview** |  |

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| **Biographical** | **Ancestors and family** My father, Hsue Chu Tsien (1915–1997), came from the “scholar-gentry” class in Hangzhou, China, where “Tsien” (now more commonly transliterated as Qian) is quite a common surname. Apparently in 907 A.D., Qian Liu, my paternal ancestor 34 generations ago, established a kingdom around Hangzhou and fostered its growth through many civil engineering projects. This fiefdom prospered peacefully under the rule of Qian Liu and his successors until 978, when they surrendered to the Sung dynasty to avoid bloodshed[\*](https://www.nobelprize.org/prizes/chemistry/2008/tsien/biographical/#one). I had thought that descent from Qian Liu was an obscure secret of our family, but this factlet somehow found its way onto Wikipedia through no fault of mine. Furthermore, this genealogy is hardly much of a distinction given that everyone in principle has 234 ancestors from 34 generations ago. 234 (about 17 billion) vastly exceeds the earth’s population in the 10th century, so practically everyone, at least from that part of China, probably has Qian Liu as an ancestor, even if not so strictly through the Y chromosome. By far the most famous Tsien in modern times is Hsue Shen Tsien or Qian Xuesen, the aeronautical engineer who was deported from the U.S. during the McCarthy era and then became father of the ballistic missile program of the People’s Republic[1](https://www.nobelprize.org/prizes/chemistry/2008/tsien/biographical/#not1). He and my father were first cousins. Several other Chinese-American bioscientists, including Robert Tjian, now President of the Howard Hughes Medical Institute, and Shu Chien, a prominent bioengineer at UCSD, also have the same Chinese surname as mine and are likewise descended from Qian Liu, so we are distant relatives.  Dad too was excited by flight and airplanes, which were the cutting-edge technology of his day. In the 1930s he won a national scholarship (Tsinghua) to study in America. He went to MIT’s mechanical engineering department, where he obtained a Master’s degree for research on aircraft engines, including a proposal to boost the thrust during takeoff by injecting water into the exhaust to become steam. Before he could pursue any further studies in America, he had to return to China to serve in the Nationalist (Kuomingtang) Air Force. One of his best friends and fellow engineers, Yao Tzu Li, had an attractive and intelligent sister, Yi Ying Li, who had trained as a nurse at Peking Union Medical College, the most prestigious of Chinese medical institutions. My father courted her eagerly by letters even before they had ever met in person. When they finally did meet, she found him socially awkward and overly impressed with his own academic prowess[2](https://www.nobelprize.org/prizes/chemistry/2008/tsien/biographical/#not2). Despite her lack of romantic feelings for him, she agreed to marry him, perhaps because she doubted her own prospects in wartime China. Their first son, Yongyou, was born in March 1945. Soon thereafter, Dad was ordered to go to the U.S. as a liaison officer to try to extract more military aid for the Chinese Air Force. He had to travel over the Himalayas to India and then by ship, zigzagging to avoid enemy submarines, so he did not arrive in the U.S. until the day that Japan’s surrender was announced[2](https://www.nobelprize.org/prizes/chemistry/2008/tsien/biographical/#not2). His mission was therefore futile, but he knew that China would be racked by postwar civil war. Somehow he used contacts in the Defense Department to arrange for Mom and Yongyou to come to the U.S. Such permission was not trivial, because the Chinese Exclusion Act forbidding immigration from China to the U.S. had been repealed only in 1943, at which time the national quota was set at just 105 immigrants per year and thousands were ahead on the waiting list.  After Mom and Yongyou arrived in America in January 1947, life was quite a struggle because Dad could not find a professional job as an aircraft engineer. Such employment at the major firms required a security clearance, which a Chinese citizen could not get. So he started a tiny export-import business in New York City and later an engineering consultancy firm in Westchester County, which yielded enough to live on but not to become prosperous. Nevertheless their next son, Yonglo or Louis, was born in October 1949. Around then, Yongyou started school and needed to pick an American name. He wanted to be “Dick”, so the school officials explained to my parents that this was a nickname for “Richard”. “Yongyou” was somehow transliterated as “Winyu” to become Richard’s middle name in English.  According to Mom, she always planned to have three children, though this statement came many years after the fact. After two sons, even Dad was looking forward to a girl[2](https://www.nobelprize.org/prizes/chemistry/2008/tsien/biographical/#not2), but in February 1952 they got me instead. Dad picked my Chinese name, Yongjian (transliterated Yonchien to become my middle name in English), but Dick insisted that my American name should be Roger. My mother later told me this was because Dick had a playmate at the time named Roger. Much later, perhaps when I was in college, I quizzed Dick about this mysterious namesake. Dick confessed that he actually named me after Roy Rogers, the famous cowboy actor. I mention all this to clarify the origins of the similarity between the names “Richard W. Tsien” and “Roger Y. Tsien”, which has continually confused many scientists and their secretaries even up to now. I don’t know why my parents chose two different transliterations for “Yong”, but if they had not, Richard and I would be completely indistinguishable (“Tsien RY”) in bibliographical databases.  **Growing up: Home chemistry experiments** One of my earliest memories, probably from age 3 or 4, is of building a sand path at the beach across a strip of coarse pebbles that hurt my feet to cross. I loved to draw maps of imaginary cities with freeways vaulting over or tunneling under the surface streets. Perhaps these were the first signs of my future obsessions with bridge-building and activity-mapping. Some time in elementary school my parents bought a Gilbert chemistry set, but I didn’t find it very interesting because the experiments seemed so tame. Then I discovered a book in the school library that had much better experiments and illustrations. Regrettably, I cannot now remember the book’s name or author, though I hand-copied many sketches of its experiments into a notebook dated around 1960, now deposited in the Nobel Museum. Two experiments I remember best: 1) silica gardens, in which crystals of metal salts (e.g. CoCl2, NiSO4, CuSO4) dropped into a solution of sodium silicate would develop bright magenta, green, or blue gelatinous coatings from which vertically rising dendrites would sprout; 2) preparation of a strongly alkaline (0.5M NaOH or KOH) aqueous solution of dilute (~ 0.5 mM) potassium permanganate, which colored the liquid an intense purple. As this solution passed through a folded cone of filter paper, its color changed to a beautiful green, reflecting reduction of MnO4– to MnO42–, presumably by the cellulose. In November 2008, I reproduced this surprisingly little-known demonstration for Swedish television and Nobel Media as an example of what got me interested in chemistry. Both experiments reflect an early and long-lasting obsession with pretty colors.  In 1959, Dad closed his consulting firm and started working for RCA’s vacuum tube division in Harrison, NJ. Mom and Dad looked for a town with affordable homes, within convenient commuting distance, and with good public schools for the three of us. A photo from around then is Figure 1. They chose a new housing development in Livingston, NJ, but the developer refused to sell to us, saying that they could not permit Livingston to become a Chinatown, nor could they afford the likelihood that other customers would refuse to buy houses next to a Chinese family. My parents appealed to the Governor of New Jersey, Robert Meyner. His office sent a letter to the developers warning them that racial discrimination was illegal. Finally a compromise was reached: the developers sold us a house completely surrounded by houses that had already been sold. The problem for us kids was that Livingston has lots of rocks in its soil, left from the glaciers. My parents were determined to have a respectable American-style grassy lawn, which required removal of the rocks. We had to cart away not only our own stones but many from our neighbors, who had used the unoccupied leftover lot as a dumping ground, or so we believed. The many weeds in the lawn revealed a deep personality difference: Dad, as an impatient mechanical engineer, liked the instant solution of digging them up one by one from close enough to extirpate all the roots. I was an occasionally asthmatic hay fever sufferer, deeply afraid of pollen, so I advocated a chemical approach, sprinkling herbicide on the weeds from a safe distance. We tried my way once. The weeds slowly turned brown but eventually recovered. Dad declared the experiment a failure and went back to hand weeding. I still think about this result in relation to our current research on cancer therapy.  In 1960, RCA closed its vacuum tube division, presumably because semiconductors were replacing tubes, so Dad moved to Esso (later renamed Exxon) Research and Engineering. Esso provided much better projects and pay, so he stayed until his retirement in 1983. I believe some of the chemicals and glassware that enabled me to do the more interesting chemistry experiments were diverted from the company stockroom. Other supplies could be bought by mail order in those days with a parent’s signature. Over the next 5 or 6 years I gradually did many of the classic experiments of inorganic chemistry in the basement of our house: preparing and burning H2 gas, preparing O2 and burning steel wool in it, preparing NH3 in a flask and watching it suck water up as a fountain inside the flask. I distilled HF from CaF2 + H2SO4 in plastic apparatus and was delighted to see its ability to etch glass. I electrolyzed molten NaOH using a step-down transformer and rectifier from a model train set, the nickel crucible as cathode, and a carbon rod salvaged from a dead flashlight battery as anode. I managed to get a few granules of very impure metallic sodium, which gave off a satisfying hiss when dropped into water. Pyrotechnics were naturally of great interest: I made and ignited gunpowder, ammonium dichromate volcanoes, and even a spectacular thermite reaction with powdered aluminum and chromium oxide. My most ambitious attempt was a multistep sequence aimed at synthesizing aspirin, for which I needed acetic anhydride, which had to be made from acetyl chloride, for which I needed phosphorus trichloride, for which I needed to burn red phosphorus in a stream of chlorine gas. I tried to do this reaction sequence in flasks with rubber stoppers (Figure 2), because I had no glassware with ground glass joints. The corrosive chemicals largely chewed up the rubber, so I did not get beyond acetyl chloride. Because I had no fume hood, I did the more dangerous experiments outdoors on a picnic table on the backyard patio. Looking back, I am appalled at how dangerous all this was for an unsupervised boy of 8 to 15, but it was also very good training in how to improvise equipment, plan and execute experiments, interpret confusing results, and decide how to do things better. These experiments made me confident enough that when I had to earn my first merit badge as a Boy Scout and was advised to pick something really easy, I chose Chemistry. Tougher merit badges like Hiking, with its requirement for a twenty-mile hike in one day, I got later.  **Elementary school to high school; Westinghouse science talent search** School was usually bearable but frequently boring. I really looked forward to days in winter when heavy snow would close school, so that I could spend the day sledding. I was terrible at ball games at school, such as football, soccer, basketball, and softball, because I was small, nonathletic, and two years younger than my classmates at an age when this makes a huge difference. But I was popular enough in high school to be elected student council treasurer by an overwhelming majority.  Mom tried hard to teach us Chinese after school, but as I got older I found these lessons increasingly tedious. I well understood spoken Chinese at a child’s level (e.g. the Chinese for “Tidy your room!” is permanently etched into my brain) but was reluctant to speak it myself, due to the wish (all too common among children of immigrants) to distance myself from my parents’ accents and intense pride in their ethnicity and traditions. Likewise they despaired over my refusal (like a “foreign devil”) to eat most Chinese food, especially the most authentic dishes with the strongest tastes or smells, or prepared from exotic creatures.  My first exposure to a research environment was in a National Science Foundation-sponsored summer research program at Ohio University in 1967, where I was assigned to work in the laboratory of Prof. Robert Kline on the ambident coordination of thiocyanate (SCN–). The Pearson theory of hard and soft ligands and metals was new and fashionable at the time, so Prof. Kline wanted me to find out if thiocyanate could simultaneously bind with its “soft” sulfur to a soft metal and its “hard” nitrogen to a hard metal, e.g. PhHg–SCN–Cr(III). He hoped that the infrared absorbances of thiocyanate would tell us whether such bridging was taking place. I prepared a lot of amorphous precipitates of rather ill-defined composition and measured their infrared spectra. In the winter of 1967, my senior year at Livingston High School, I entered the Westinghouse Science Talent Search, the nationwide “science fair” competition. (This annual event still exists, though sponsorship was taken over by Intel in 1998.) For lack of any alternatives, I wrote up my Ohio University project, trying my best to draw some conclusions from a mess of dubious data. Prof. Kline largely disowned those conclusions, pointing out that my preparations had not given correct carbon, hydrogen, and nitrogen microanalyses. The 40 finalists were summoned to Washington DC in March 1968 for interviews and a public poster session. I remember being envious of my fellow finalists, who were much more adult and sophisticated. Also their projects and exhibits seemed much more exciting and explainable than mine. I felt intimidated by the senior judge, [Glenn Seaborg](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1951/), partly because of his commanding height, partly because he was chairman of the U.S. Atomic Energy Commission, partly because of his 1951 Nobel Prize for work in inorganic chemistry. The awards ceremony was very tense for us because the ten scholarship winners were announced in reverse order, forcing everyone to hope their name was called but as late as possible. I am still mystified how I won first prize despite the unsoundness of my project, and I retain a dislike for scientific competitions. Dad did his bit to keep me grounded: when I phoned home, his first comment was that it was a good thing I now had a $10,000 scholarship, because he had recently lost that amount on the stock market. One of the most satisfying compliments I received was that the developer who had not wanted to sell a house to Mom and Dad in 1960 now used my photo in one of their advertisements as evidence of the quality of the local school system.  **Harvard** In April 1968 I had to choose between four colleges: Columbia, MIT, Caltech, and Harvard. Dad vetoed Columbia because of the student unrest that spring, and I did not mind because I wanted to get further away from New Jersey. I rejected MIT because Dick and Louis had both gone there and I was tired of being compared to them. The small size of Caltech’s undergraduate class sounded attractive, but I finally decided against Caltech because [Richard Feynman](https://www.nobelprize.org/nobel_prizes/physics/laureates/1965/) was no longer teaching introductory physics and because the music department was tiny and of negligible fame compared to Harvard’s. Indeed Harvard did turn out to be a salutary experience on the whole. Friendships with classmates were crucial in helping me grow up. The student protests of spring 1969 and 1970 provided my first exposures to cannabis, police brutality, and participatory politics. The diversity of courses let me sample art history, visual design, economics, Colonial history, constitutional law, psychology, both music theory and chamber music performance, etc. Ironically, the worst courses were those intended to lead Harvard’s elite chemistry majors into research careers. These required courses were so distasteful I abandoned chemistry. Looking for alternatives, I dabbled in molecular biology (taught by [Walter Gilbert](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1980/), who later shared a Nobel Prize for DNA sequencing), oceanography, relativistic quantum mechanics, and astrophysics. But what I finally chose was neurobiology, partly because the relationship between brain and mind seemed philosophically the most important problem in science, partly because [David Hubel](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1981/), John Nicholls, and [Torsten Wiesel](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1981/) ran a course charismatically proselytizing undergraduates to become neuroscientists. Hubel and Wiesel were still doing the research on visual cortex that eventually won them the 1981 Nobel Prize in Medicine or Physiology. I asked Prof. Hubel if I could do a summer internship in their lab, but he told me they had no space for undergraduates and suggested that I apply to Nelson Kiang at the Massachusetts Eye and Ear Infirmary instead. In summer 1971, Kiang gave me intensive tutorials in auditory neurophysiology and an interesting project analyzing spike trains from the cochlear nucleus. I am still plugging away at neurobiological problems almost four decades later.  **Cambridge** When I asked Hubel and Kiang for advice on where to apply to graduate school in neuroscience, their only point of agreement was that the top places were Cambridge, MA and Cambridge, UK. I felt it was time to leave Cambridge, MA to broaden my horizons, so I applied for a Marshall Scholarship to go to the other Cambridge. In early 1972, while still a senior at Harvard, I learned my application was successful, and that my Ph.D. supervisor would be a Dr. R. H. Adrian, whom I had never heard of. I phoned my brother Dick, who had just become an Assistant Professor at Yale after finishing his D. Phil. from Oxford on cardiac electrophysiology. Dick informed me that R. H. Adrian was one of Britain’s most eminent skeletal muscle electrophysiologists, and son of [E. D. Adrian](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1932/), a Nobel Laureate in neurophysiology. Moreover R. H. Adrian had been the external examiner on Dick’s D. Phil. degree. “But muscle is a backwater,” I exclaimed. “I want to work on the brain.” Dick assured me that Richard Adrian was a true British gentleman, who would let me work on a topic of my own choosing. So I decided to wait and see. After a summer intensively studying music at Fontainebleau, near Paris, I arrived in Cambridge in October 1972. At my first lunch in Churchill College, an aristocratic-looking don sat down opposite me and asked if I was Roger Tsien. I immediately realized he was Richard Adrian, because only someone who knew a member of my family could pronounce our surname correctly, as he just had. Within the first few minutes of our conversation, he asked “Is it true you think muscle is a backwater?” I had to admit the accuracy of the quotation. (I later found out that Dick had mischievously teased Adrian about this at a conference they had both attended that summer.) Adrian looked a bit pained at my confession, but immediately said that he would not object whenever I wanted to transfer to one of the real neurophysiologists in the department.  Thus began my Ph.D. training. I never did switch to another official supervisor, because I soon realized I did not enjoy doing conventional electrophysiology of the central nervous system. The traditional thesis project, basically following the paradigm so successfully employed by Hubel and Wiesel, was to drop an extracellular microelectrode into the brain of an anesthetized animal and record the activity of individual neurons while providing sensory stimuli. After several hundred such recordings, one could classify the different response patterns and write up a thesis and several publications. To me this seemed too much like ice fishing, i.e. cutting a hole in the ice covering a lake, dropping a fishing line into the opaque water beneath, and patiently waiting for a bite. The brain derives its power from trillions of neurons working in parallel, so I wanted to see lots of neurons simultaneously signaling to each other and processing information. Ideally one would stain the neurons with a dye that would visibly light up or change color whenever and wherever a neuron fired an action potential. A few commercially available dyes had indeed been found that responded to neuronal action potentials, but the optical responses were extremely tiny, e.g. a 10–4 or 10–5 change in fluorescence.  They were detectable only if thousands of action potentials driven by the investigator were averaged under highly simplified conditions[3](https://www.nobelprize.org/prizes/chemistry/2008/tsien/biographical/#not3). Many orders of magnitude improvement would be necessary to detect endogenous signals in a complex brain. I rashly decided in winter 1972 that I would try to design and synthesize new dyes for the specific purpose of imaging neuronal activity. One strategy was to target the dye to the vicinity of sodium channels, which were believed to undergo large conformational changes as they generated action potentials. Another strategy was to create “electrochromic dyes” with large changes in dipole moment between ground and excited state, so that a change in neuronal membrane potential could shift the peak wavelengths of absorbance or fluorescence[4](https://www.nobelprize.org/prizes/chemistry/2008/tsien/biographical/#not4). In either case I would have to learn organic synthesis, which I had hated in those Harvard chemistry courses and which nobody in the Physiological Laboratory could teach me. Fortunately, Dr. Ian Baxter, a junior faculty member in the Chemistry Department and a friend of a friend of Richard Adrian’s, was intrigued by my idea for targeting sodium channels and agreed to supervise me unofficially. Baxter had no other students and had the time, kindness, and patience to look over my shoulder several times a day and show me the necessary techniques. I found to my own surprise that I could do and enjoy organic synthesis once it was for a biological purpose of my own choosing. I remained hooked on this type of research even though the molecule I synthesized proved incapable of binding sodium channels, even though Baxter soon left to become a careers counselor in the north of England, and even after other generations of my synthetic voltage sensors proved inferior to those found by other labs screening large numbers of commercially available dyes and their close analogs[5](https://www.nobelprize.org/prizes/chemistry/2008/tsien/biographical/#not5).  My first glimmer of success required shifting to another biological target. Action potentials almost always generate large increases in intracellular calcium to exert any biological effect such as the release of neurotransmitters to excite or inhibit the next neuron in the pathway. In 1975 there was great excitement over the discovery that arsenazo III, a dye invented to measure heavy metals in nuclear waste, could also be used to monitor calcium in giant axons from squid neurons, though the signals from this dye were very small and somewhat ambiguous[6](https://www.nobelprize.org/prizes/chemistry/2008/tsien/biographical/#not6). I felt that designing a dye to measure Ca2+ should be a far easier problem than designing a dye to track fast changes in neuronal membrane potential. Hundreds of dyes were already known in the chemical literature to respond to Ca2+, e.g. for determination of water hardness. The real problem was that inside cells, the free Mg2+ concentration is about four orders of magnitude higher than that of Ca2+, so that an intracellular Ca2+ indicator needs yet higher selectivity for Ca2+ over its sister ion Mg2+. No chemist had yet recognized the biological need for such a selective indicator. A colorless buffer called EGTA was the only synthetic molecule known to have the necessary Ca2+:Mg2+ selectivity[7](https://www.nobelprize.org/prizes/chemistry/2008/tsien/biographical/#not7), but it had never been made into any sort of dye molecule. By doodling on paper and playing with molecular models, I saw a way to make EGTA into a very rudimentary dye molecule. I started on this brand new project without telling Richard Adrian, because any prudent supervisor would have told me I should be bringing older projects to closure rather than starting radically new ones. Fortunately, within a few weeks I managed to make a small, impure sample of the target molecule (much later given the acronym “BAPTA”) and found that it had the expected optical response to Ca2+ combined with high Ca2+:Mg2+ selectivity[8](https://www.nobelprize.org/prizes/chemistry/2008/tsien/biographical/#not8). After many more years and discoveries, better dyes descended from BAPTA[\*\*](https://www.nobelprize.org/prizes/chemistry/2008/tsien/biographical/#two) became the most popular way of seeing endogenous intracellular Ca2+ signals, screening for ligands and receptors linked to Ca2+ signaling, and imaging neuronal activity microscopically.[10](https://www.nobelprize.org/prizes/chemistry/2008/tsien/biographical/#not10)  After my Ph.D., I stayed in Cambridge as a postdoctoral Research Fellow at Gonville & Caius College. My change in focus towards Ca2+ signaling led me into collaboration with Dr. Timothy Rink, a new faculty member in the Physiological Laboratory, because Tim wanted to make Ca2+-selective electrodes from materials sent from Switzerland[11](https://www.nobelprize.org/prizes/chemistry/2008/tsien/biographical/#not11). The directions for assembly were in German, which Tim could not read. I had learned to read chemistry papers in German, so I translated the instructions. Our collaboration started with these Ca2+-selective electrodes and continued with the biological testing and exploitation of my fluorescent indicators for Ca2+. Even more importantly, Tim and his wife Norma invited me to their Christmas party in 1976, where I first met their sister-in-law, Wendy. Soon I was spending every weekend visiting Wendy at her house in North London. When Tim and Norma found out several months later, they were quite astonished at the effectiveness of their entirely unintentional matchmaking. Wendy (Figures 3–4) is still the love of my life.  **Berkeley** My fellowship at Gonville & Caius College was to end in late 1981, so in 1979–1980 I started looking for an independent position. Because of Wendy’s residence in London, I applied to the National Institute of Medical Research in Mill Hill, but was rejected without an interview. This was not a good time to search for a research job in Britain, because of the austerity program of the new Thatcher administration. It was time to return to the U.S., yet I had almost no contacts and few publications. Almost all my applications were unsuccessful. Biological departments considered me a chemist, while chemistry departments rejected me as a biologist. Nowadays the application of chemistry to solve biological problems is a very fashionable subdiscipline dubbed “chemical biology”, but in 1980 the only venue for such interdisciplinary efforts was in the pharmaceutical industry. Even there, individual scientists were typically either chemists or biologists, not both simultaneously.  Luck intervened. The Department of Physiology-Anatomy, University of California, Berkeley, had a vacant assistant professorship, for which the chair of the search committee was Terry Machen, whom I had gotten to know while he was on sabbatical in Cambridge. Also Berkeley had two faculty members, Richard Steinhardt and Robert Zucker, who were interested in Ca2+ signaling. These connections enabled me to get an interview at Berkeley. Fortunately, the fluorescent indicators for Ca2+ had finally progressed enough to enable the first direct measurements of cytosolic Ca2+ in lymphocytes, including the elevation due to mitogenic stimulation[12,13](https://www.nobelprize.org/prizes/chemistry/2008/tsien/biographical/#not12). Now one could investigate Ca2+ signals in populations of small mammalian cells, whereas previous techniques required single cells large and robust enough to withstand microinjection. This prospect, together with the fact that my Ph.D. was in Physiology, convinced the Department to offer me the Assistant Professorship, which I accepted before I found out that Berkeley was suffering a financial crisis. The startup package to get my laboratory going in early 1982 was cut to just a few thousand dollars, and each item had to be justified as a replacement for obsolete instructional equipment. For example, to get me a UV lamp for viewing thin layer chromatography plates, an old microscope illuminator from the teaching lab had to be junked. More importantly, the Department had no resources to provide a fume hood, which I needed to continue synthesizing the Ca2+ indicators. Prof. Robert Macey, whose lab was next to mine, kindly donated an old fume hood including its irreplaceable ductwork extending to the roof of the building. For the remainder of my seven years at Berkeley, all our synthetic reactions took place in this single wooden fume hood, less than 4 feet wide, with wire netting embedded in the glass of the front window. The entire lab stank from chemicals in unvented storage cabinets, and became lachrymatory when reactions using excess ethyl bromoacetate had to be worked up outside the hood. I mention these austerities only to remind young scientists that some good research can be accomplished without lavish facilities and startup funds.  Despite these troubles, my time at Berkeley was scientifically quite productive, including collaborations with Machen[14](https://www.nobelprize.org/prizes/chemistry/2008/tsien/biographical/#not14), Steinhardt[15](https://www.nobelprize.org/prizes/chemistry/2008/tsien/biographical/#not15), Zucker[16](https://www.nobelprize.org/prizes/chemistry/2008/tsien/biographical/#not16), and others. I recruited Drs. Grzegorz Grynkiewicz and Akwasi Minta, who synthesized much improved Ca2+ indicators (fura-2, indo-1, fluo-3)[17,18](https://www.nobelprize.org/prizes/chemistry/2008/tsien/biographical/#not17) and a Na+ indicator (SBFI)[19](https://www.nobelprize.org/prizes/chemistry/2008/tsien/biographical/#not19), all of which are still in use today. After the budget crisis eased, the Berkeley administration helped me buy a primitive image processor, which I painfully programmed[20](https://www.nobelprize.org/prizes/chemistry/2008/tsien/biographical/#not20) to calculate images of the ratio of fluorescences at two alternating excitation wavelengths. Such real-time ratioing revealed Ca2+, Na+, and pH signals[14](https://www.nobelprize.org/prizes/chemistry/2008/tsien/biographical/#not14) inside single living cells, often with unprecedented spatiotemporal resolution.  **Moving to UCSD** However, I began to worry about being trapped in a career of imaging inorganic ions. I wanted to explore signals transmitted through more complex biochemicals such as cAMP (cyclic 3′,5-adenosine monophosphate) and the wider, more fashionable world of macromolecular interactions. As my bargaining power grew, I also came to want a lab with enough fume hoods, vented storage cabinets, and small darkrooms for fluorescence microscopy to support my unusual combination of chemistry and biology, as well as a joint appointment in a Chemistry department and support from the Howard Hughes Medical Institute. None of these were possible in Berkeley, so in 1989 we moved south to the University of California, San Diego, where we still are. UCSD satisfied the above desires and was much younger, roomier, faster-growing, and less tradition-bound than Berkeley, which I felt more than compensated for its lesser fame. The highlights of the science started at UCSD are recounted in my [Nobel lecture](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/2008/tsien-lecture.html).  **Conclusions** Writing this autobiography has reminded me how my career has been shaped by a strange mixture of chance and fateful predisposition. The use of chemistry to build biologically useful molecules is a form of engineering, so I did not escape the tradition set up by my father, uncles, and brothers. However, I avoided the mechanical, aeronautical, electrical, and computer specialties they chose, probably because like many youngest siblings[21](https://www.nobelprize.org/prizes/chemistry/2008/tsien/biographical/#not21), I had to seek a distinct niche. But if I had not found Ian Baxter to re-instill my enjoyment of chemistry, perhaps I would have chosen yet another direction. My interest in imaging with multiple glowing colors also reflects visual interests from early childhood, which I have been lucky enough to align with a professional career. From a strictly biological point of view, our contributions have mainly been in the development of techniques. Man-made techniques do have a habit of becoming obsolete, whereas basic discoveries about how nature works should last forever. But truly fundamental insights such as those of Darwin or [Watson & Crick](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1962/) are rare and often subject to intense competition, whereas development of successful techniques to address important problems allows lesser mortals to exert a widespread beneficial impact for at least a few years. Moreover, the same engineering approach is what creates new therapeutic strategies to alleviate disease, not just tools for our fellow researchers.  \* The benevolent reign of these kings is commemorated in at least two immaculately maintained shrines, one in Lin’an, a medium-sized city in Zhejiang Province, the other constructed in 2002 on prime real estate on the famous West Lake at the center of Hangzhou. My mother, my wife, and I visited both shrines in 2004. My mother interpreted the prominence of these shrines as an attempt by the current Chinese regime to advertise a historical precedent for reunification with Taiwan.  \*\* The invention of a generalizable structure that sensed Ca2+ with unprecedented selectivity was duly reported to the National Research Development Corporation, as required for work funded by the UK Science Research Council. Initially NRDC was enthusiastic enough to file a patent application, 42927/78, but the administrators soon decided that measuring intracellular Ca2+ was of negligible commercial value. They felt that the only possible use for biological Ca2+ measurements was in clinical assays in blood serum, an application with completely different performance criteria, so they abandoned the patent application. In principle I could have taken over the patent costs out of my own pocket, but the NRDC’s estimate of the fees equaled about 20 years of a postdoctoral salary, so I did not try. Eventually, follow-up patent applications by the University of California covering narrower variations in molecular structure proved quite lucrative. A much more important example of the NRDC’s conservatism[9](https://www.nobelprize.org/prizes/chemistry/2008/tsien/biographical/#not9) was their failure to patent [Milstein and Köhler](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1984/)‘s monoclonal antibodies, another Cambridge invention of the mid-1970’s. |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** | [RT]  [Roger Tsien] Hello.  [Adam Smith] Hello, this is Adam Smith from Stockholm. Is that Roger Tsien?  [RT] Yeah.  [AS] Thank you very much for making time for this. How have the last 24 hours been?  [RT] A little bit surreal, but all I can do is put one foot in front of the other. Just try to keep going.  [AS] Yes, it will be the weekend soon, although I don’t know if things will abate.  [RT] Yeah.  [AS] I’ve read that, like many Laureates, you started your science career as a child doing chemistry experiments at home. Did you always know you were going to be a scientist?  [RT] No, I didn’t know. Obviously, it was one of the well-known possible options. I think I did go through the usual small-child phase of imagining being a fireman and so on, but yeah, I think being a scientist was more of a possibility for me than probably for most kids.  [AS] When did you actually realise you were a scientist?  [RT] I guess I realised I was most interested in being a scientist in the … Oh I guess it would have been junior high school, say, probably the age of 9 or 10.  [AS] That’s pretty young, that’s pretty young.  [RT] Well I, yeah, I guess I think … I’m trying to remember when I started playing around with chemistry experiments at home. It was probably around then. Much to the horror of … Well, a mixture of fear in my parents and a little bit of encouragement.  [AS] Right. Yes. The Prize has been awarded for your work on GFP of course, and for your revelation of how GFP fluoresced, and then using that knowledge to create mutants which extended the palette of colours of tags available. What does this extended range of tags allow you to do?  [RT] Well, several things. It means you can, basically you can monitor many signals at once inside the cell and you can monitor interactions of proteins by the phenomenon of fluorescence resonance energy transfer. If that’s what you’re referring to – the use of the different colours.  [AS] Yes.  [RT] Of course, in the process we had to improve all of the colours, and the original wild-type GFP was very difficult to use, for many reasons. It was made by the jellyfish for its own reasons, some of which, as I said, have been very obscure. One remarkable property of the original jellyfish protein is that it actually isn’t just green. It excites, well it emits green, but it excites mostly in the UV, and only a small amount in the blue.  [AS] Right.  [RT] And that’s a strange paradoxical phenomenon because we discovered that almost any mutation of one amino acid right next to the chromophore will shift it to being all of one or all of the other – either all UV or all blue. And most people for biological purposes would rather have all blue. Occasionally it’s useful to have nothing but UV, and there’s I think only one amino acid that will make it either UV or blue. And when it is UV it is unable to do the energy transfer from aequorin. And therefore the jellyfish would presumably glow blue. And one of the great mysteries that I’ve never figured out is why the jellyfish chose the only amino acid that would compromise, and be schizophrenic, and be partly UV and partly blue in its absorbance. And it could have so easily shifted it to all of one or all of the other. And instead it’s preserved this split character. We don’t know why. But that is a nuisance for anyone else using it pretty much. Almost anyone else.  [AS] Apparently it doesn’t bother the jellyfish in evolutionary terms – it gets on fine. So …  [RT] Well, we have even wondered if there are times the jellyfish wants to turn on GFP’s ability to switch blue into green, and there are times it wants to turn it off. But I’m not enough of an ecologist to … Since we don’t even know why it wants to glow, and if it does want to glow why does it sometimes want to glow green, then I cannot answer the question. I’m certainly not going to answer the question of why doesn’t it always want to glow green?  [AS] But from your point-of-view, modulating these proteins, it’s beautiful that the selectivity resides in just single amino acids.  [RT] Well, it’s more complicated than that. At least for the wild-type, there’s one amino acid that controls really primary colour of the emission, and the next one to it controls, if you are going to be green, what is your absorbance spectrum. I think that’s a fair summary.  [AS] Okay.  [RT] And then many other surrounding amino acids have influences as well, which we’ve gradually pieced together.  [AS] And learnt to tweak, yes.  [RT] But simply changing the colour of the fluorescent protein’s a sort of very visible thing to do, but I don’t know that it’s that terribly significant.  [AS] Are there are applications of the use of the probes you’ve produced that you’re particularly fond of?  [RT] I have to say that of course the fluorescent proteins have actually only been less than, it’s a minority part of my career, which was mostly spent building probes based on other things. But the fluorescent GFP work is obviously now the most famous. So I started out my, the successful part of my scientific career started out building calcium dyes …  [AS] Yes.  [RT] … By synthetic organic chemistry. But, and more recently we’ve begun to get out of fluorescent proteins more and more and back towards synthesis, because we cannot treat people with gene therapy. And so we need non-genetic means of imaging processes in the human body. But, as far as the GFP, we soon switched on to the homologous proteins from corals, and those were discovered by the Russians not by us.  [AS] But you modified them to make them work.  [RT] Again, they needed extensive modification to make them user-friendly for the biological community. Most notably killing the intense tendency to form tetramers. It was actually great good luck that the green fluorescent protein from jellyfish was not nearly as obligately multimeric as the corals were. Because if they had been, a lot of the early applications of GFP would have been choked away, and the whole revolution would take a lot more time to get started. But because GFP at least didn’t have a tetramerization or severe dimerization problem – it only has a very mild one – that sort of got people hooked on what a wonderful tool this whole system was. So we were more able to cope with the tetramerization when it came up a few years later.  [AS] Does it ever have a detrimental effect on the things you’re studying? I mean, obviously if it’s starting to form …  [RT] GFP?  [AS] Yes.  [RT] Yeah. There … It is … It can do. One of the maybe more-forgotten facts about GFP, for example, is that in its maturation process it inherently generates a molecule of hydrogen peroxide. Hydrogen peroxide can be bad news inside cells. There are other times when if you fuse GFP to a particular protein, that particular protein just doesn’t like it. It says “No, I will collapse into a heap if you stick anything onto me, or at least onto my N-terminus or onto my C-terminus”. So you hope it’s not both of them, you know. But there are times you want to follow very small proteins or even peptides, and then to put GFP on them is putting a dog on the end of a tail. The probe is much, much bigger than what you want to study. We have strategies to overcome that too, which are mixed organic synthesis and genetics, but they’re lesser well-known. Most of the time, surprisingly, GFP is not – surprisingly often it’s not injurious, seemingly.  [AS] Right, right.  [RT] And I might actually point out that the first fusions to GFP ever were made by Marty Chalfie’s wife, Tulle Hazelrigg.  [AS] Right, right. Yes, yes. Yes, and indeed it was his marriage to her that accounted for the missing two years in his development of the technique.  [RT] Well, she made up for it after, once the GFP got going.  [AS] Sorry, we were on the question of favourite applications. I don’t know if you …  [RT] Sorry if I wandered off to something …  [AS] No, no, you wandered off very interestingly. It was fascinating. But did you want to mention anything in particular that you like that has been done with all these probes?  [RT] It’s hard to single anything out. There’s been thousands of, I think tens of thousands of papers, I have to say most of them using GFP or the red varieties or the yellow varieties in a fairly routine way. There are obviously some very cute things that have been done with it, a few I think we might have actually contributed to. And, one of the showiest applications is the one say *The New York Times*picked for its lead page today, which is from Jeff Lichtman’s group. This trick of combinatorially painting neurons a whole kaleidoscope of colours.  [AS] This is the thing they call the brainbow, is that right?  [RT] Brainbow, yes. And, you know, is it fair to single that one out? Well, it’s easy for me to remember it because there was this beautiful picture this morning, but there are actually lots and lots of cute things GFPs and RFPs have done. The one thing they have never done is get us to really long wavelengths, like excitation beyond 600 nanometres. That is truly red, deep red excitation and infrared emission. And that would be very important for going into whole animals that have a lot of blood in them, like you and me, and more particularly mice. Haemoglobin absorbs quite severely below 600 nanometres, so you want to be above 600 nanometres to avoid the blood absorbance as much as possible.  [AS] So …  [RT] And finally we think we’re getting there.  [AS] So that gives you whole-body imaging, right?  [RT] Well, it will help. I mean that alone isn’t enough. We’re still pretty, mammals are still pretty opaque, but this at least gets rid of one of the big barriers.  [AS] And the dream is to have multiple sensors of body processes there at the same time?  [RT] Biochemical processes. Not always necessarily at the same time, but at least to be able to look at protein kinase activity, redox state, gene transcription, protein degradation, localization of DNAs and RNAs by slightly more indirect means, which if you use GFP and RFP to label a protein that in turn binds specifically to your favourite nucleic acid, and the list goes on and on.  [AS] I wanted just to ask about what we call all this, because you work in a Department of Pharmacology, and you’ve been awarded the Nobel Prize for Chemistry, for work that is basically involved in cell biology. Does it matter how it’s all labelled?  [RT] Yes and no. It shouldn’t, but we have to respect the fact that we work in universities with department names, and attempts to make an amoeboid department that covers all of science probably don’t tend to work very well. Some people call this area chemical biology. Sometimes it’s been hard to wonder so what’s the difference between chemical biology and biochemistry. And sometimes I like to call it molecular engineering – at least our approach to it, because we try to build molecules to solve problems. And it’s the part of chemistry that is maybe slightly more applied, at least to some people’s way of thinking. Do I really worry about it? I try not to, but I recognise that the granting agencies, university departments, students … That’s when it’s dangerous, is when students let themselves get pigeon-holed, or let their thought processes get pigeon-holed, and say “Oh, I could never do that, that’s chemistry. I don’t know any chemistry”. And it’s surprising how often biologists have that attitude. And actually chemists sometimes have that attitude about biology too. This instinctual fear that, “Oh, that’s a subject I can’t do, and nobody should expect me to know how to do, and so I will just not pay any attention to questions that lead me in that direction.”  [AS] So as a final thought, what advice would you give to students thinking of moving into the field of building sensors?  [RT] Well, I might echo the advice that my then Department Chairman gave me when I was an Assistant Professor, when I was worried about certain, choosing between some safe projects and some risky ones, and he said, “Trust your heart and your gut and go for the one that you think is really interesting and don’t worry too much about trying to think to game the system, and think about what’s going to be the most appealing to outside people. Pick the one that you think is the most interesting”. And maybe to that I would myself add in my case since I love pretty colours, that helped me often decide that I would do things that involved pretty colours, so that at least without having to worry about whether the work would be successful in 5 or 10 or 20 years, I could get some direct aesthetic pleasure out of the experiments as I went along. I have to say I myself do not find pipetting colourless droplets of liquid from one plastic tube to another awfully inspiring, and that’s what much of molecular biology often seems to be at the bench. And so it helps to have things where you can see, for me, when you can see cells do things in real time, and if they can do so in pretty colours, so much the better. And that’s part of why we wound up trying to emphasize that.  [AS] It’s nice. Keeps the left brain and the right brain happy at the same time, yes.  [RT] One tries, yeah.  [AS] Splendid. Well, that’s a nice note to stop on. Thank you very much indeed for speaking to us.  [RT] Okay.  [AS] And congratulations.  [RT] Sure, bye.  [AS] Okay. |
| **Interview** |  |

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| --- | --- |
| **Chemistry\_2024-2000** | |
| **ID** | 0346 |
| **Biographical** | I was born on 10 October 1936 in Bad Cannstatt which is part of the city of Stuttgart in the southwest of Germany. When I was 3 years old, the family moved to the nearby village of Schmiden where I entered elementary school in 1942. In summer 1946, I was admitted to Johannes Kepler Gymnasium (high school) in Bad Cannstatt where I passed the final examination (Abitur) in spring 1955. I had been a fairly good student with some (but not particularly strong) interests in science and history. Computers were not yet available in those days, and it was hence quite common for boys to do at home some chemical experiments. I had a good book on this topic and enjoyed very much to follow its prescriptions in my bedroom. There was, however, sometimes some strong smelling or strange noise so that my mother became afraid of my health and asked me to stop these activities. As a consequence, I turned my interest to radio sets and therefore from chemistry to physics. Since I was very good in mathematics I also decided to study physics instead of chemistry and entered the Technical University of Stuttgart in 1955 where I also obtained my diploma in 1961, after spending some time in between at the universities of Paris and Munich. My studies at these latter places were of more general nature but I attended also lectures from a few of the heroes of my subject – [de Broglie](https://www.nobelprize.org/nobel_prizes/physics/laureates/1929/), [Joliot](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1935/), [Heisenberg](https://www.nobelprize.org/nobel_prizes/physics/laureates/1932/).  Since my childhood I was also interested in music and played the piano. While being a student I became among others member of a band and earned in this way quite some money. As can be seen from fig. 1, in those days there existed no electronics but simply only acoustics.  For my diploma thesis work I decided to return to chemistry, and hence physical chemistry became my subject of choice. I had the great luck to find a mentor who was not only an outstanding scientist but also an inspiring person with great humanity: Heinz Gerischer (fig. 2) was one of the leading electrochemists of the 20th century, but also interested in other problems of physical chemistry. Just before I joined his group [Manfred Eigen](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1967/) in Göttingen had developed novel techniques for studying the kinetics of very fast reactions in solution for which work he received the Nobel Prize in Chemistry in 1967. Gerischer had the idea that such a method could also be based on rapid heating of an aqueous phase by a short pulse of microwave radiation. This was my first contact with real research, and I became fascinated by the challenge to develop such an apparatus and measure the rate constant of one of the most fundamental reactions in chemistry, the recombination between H+ and OH– to H2O. I could solve this task successfully, but it became soon clear that the applicability of this technique would be limited, and hence I asked Gerischer for another project for my Ph.D. work. After briefly considering some more conventional problems of electrochemistry, he told me: “If you really want to enter a field on which we know only little, instead of studying the solid/liquid interface think what you could find out about the solid/gas interface. I have no idea about this field, but you will have all freedom and my full support as far as available to me.”  At this time Gerischer accepted an offer from the technical University of Munich, and I joined him as an assistant and made my first steps in the just emerging area of surface science. In order to keep a surface clean for long enough time, ultrahigh vacuum (UHV) was required which in those days could only be achieved by sealed glass systems evacuated by mercury diffusion pumps and baked to 450° C – a real adventure. I managed to build such an apparatus and was studying the reaction 2H2+O2 -> 2H2O at surfaces of Germanium single crystal surfaces – not the best choice, but at least sufficient to provide me my Ph.D. degree in early 1965. Much more successful and rewarding was meeting Gerischer’s secretary Barbara Maschek. In the meantime we have been married for 43 years and have two (also married) children and four grandchildren.  During my thesis work the first stainless-steel UHV systems and low energy electron diffraction (LEED) as experimental tool providing information about atomic structures of surfaces became commercially available, and the German Science Foundation (DFG) was soon willing to fund such an apparatus for us.  Now the real surface science era began. I first studied the interaction of oxygen with various Cu single crystal surfaces and made also the first attempt to study the progress of a surface reaction along this approach. This was continued together with my first Ph.D. student, P. Rau, where we combined structural information from LEED with thermodynamics and kinetics in the interaction of O2 and CO with a Pd(110) surface. In 1967, I received my next academic degree (Habilitation), and soon afterwards I was appointed professor of physical chemistry at the Technical University of Hannover. There the studies on adsorption and reactions of small molecules at metal single crystal surfaces were continued, new experimental techniques were incorporated, and the group was continuously growing until 1973 (fig. 3) when I accepted an offer from the University of Munich to succeed one of the ‘grand old men’ in catalysis, G. M. Schwab.  Practically all coworkers joined me. New equipment was acquired, and new problems were studied. In this period, for example, the mechanism of catalytic ammonia synthesis was elucidated after I learned at a conference, that despite of fifty years of research this was still an open problem. But also more physical problems were investigated, such as the study of the electronic properties of the outermost atomic layer by deexcitation of metastable noble gas atoms, and the construction of a molecular beam apparatus initiated our studies in the field of gas/surface dynamics. Fig. 4 shows me in the yard of the institute in front of [A. von Baeyer](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1905/), the 1905 winner of the Nobel Prize in Chemistry. In between I spent two half-year sabbaticals in California (Caltech and Berkeley).  But also this fruitful era came to an end when I received an offer from the Max-Planck Society to become the successor of my teacher Heinz Gerischer as director at the Fritz-Haber-Institut in Berlin. Gerischer served in this position since 1969 and was a student of Karl-Friedrich Bonhoeffer who in turn was Fritz Haber’s assistant until his emigration in 1933. This continuing genealogy was certainly also a factor influencing my decision to move to Berlin. There I took over the fairly large department of Physical Chemistry which grew even further by all the coworkers arriving from Munich. Our main activities concentrated there on the investigation of nonlinear dynamics and spatio-temporal pattern formation (including theory), following surface processes on atomic scale by scanning tunnelling microscopy, the dynamics of fast surface processes studied by femtosecond laser techniques, but also exoelectron emission in surface reactions and atomic-scale electrochemistry etc.  After official retirement in October 2004, I am still active in writing and giving lectures. |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** | [GE]  [Gerhard Ertl] – Ertl.  [Adam Smith] – Oh, hello, this is Adam Smith calling from the Nobel Foundation’s official website.  [GE] – Ja. The problem is I’m waiting for a call from our Bundeskanzler, Frau Merkel, so could you call back in a couple of minutes perhaps?  [AS] – Most certainly. It’s very nice to talk to you and congratulations.  [GE] – OK, OK.  [AS] – Thank you. Bye, bye.  (Telephone rings again)  [GE] – Ertl.  [AS] – It’s Adam Smith again. Is it possible to talk at this point?  [GE] – Ah, sorry, I’m still waiting for this other call.  [AS] – Oh, I’m so sorry, I will ring back.  [GE] – Will it be for a very short time?  [AS] – It would be just three minutes.  [GE] – OK.  [AS] – You’re the second German Laureate to win this week. Do you know each other, do you know Peter Grünberg?  [GE] – I don’t know him personally but I of course know all his work and I know the institution where he’s working.  [AS] – And this is the first surface chemistry Nobel Prize since 1932, since [Irving Langmuir](https://www.nobelprize.org/prizes/chemistry/1932/langmuir/facts/) …  [GE] – That’s right.  [AS] – … that must make it special also.  [GE] – That’s right, that’s fine. That’s right, so I’m very, very much honoured about that.  [AS] – And one of the things the Committee has emphasized is the fact that you have continually revisited problems; old problems and problems that you yourself have addressed. It makes it sound as if a scientist’s work is never done. Could you say that?  [GE] – That’s right, ja, a scientist is never, never at the end, and when we solve a problem, five other problems develop anew. So that’s why a scientist will always think about his work and what he can do next.  [AS] – And you’ve had over a hundred students work for you I gather …  [GE] – Ja, ja.  [AS] – … what do you try and teach them?  [GE] – These were doctoral students, and of course they were working for their theses with me for about three years or so, and so that’s how they learned how to tackle problems in surface chemistry.  [AS] – But what’s the most important lesson they should learn from you, do you think?  [GE] – It’s hard to say, but I think you never should give up, you should always try to solve the problem as far as it is possible. And you must be patient. You *must* be patient. That’s very important.  [AS] – The last real question is; the field you’ve helped to develop will contribute greatly to the benefit of mankind, what do you think the main benefit might be in the short term?  [GE] – The work that we were doing was related to heterogeneous catalysis and this is a topic which is of great industrial importance, but also of environmental importance. Think of the car exhaust catalsyst, or of all these industrial processes. So, as soon as you understand something better then you can also think of improving it. I think that’s the main message you can learn from it.  [AS] – OK. Thank you very much indeed.  [GE] – OK.  [AS] – Well I gather it’s your birthday today, so …  [GE] – That’s right. Thank you, thank you.  [AS] – … congratulations, bye, bye.  [GE] – Bye, bye. |
| **Interview** |  |
| Q4 | **Given how ubiquitous surface chemistry is, it might be thought to be a little surprising that this is the first Nobel Prize for surface chemistry since Irving Langmuir got it in 1932. Is part of the problem that it’s very difficult to study surface chemistry?** |
|  | Gerhard Ertl: It’s certainly very difficult to study and as you mentioned [Irving Langmuir](https://www.nobelprize.org/prizes/chemistry/1932/langmuir/facts/), he was really groundbreaking, as his ideas, but many of these ideas couldn’t be studied at that time because we needed new techniques and /- – -/ This started only in the 1960s and ‘70s, that’s why surface chemistry is a relatively new field of chemistry in this sense. |
| Q2 | **What are the challenges, the difficulties in the instrumentation that one faces?** |
|  | Gerhard Ertl: If you are interested to learn what is really taking place on an atomic scale on the surface, you have to keep in mind that the structure of a solid surface is usually very complex. It consists of different crystal planes, different defects, different compounds at the surfaces and if you expose it to an atmosphere, then impurities from the gas face will accumulate there, so it’s very badly defined. If you want to study really the elementary processes, you first have to start with preparation of clean and well defined surfaces. It needs very high vacuum and the use of single crystal surfaces. This was the event of surface science in the 1960s, when this whole field started. |
| Q15 | **That’s a lovely challenge. Has it made any practical difference to the process, that you now understand?** |
|  | Gerhard Ertl: With the knowledge about the process and about the rates of the individual steps, it was also possible to develop a kinetic model and this was done by people in Denmark working with Haldor Topsoe, the company who is one of the big manufacturer of plants for the ammonia synthesis. They tell me, now in the meantime, they developed their plants on the basis of data they have about the kinetics, so it makes it much, much easier for them also. |
| Q4 | **You defined the rate limiting steps for the reaction?** |
|  | Gerhard Ertl: Yes, that’s right and we identified also other steps and with all this knowledge putting together, these people, Nørskov and his co-workers, they were able to develop this kinetic model. |
| Q2 | **One of the things that you’re known for is that you re-visit problems, when a new technology becomes available, you go back to an old problem that you studied previously and you’ll study it again using the new technology. Is the Haber Bosch process one of those that you have looked at more than once?** |
|  | Gerhard Ertl: We continue to work on this because there was still the question is the iron catalyst the best catalyst? It was invented almost 100 years ago and, in the meantime, there are other catalysts being proposed, mainly by Japanese workers based on ruthenium and indeed it seems to be a better catalyst than iron but it’s very hard to transform this on an industrial scale and … |
| Q2 | **Do you think it’s unusual that you re-visit problems?** |
|  | Gerhard Ertl: I don’t think so. Whenever you solve a problem or answer a question, you are faced with two or three new ones so you are still left with open questions. I think it’s not very unusual that you go back to another question which you had left a couple of years ago. |
| Q2 | **What led you to surface chemistry in the first place? What was your path that ended up there?** |
|  | Gerhard Ertl: I am not a chemist, I am a physicist, but I was always interested in both chemistry and physics and that’s why I did my first degree where the diploma work was a physical chemist and he was a famous electro-chemist. Electrochemistry is the science of solid/liquid interface, with charge transfer. I did my first work on the reactions in liquid fase but then I wanted to continue for my PhD and I asked my thesis advisor, Is there anything else I could do – everybody here in the laboratory is working on electro-chemical systems? He told me, We know quite a bit about solid/liquid interfaces, but very little about solid/gas interfaces. There is no electrochemistry. If you think you could start with that, you can do it as you like. He gave me completely free way and this was the advantage. He was not an expert in this field but he just trusted me and that’s how I came interested in that. |
| Q7 | **When you yourself recruit students to your lab, and you’ve recruited many, what do you look for in them? What are you trying to identify in a new student?** |
|  | Gerhard Ertl: First of all, I had about the same number of students from physics and chemistry and this is very advantageous because both parts have their pros and contrasts and their collaboration was always very fruitful. Then I always check if they are really motivated and interested. It’s not so much the marks they got in their examinations but are they curious enough and also brave enough to take a new problem? You can recognise that very early and I think that was, shall we say, a recipe which worked. |
| Q7 | **You can recognise their passion for the science?** |
|  | Gerhard Ertl: Definitely, yes. If somebody really gets interested in a problem, you’ll explain to him. |
| Q11 | **You say you have an equal mix of chemists and physicists. Is it easy to get the physicists to come across to what is essentially a chemistry environment?** |
|  | Gerhard Ertl: Yes, because the methods we are applying are physical methods, so many, many physics students are really interested to see what they can do with the physical techniques. These are problems they are usually not faced with, so I never have problems to get good students from physics. |
| Q5 | **Ok, that’s what you look for in them. What do you think that they look for in you? What are they hoping to get from you as a mentor?** |
|  | Gerhard Ertl: I think there is a lot of networking between the students. They know in advance what kind of professor is that. They told me that many years later, very often, I went to you because my friend said you should go there and so, yes, and obviously … |
| Q5 | **And in the main they respond well to that?** |
|  | Gerhard Ertl: Oh yes. This is just the kind of responsibilities they get in this way. Of course I was told later that very often I had convinced them to do something else than they had in mind but they always agreed that later this was the right decisions I made. |
| Q5 | **Your students must have gone off and inhabited many, many other departments?** |
|  | Gerhard Ertl: I’ve many students now who are professors at universities or in leading positions. I’m very proud about that, I must say. |
| Q3 | **A question that I often ask, but what is it that you enjoy the most about the practice of science? About the science that you do?** |
|  | Gerhard Ertl: I think it’s always an adventure to ask a question and to enter a new field where you don’t know the answer in advance. If you then get an answer and if this answer is really surprising, this creates a great joy, always. And this continues, yes. |
| Q6 | **And do you enjoy the lab work very much?** |
|  | Gerhard Ertl: That’s right, yes. I have spent quite some time with the laboratory. I’m no longer working with my hands but just discussing with the people there and so on. It’s very rewarding also to see how the results come out. |
| Q6 | **Why do you no longer work with your hands?** |
|  | Gerhard Ertl: I’m retired. I retired three years ago, so I no longer have a laboratory any more. The more advanced you get, the more other responsibilities you have. You are no longer able to really spend hours in the laboratory, that’s correct. You have to rely on your co-workers and I had always the luck to have excellent co-workers. |
| Q10 | **What are your feelings about the future of German, European science? Are you optimistic about the way things are going?** |
|  | Gerhard Ertl: I think the research going on in Europe is not of the same quality as the research going on in the United States. Also funding, of course, that would need better funding for research but this is not the main issue. The main problem of our universities is the structure, the undergraduate training and the structure of the universities. There are many, many students who leave the university after two or three years or so and there is no real challenge for them. They’re just there and of course many professors are a little bit frustrated because they don’t get the support for their teaching which would be necessary. This is something which has to be reformed, quite obviously. |
| Q10 | **Right, and tuition fees would add that driving force?** |
|  | Gerhard Ertl: Yes, of course. As soon as you have to pay something … If you don’t pay for something it’s not worthwhile. We have a long standing debate on this issue in our country at the moment and some parts of Germany now have introduced small tuition fees and I think that will help. |
| Q9 | **That’s nice. But presumably there is perhaps now a pressure to take part in further planning for the future of German science, as a Nobel Laureate?** |
|  | Gerhard Ertl: So far, I was not approached directly in this respect but, as I told you, I was for many years vice president of the German Science Foundation. I was always involved in the planning of the research funding in Germany so I am familiar with the attempts to improve the situation for German research and I’m sure that I will also be approached in the future again. |
| Q9 | **On the subject of being a Laureate, how are you finding it? How have you found the last couple of months since the announcement?** |
|  | Gerhard Ertl: Hectic and chaotic, so it still needs some time for me to really recover from the announcement, I must say, because now many, many people approach you and want answers to questions you never had thought before and on quite different things. |
| Q9 | **Do you have any intentions of how to use the status of being Nobel Laureate in the future or is it too early to say?** |
|  | Gerhard Ertl: I still have to recover from all these hectic weeks now, so after Christmas, I will retreat into my resort and stay there for a week or so and just think over the whole situation. |

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| **Chemistry\_2024-2000** | |
| **ID** | 0347 |
| **Biographical** | My adult scientific career began with graduate study in chemical physics with Harden McConnell at Stanford. I had the idea of elucidating the mechanism of ion transport across biological membranes by nuclear resonance. I thought ion transport must involve rotation of the transport protein in the membrane. Struggling to prove this wrong idea, it occurred to me to study the rotation in the membrane of a lipid molecule, about 1,000 molecular weight, rather than a protein fifty times larger. This led to my discoveries, by nuclear and paramagnetic resonance methods, of phospholipid flip-flop, an exceedingly slow process, and lateral diffusion, exceedingly fast (Kornberg and McConnell, 1971a ; Kornberg and McConnell, 1971b).  For postdoctoral work, I wanted to learn about the other important method of physico-chemical analysis of macromolecules, X-ray diffraction. The obvious choice was the Laboratory of Molecular Biology (LMB) in Cambridge, where protein crystallography was developed and still most intensively practiced at the time. I went in the spring of 1972 to work with [Aaron Klug](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1982/index.html), who was not only a leading crystallographer, but also responsible for the application of Fourier methods to electron microscopy and image processing. While looking for a problem to study by X-ray diffraction, I got to know Mark Bretscher, the only person at the LMB interested in membrane structure, and he suggested reading a paper just published by [Francis Crick](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1962/index.html) titled “A General Model for Higher Organism Chromosomes” (Crick, 1971). Figure 3 of that paper was a diagram showing a loop of DNA crossed by a dashed line, said to symbolize a histone molecule. When I raised the subject with Aaron Klug, he immediately produced a sheaf of papers on the X-ray analysis of chromosomal material, or “chromatin,” known for nearly a century to contain roughly equal weights of histones and DNA. Aaron had discussed the interpretation of the X-ray pattern of chromatin extensively with Francis, and he encouraged me to pursue the problem. He warned me, however, that it was a “messy” problem.  Notorious might have been a better word. Many had succumbed to the allure of the problem, with its potential for insight into genetic chemistry, only to be frustrated by the intractability of the histones. These proteins were, on the one hand, surprisingly simple, and on the other hand, hopelessly complicated. There are only five types of histone, designated H1, H2A, H2B, H3, and H4. Upon isolation, however, the individual histones proved to be extraordinarily sticky, binding avidly to DNA and interacting with one another in every possible combination. Whereas the X-ray diffraction pattern of chromatin was indicative of repeating order, the biochemical behavior of the histones did not appear to explain it. There was, moreover, sufficient variation in the relative amounts of the histone types in various tissues and organisms “to make the idea of a unique repeating order untenable” (Huberman, 1973). The histones came to be regarded as a kind of amorphous glue, coating the chromosomal DNA, with no obvious significance.  I began by repeating the work of others, isolating the individual histones, mixing them in various combinations with DNA, and recording X-ray diffraction patterns. I also scoured the literature and came across two papers that influenced my thinking. A paper by Hewish and Burgoyne reported the cleavage of about 10% of chromosomal DNA by an endogenous nuclease in isolated rat liver nuclei to multiples of a unit size (Hewish and Burgoyne, 1973). When I mentioned this to Francis Crick, he shot off a letter to Hewish inquiring about the size. The reply came from Burgoyne, giving the sedimentation coefficient of the unit length of DNA. Assuming the measurement was made under alkaline conditions, as was customary for sedimentation analysis of RNA, much studied at the LMB at the time, the value from Burgoyne corresponded to about 500 bases. This unit size did not relate to any other information about chromatin, and the appearance of multiples of the unit size simply confirmed what we already knew from X-ray diffraction, that chromatin contained some amount of repeating substructure.  The second paper, by van der Westhuyzen and von Holt, reported the extraction of histones from chromatin by mild methods, rather than with strong acid or other harsh treatment, as was customary at the time (van der Westhuyzen and von Holt, 1971). Mild methods failed to resolve the histones entirely from one another, so the paper was ignored. What attracted my attention was the clean separation of the mildly extracted histones into two groups, H2A/H2B, and H3/H4. This separation contrasted with the promiscuous interactions of the histones previously observed. I realized this promiscuity was likely attributable to the denaturation of histones during isolation in the past. From the data in the paper, I could also deduce that the H3/H4 group behaved as if twice the size of the H2A/H2B group, although all four individual histone proteins were about the same size. I concluded that H3 and H4 must form a dimer, and I thought I might crystallize and solve the structure of this unique histone oligomer.  What followed was truly astounding. I measured the molecular weight of the purified H3/H4 preparation by equilibrium ultracentrifugation, while Jean Thomas offered to analyze the material by chemical cross-linking. Both methods showed unequivocally that H3 and H4 were in the form of a double dimer, an (H3)2(H4)2 tetramer (Kornberg and Thomas, 1974). I pondered this result for days, and came to the following conclusions (Kornberg, 1974). First, the exact equivalence of H3 and H4 in the tetramer implied that the differences in relative amounts of the histones from various sources measured in the past must be due to experimental error. This and the stoichiometry of the tetramer implied a unit of structure in chromatin based on two each of the four histones, or an (H2A)2(H2B)2(H3)2(H4)2 octamer. Second, since chromatin from all sources contains roughly one of each histone for every 100 bp of DNA, a histone octamer would be associated with 200 bp of DNA. Finally, the (H3)2(H4)2 tetramer was reminiscent of hemoglobin, an a2b2 tetramer. The X-ray structures of hemoglobin and other oligomeric proteins available at the time were compact, with no holes through which a molecule the size of DNA might pass. Rather, the DNA in chromatin must be wrapped on the outside of the histone octamer.  As I turned these ideas over in mind, it struck me how I might explain the results of Hewish and Burgoyne. What if their sedimentation coefficient of unit length DNA fragments was measured under neutral rather than alkaline conditions? Then the DNA would have been double stranded and about 250 bp in length. Allowing for the approximate nature of the result, the correspondence with my prediction of 200 bp was electrifying. Then I recalled a reference near the end of the Hewish and Burgoyne paper to a report of a similar pattern of DNA fragments by Williamson. I rushed to the library and found that Williamson had obtained a ladder of DNA fragments from the cytoplasm of necrotic cells and measured the unit size by sedimentation under neutral conditions: the result was 205 bp! I was euphoric. In the months and years to follow, it was often pointed out how thin was the support for my ideas and how extended the line of reasoning, but I never really doubted the conclusions. The prediction of the DNA unit size and its verification convinced me completely.  Support for a particulate substructure of chromatin came from electron microscopy and from nuclease digestion and sedimentation analysis. Some work on these lines was done even before my own, and though not definitive, was nicely coincident with my ideas. In the years to follow, with colleagues in Cambridge, I proved the existence of the histone octamer and the equivalence of the 200 bp unit with the particle seen in the electron microscope (Kornberg, 1977). This chapter of the chromatin story concluded with the X-ray crystal structure determination of the particle, now known as the nucleosome, showing a histone octamer surrounded by DNA, in near atomic detail (Luger *et al*., 1997).  At this natural break in the work, I returned to the US, first as faculty member of the Department of Biological Chemistry of Harvard Medical School in 1976, and then the Department of Structural Biology of Stanford Medical School in 1978. I had decided to pursue the function rather than the structure of the nucleosome, and was joined in this by Yahli Lorch, who became my lifelong partner in chromatin research, and also my partner in life. We investigated the consequences of the nucleosome for transcription. It was believed that histones are generally inhibitory to transcription. We found, to the contrary, that RNA polymerases are capable of reading right through a nucleosome. Coiling of promoter DNA in a nucleosome, however, abolished initiation by RNA polymerase II (pol II) (Lorch *et al.*, 1987). This finding, together with genetic studies of Michael Grunstein and colleagues, identified a regulatory role of the nucleosome in transcription. It has since emerged that nucleosomes play regulatory roles in a wide range of chromosomal transactions. A whole new field has emerged, one of the most active in bioscience today. It involves a bewildering variety of posttranslational modifications of the histones, and a protein machinery of great complexity for applying, recognizing, and removing these modifications.  Although Yahli’s first priority was the rearing of our children, Guy, Maya, and Gil, she performed a series of important studies of chromatin remodeling, believed to oppose inhibition by nucleosomes. She began with Brad Cairns, who discovered the RSC chromatin remodeling complex. Subsequent work showed that RSC disrupts nucleosome structure and slides histone octamers along the DNA (Lorch *et al.*, 1998; Lorch *et al.*, 2001). Most recently, we found that RSC can transfer a histone octamer to a histone chaperone protein, exposing the nucleosomal DNA for transactions such as transcription (Lorch *et al.*, 2006).  For studies of transcriptional regulation, it was necessary to identify the transcription machinery. Biochemical work, in the laboratories of Robert Roeder, Ronald and Joan Conaway, and others, revealed the complexity of the RNA polymerase II transcription machinery of mammalian cells, and it was apparent there was much to be gained by studies in yeast. A combined genetic and biochemical approach, possible only in yeast, would be advantageous for the solution of such a difficult problem. There was, however, a major obstacle. The development of a yeast pol II transcription system had been attempted unsuccessfully in many laboratories for more than a decade. Efforts to develop biochemical systems from yeast for RNA splicing, membrane transport, and other processes had also met with failure, leading to the widely held view that yeast, although the organism of choice for eukaryotic genetic analysis, was unsuited to biochemical investigation. First Yahli, and then graduate student Neal Lue, took up the challenge. Neal was eventually successful, by changing a number of procedures and conditions used in the past, including the replacement of chloride by acetate ion (Lue and Kornberg, 1987). Remarkably, chloride, though a component of other transcription systems, is highly inhibitory to yeast pol II transcription.  Neal, Ray Kelleher, and Peter Flanagan undertook fractionation of the yeast system, followed by Mike Sayre, John Feaver, Herbert Tschochner, Opher Gileadi, and Lynn Henry. The yeast system was problematic, since the starting transcription signal was a thousand-fold less than that in mammalian systems, and we soon reached an impasse. After enriching the transcription proteins about a hundred-fold through two chromatographic steps, we could proceed no further. Every subsequent step eliminated transcription completely. Mike achieved a breakthrough by starting over. He realized the problem was the loss of essential components and an accumulation of inhibitors, and he devised a new fractionation procedure that was ultimately successful (Sayre *et al.*, 1992).  An important outcome of this work was the discovery that yeast and mammalian pol II systems are the same. Differences in promoter structure believed to reflect fundamental differences in the transcription proteins proved to be insignificant. The real payoff, however, was in the study of transcriptional regulation. In the late 1980s, it was thought the communication between gene activator proteins and the transcription machinery was direct. In 1990 and 1991, Ray and Peter produced evidence for an additional factor required for this communication in a still crude yeast system (Flanagan *et al.*, 1991; Kelleher *et al.*, 1990). This additional factor, which we referred to as Mediator, proved elusive. The requirement for the factor was variable over the course of fractionation. As so often happens, the solution of the problem came from an unexpected direction. The most difficult protein of the pol II transcription system to purify, known as factor IIH, was contaminated with Mediator, and only after entirely pure IIH was obtained by Jesper Svejstrup (Svejstrup *et al.*, 1995) were Stefan Björklund and Young-Joon Kim then able to complete the isolation of Mediator (Kim *et al.*, 1994). To our astonishment, pure Mediator proved to be an assembly of nearly two dozen proteins, more than half of which were known from genetic studies in yeast to be involved in transcriptional regulation.  In parallel with these biochemical studies of pol II transcription, we pursued the structure of the transcription machinery. Pol II, the central component of the machinery, is an assembly of a dozen proteins, several times the size of any asymmetric structure determined by X-ray diffraction in the early 1980s when we began. The story of our solution of the pol II problem is told in my [Nobel Lecture](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/2006/kornberg-lecture.html), except for its origins in my graduate studies of lipid diffusion. While I was in Cambridge, Aaron Klug and collaborators were developing electron microscope crystallography for the solution of protein structures too large for X-ray crystallography. As the name implies, the electron microscope approach also requires protein crystals, only they must be thin, preferably a single protein molecule thick, or “two-dimensional,” for transmission of the electron beam. The work in Cambridge at the time was limited to naturally occurring ordered arrays of proteins, and it was apparent that a general method of forming two-dimensional crystals was needed to bring any protein of interest within reach of the electron microscope procedure. I thought I might exploit lateral diffusion in lipid layers for the purpose. A protein bound to a lipid layer would be constrained in two dimensions but free to diffuse and, I hoped, to crystallize. I tried this idea, beginning with nucleosomes and positively charged lipid layers. Finally, after repeated failures over a period of about five years, a sabbatical visitor, Ed Uzgiris, was successful, with the combination of a monoclonal antibody directed against a lipid hapten (Uzgiris and Kornberg, 1983). This work led eventually to twodimensional crystals of pol II, and then to large single crystals and the X-ray structure of pol II.  Our biochemical and crystallographic work converged in the X-ray structure determination of pol II. This convergence was the culmination of a long effort, but also a beginning. Pol II associates with two dozen additional transcription proteins and with Mediator in a giant assembly formed at every promoter prior to the initiation of transcription. The ultimate goal of our work is to solve this giant complex and thus to understand the mechanism and regulation of transcription. We believe we will achieve this goal within the next decade, through crystallography and, possibly, another development in electron microscopy. Inspired by graduate student Grant Jensen, we have pursued the synthesis of large heavy atom clusters, for the purpose of structure determination without crystals at near atomic resolution (Jensen and Kornberg, 1998). This work has opened a window on a whole new realm of inorganic chemistry and materials science, through which we may pass into the future. |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** | [RK]  [Roger Kornberg] – Hello.  [AS] – Hello, Professor Kornberg?  [RK] – Hang on one second please.  [AS] – Yes, of course.  [RK] – Hello.  [AS] – Hello, yes sorry, my name’s Adam Smith, I’m the …  [RK] – Yes.  [AS] – Yeah, OK. We have a tradition of recording very brief telephone interviews with Laureates as soon as they’ve been awarded.  [RK] – I’ll be glad to do that.  [AS] – That’s very, very kind of you, thank you.  [RK] – Not at all.  [AS] – First of all, needless to say, congratulations and …  [RK] – Thank you very much indeed.  [AS] – You must already be exhausted at the start of a very busy day.  [RK] – You know I was exhausted before it began, actually. I had been traveling for the previous almost 48 hours and then just got to sleep, and was almost immediately awakened by this news. And I can tell you that, besides feeling bewildered, I’m not at all tired any longer.  [AS] – Yes, you’ll be running on adrenaline for days to come I imagine.  [RK] – I’m sure, it’s extraordinary news.  [AS] – Well, it’s wonderful news. And particularly nice that it’s a family prize, that must make it special in all sorts of ways.  [RK] – Of course.  [AS] – You’ve been awarded the Nobel Prize for uncovering the structure of the cellular apparatus that gives voice to otherwise silent DNA. Is this the machinery that really holds the key to which pages of the book of life get read by individual cells, would you say?  [RK] – I think you’ve put it even better than I might have done. That’s precisely what it does. The information is one thing, but its use in the right place at the right time is ultimately decisive, and the machinery that we and many others have studied is directed towards that purpose, and our particular contribution has been analyzing the central molecule of the process and discovering the arrangement of the many thousands of atoms that make up that molecule.  [AS] – And you also found that that machinery appears to be essentially the same in all animals, plants and fungi. Did that similarity strike you as very surprising?  [RK] – The similarity goes far beyond anything we had anticipated. And I might say that when we began our work we made the decision to focus on a simple, unicellular eukaryote, baker’s yeast, and the decision at that time was one of uncertain wisdom because it did seem from the available information there might be profound differences between this fundamental process in yeast and, for example, in human cells. The extent to which, as I have said, the similarity has proved to hold between yeast and human cells is perfectly extraordinary. It begins with that central molecule to which I referred which is very nearly identical. But then after that, the larger cast of characters that assist that molecule in performing its role prove also to be remarkably alike between yeast and human cells. As recently as ten years ago, when we discovered the last members of that cast of characters, a set of about twenty that play a crucial role in the regulation of the process, it was believed for quite a long while that, at that level at least, there would be a divergence, and that humans would prove to differ fundamentally from yeast. Even at that level it has turned out that the process and the molecules responsible are virtually the same in yeast and in higher, including human, cells.  [AS] – It makes one wonder where the differences do lie really.  [RK] – So the differences of course lie in sets of genes that go beyond what is present in yeast. But the process we study is a fundamental one that applies to all genes everywhere, and it is for that reason that it is conserved.  [AS] – The transcriptional machinery you’ve described is I think the most complicated protein structure seen to date …  [RK] – Yes.  [AS] – … and just to try to give us an indication of what that apparatus is like, could you tell me how you envisage it working when you see it in your mind’s eye?  [RK] – So the machinery that we study is made up of about sixty protein molecules. Each protein molecule is made up of several thousand atoms. The remarkable thing about the machinery is the extent to which it truly functions in the way you and I imagine or think of a machine. So it has moving parts, the moving parts function in synchrony, in appropriate sequence and in synchrony with one another. They execute remarkable transitions from one stage or step in the process to the following one and part of the pleasure and the fascination of what we do has been in discovering the mechanics, the inner workings of that machine.  [AS] – Do you know what speed it works at?  [RK] – It copies approximately ten DNA, or RNA (as they are called), letters per second.  [AS] – And it must achieve an extraordinary fidelity in its copying because the room for error is very small.  [RK] – It achieves very great fidelity, but beyond that it has inherent mechanisms for proof-reading and correcting errors that may be made in the process.  [AS] – Perfect machine! Am I right in thinking that all the work that’s led up to this point has been publicly funded?  [RK] – Yes, that’s right. All the work that we have done, virtually without exception, has been funded by the National Institutes of Health of the United States. We have received some funding from other sources, principally through fellowships given to postdoctoral members of the laboratory and graduate students over the years. But the principal source of funds, and what has made it all possible, is without a doubt the extraordinary support of science by the National Institutes of Health.  [AS] – Is that also a conscious choice on your part to avoid industry funding, or is it just that there’s an abundance of public funding?  [RK] – It’s not a conscious choice. But on the other hand, what we do is so fundamental that it would not be likely to receive industry funding. It would require a very farsighted commercial organization to invest in something which will doubtless have a payoff, but only in the decades to come.  [AS] – In a way it’s rather refreshing to hear that, that one’s not rushing to application immediately with something like this.  [RK] – And I would say that I think it’s one of the finest and the highest achievements of we, collectively as people, to have been willing to make such an investment, and to have gained something from it.  [AS] – I mean, indeed, the complexity of what you’ve achieved in structural resolution must have taken enormous investment of time, and faith.  [RK] – Certainly faith because when we began it was obviously impossible, and for much of the time the problems were evidently insuperable. Also a very great investment in time in as much as the origins of the work were about thirty years ago and the work began really in earnest towards this objective about twenty years ago.  [AS] – OK, well I know that you’re on a tight schedule and I’ve taken up, I think, enough of your time.  [RK] – A pleasure to talk with you.  [AS] – We speak at greater length with the Laureates when they arrive in Stockholm in December so …  [RK] – I look forward.  [AS] – … hopefully we’ll have the chance to continue then. Thank you very much and congratulations again.  [RK] – Thank you. Bye.  [AS] – Bye, bye. |
| **Interview** |  |
| Q4 | **You know what pinnacle’s like here. I’d like to turn first to the relationship between biology and chemistry. You work on a system which many would think of as a very fundamental biological mechanism, and yet you’ve been awarded the Nobel Prize for chemistry. Why is that?** |
|  | Roger Kornberg: In the very first place the work we’ve done is purely chemical. The discovery for which the prize was given is the arrangement of atoms in a large molecule, that is as much the definition of chemistry I think one could hope to define. Beyond that, and I think it’s important to bear in mind that what we study is not so much biology as life chemistry, so the answers to the questions that we have about biology all lie at the level of chemistry, and the thrust of modern biologic science and modern biomedicine is to discover of a chemical basis for all that goes on.  Now, it’s also worth mentioning my background is from chemistry, and the work that lead up to the structure for which the prize was given began in what I did, which even the most traditional chemist would today regard as the proper domain of chemistry, so this sprang from chemistry, what eventually emerged is indisputably chemistry, the connection to biology is in explaining a life process. One last point on those lines, what is traditionally the preserve of chemistry always involved the study of molecules derived from nature, one of the most classical undertakings in traditional organic chemistry has been the structure determination of the total synthesis of molecules derived from nature, some of the famous molecules that you know of, vitamin B12, chlorophyll, what have you, these are all molecules derived from nature, many organic chemists over the years pursued the structures and synthesis of alkaloids derived from nature, protein molecules nucleic acids are no less or more chemical molecules than vitamins or alkaloids. |
| Q2 | **We hear constantly though that chemistry as a discipline is rather under fire, and that people are not going into chemistry in the way they used to, so do you think it matters how one labels the research? For instance you work in a department of structural biology, is it important the label which one gives to the research one does?** |
|  | Roger Kornberg: You’ve come absolutely to the heart of the matter, so labels were once applied as a way of identifying the distinct nature of the various disciplines, of course the boundaries have become blurred, the disciplines have to some extent merged, I think labels are always useful for administrative purposes of dividing up research groups into manageable units and the traditional labels from the past are just as useful for that purpose today as they ever were before.  The fact remains that as I said the boundaries have blurred, but what is more, the work that we do in the structural biology department is it’s in some places done in the departments of chemistry and in other places done in departments of biology, beyond that I might add that in my personal view chemistry is really the queen of the sciences, chemistry is the common ground for all scientific investigation. So our best hope of applying physical principles for the world around us is at the level of chemistry, our best hope of understanding the biological organism and ultimately the form and function of the human body is at the level of chemistry. I have said before and I would repeat that if there is any one subject that an educated person should know in the world that is chemistry. |
| Q11 | **Nice message. So would you describe the work you do as interdisciplinary? Or do you think that’s a very overused term these days?** |
|  | Roger Kornberg: In the sense that what were traditionally regarded as distinct disciplines have come together in our work then it would be regarded as interdisciplinary, people have remarked that the culmination that we make of functional studies commonly referred to as biochemistry with structural studies, which more commonly lie in the province of physical chemistry is distinctive. For myself I see really no alternative, I think the problems that we study and that others will do of a similar nature in the future can only be approached in this way. |
| Q7 | **When you chose students, young people, to come into the lab do you look for any particular background in them or … I think there’s an increasing tendency for people to want to use lots of different techniques in their research, they tend to quickly want to quickly want to jump to the point of using lots of things, is that something that you would go against?** |
|  | Roger Kornberg: I have a very straight forward answer to your question, the one thing I look for is chemistry.  Roger Kornberg: People come to my lab from a background in biology, they come from a background in physics, and the question I always ask is about their training in chemistry, if they have studied chemistry then what chemistry did they study and how well did they do it. If someone comes along who has studied physical and organic chemistry and then obviously been good at it, then I know that they will fit in well, that they will succeed in what we do. |
| Q2 | **You yourself became interested in science at a very young age, do you think that that’s an essential attribute of a scientist to have become a scientist when they were still a child?** |
|  | Roger Kornberg: I would say that my own serious interest in chemistry dates from high school, and I think that’s not uncommon, that young people’s interests become defined at that age as they grow to maturity and they think seriously or can begin to comprehend what lies within them concerning the logical or natural directions they’ll pursue. I was exposed to science at a younger age but I don’t think that mattered so much as the inspiration I drew from a particular chemistry teacher in high school.  was very fortunate that I studied chemistry in high school during a narrow window of time when the particular textbook that was used was of an exceptional nature, I’ve … it was from a programme in the state of California put together by a large number of practicing chemists who wanted to convey the principles of chemistry, and they did so superbly well, I learned the principles and they have served me all my life, and I think I’ve had an advantage over many others because I was taught so effectively at that time, these principles became deeply engrained and they stuck in mind, the course consisted of a series of very simply but well chosen chemical experiments each of which illustrated a principle in a way, which as I say I myself found unforgettable. |
| Q5 | **Having explored a little what you look for in your students, what do you think your students look for in you? What makes a good mentor?** |
|  | Roger Kornberg: My opinion about that is quite straight forward, I think that the relationship between student and mentor in my lab, and doubtless in many others, is one of equals pursuing the solution of a problem. And I think what I know my students look to me for guidance but I don’t seek to guide so much as to share, at the end of what is often quite some years of mutual struggle with a problem, and more often than not a period of frustration and in the case of the student significant self doubt, there comes a resolution, a discovery or an answer to the question or a way of surmounting whatever obstacle it was that confronted us. And that has the affect of binding us together as lifelong friends because we shared that struggle, and then has the effect on the student of giving the most important thing which is not so much specific information or even knowledge of how to attack a scientific problem as the self confidence, the belief, the knowledge that one can struggle with something which seems to be at some stage impossible and then ultimately succeed. I think if there’s anything I can convey to the people who work with me it’s ultimately that belief in one’s capacity to succeed and eventually a satisfactory outcome. |
| Q3 | **It might not be a sensible question but what is that you think drives you? Is it trying to find the solution to individual problems? Or is it just a fascination in the area you study in general?** |
|  | Roger Kornberg: It’s the conventional wisdom about scientists is they’re driven by curiosity. The other common reason that is supposed why people do it is some form of altruism, wanting to do something that is good for people if be enviromedicine or for the world in some other area. I think almost all scientists do it for the reason I do which is the challenge of solving problems, and naturally we grapple with specific problems, if one can’t … and the key to solving them is actually to keep narrowing the focus until finally one has redefined the problem in a way that it can be solved, so the answer to your question is very much what motivates us and our source of satisfaction is in grappling with specific issues, and then as I say having the pleasure of finally discovering the way to either overcome a technical limitation or find an answer to a paradox about the material or whatever it may be. |
| Q10 | **You also focused on this area that, it may be a meaningless question, but how do you avoid getting excited by problems that lie outside of the mainstream of what you’re studying? Because there must be lots of distracting nuggets that you could find?** |
|  | Roger Kornberg: So on the one hand I would say that one of the things that I most enjoy about science, especially 20 years ago, was the possibility at that time of being interested in everything going on in science and following it and attempting to think in a creative way about almost every area of science, this was the style of [Linus Pauling](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1954/pauling-facts.html), and of other people of that stature who I admired and may have wished to emulate, but above all it was just the general fascination with science, there isn’t one area that’s more interesting than another and it was fun to learn about, as an undergraduate student I learned about and tried to study in the greatest depth that I could all areas of science, mathematics, science extending from physics to biology.  Up until about 20 years ago as I say it was possible to be aware of what were the outstanding issues in all of the areas, to read the literature, to follow the developments and occasionally to have ideas about them which may have been worthwhile. That ended with the explosion of information and with the exponential growth of science, and today it is simply no longer possible for anyone to be a generalist in the same sense. Even so, the distractions abound because the amount of information in the immediate vicinity of one’s own specific area really exceeds anybody’s possibility for comprehension, and so what I would say, despite the pleasure of the general interest in science before or the need to try and assimilate as much as possible of the relevant information that surrounds one’s own work today, the key to success is ultimately focus, it is in a way what I was saying before, it’s to narrow the description of the problem in a way quite contradictory to the notion of an interdisciplinary approach, on the contrary, one needs to be as narrow as possible to succeed, and the solution of any one problem as particular, and to find it you need to eventually hone in on something that is with pinpoint precision. |
| Q10 | **Given the explosion of science do you think that the finding environment for the sort of long term approach that you’re taking is getting better? Or worse?** |
|  | Roger Kornberg: I think that funding for a venture of the sort in which we’ve been engaged which extended over a period of many years was never really possible and never really will be, so it isn’t in general possible in the United States or anywhere else that I know of to seek funding for something that is open ended, that has no certain or even very likely prospect of success and it will obviously take a very long time, and the only way such work can be done is to define interim objectives and in the case of the work we do in the United States, and here I don’t know whether the same situation would apply elsewhere, to do related work that can be funded, but to draw upon the funds that are given for that also to pursue these longer term objectives which is very much encouraged in the American system, it’s understood that one may use the funds to do other science and the only constraint is at the end of the day one must demonstrate success. |
| Q15 | **What about the relationship between basic science and applied science? There’s a tendency for people to say okay, how can we use this, as soon as one reports any result and clearly in this case that question … one can come up with an answer to it, but the question doesn’t really mean that much, this is basic stuff, do you feel that it’s a worrying trend that people always want to apply what one is producing?** |
|  | Roger Kornberg: On the one hand yes, it is a worrying trend in so far as it diminishes the support available for the pursuit of basic knowledge. On the other hand like all worrying trends in the world they have always been there and they always will be. And what the countervailing force is the drive on the part of individuals to seek the most basic truths and people will find a way, we do in our work, that’s the purpose, we delve as deeply as we can. There is no doubt that the future lies in all regards in the acquisition of increasingly fundamental, so the most basic knowledge, and useful applications always spring from that, and they are limited by the extent of our basic knowledge. That tends to be sometimes forgotten and there’s an understandable tendency on the part of people to want solutions to pressing problems now, nonetheless the drive to discover the most fundamental basis is something which is also strong, it can’t be prevented, it will go on, it will succeed. |
| Q2 | **Shifting track a little bit, one of the things that you’ve described as giving you greatest pleasure is to imagine the molecular machine that you study, and when we spoke in October just after you’d heard the news that you’d been awarded the prize you began to describe how you see it, could I get you to elaborate a little on how you picture this machine working when you see it in your mind’s eye?** |
|  | Roger Kornberg: What is most fascinating about the very large molecular structure that we discovered from our work over the years is the extent to which it resembles a piece of machinery such as we know from daily life, so molecules have been … a good deal smaller molecules have been studied in the past and they are capable of executing specific transactions. What is astonishing about the piece of machinery that we have investigated, so much larger than those studied previously as I have mentioned, is that it executes many transactions, it contains multiple moving parts, these function in sequence and in ways that we still don’t fully understand, to execute an extraordinarily complex molecular transaction. Now the individual pieces can be viewed as the counterparts of tools or the components of machinery as we know it, and we name them accordingly, so the device that we study has a jaw, it has a rudder, it has parts that we call trigger and lid, and so on. |
| Q2 | **Do you envisage them as solid or fluid?** |
|  | Roger Kornberg: The components of such molecules must on the one hand be perfectly rigid in order to have a defined shape, much like the parts of a machine, to execute their function. At the same time at appropriate times they’re capable of bending, flexibility, they can adopt multiple states of organisation as appropriate for their function. But I think the underlying principle is one of rigidity and so precise definition in much the same manner as one would envisage a piece of /- – -/ combustion engine or what have you. |
| Q3 | **Right. And when people come to ask to work with you on this problem what do you think it is that draws them in first and foremost?** |
|  | Roger Kornberg: I think that when young people are attracted to research on a particular problem, they likely begin either with an interest in the broad area, in the case of our work most broadly defined it is the area of biological regulation, it is the control of gene expression. In other cases they may also be drawn to the nature of the work, the kinds of technology and manipulations that are involved. I think both are important because after all one must have some degree of fascination with the broader questions, but at the same time the work itself involves many often repetitive activities on a daily basis, and if one can’t take pleasure in the actual manipulations then it will lose its appeal. |
| Q9 | **The Nobel Prize will bring yet more notoriety for you and your work, and you’re very, very focused on what you do, how will you, do you think, cope with the increased demands?** |
|  | Roger Kornberg: In the first place I can tell you that I’m determined I absolutely will go on with the work I do simply because I enjoy it so very much, also because as you mentioned the work has gone on for a very long time and it is a way of life, it would be difficult to adopt a different lifestyle or approach or define the same satisfaction in doing something else now. So I’m inclined to, I will almost certainly decline, most of the offers and temptations to do other sorts of things, and try to maintain the focus, for the reason as I say that it comes naturally and it’s what I enjoy. I wouldn’t, there’s nothing I wish to change about my scientific life before this point, so I have no reason to allow it to happen after. |
| Q4 | **Thank you. And lastly, Louisetta Moody from the United Kingdom asks whether during the processes of transcription it is necessary to make perfect copies or whether there’s some allowance for error possible?** |
|  | Roger Kornberg: The answer is at two levels, no process is perfect and mistakes are made. And there are mechanisms for correcting the mistakes, those mechanisms are not perfect either and sometimes the mistakes slip through. Now the mechanisms for correction are extraordinarily, are no less intricate and remarkable than the mechanism of transcription itself. It’s only in the last few months that we’ve actually understood how common errors are avoided and how accuracy is achieved in transcription, and that work from the last several months has only been published in the last week. |

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| **Chemistry\_2024-2000** | |
| **ID** | 0348 |
| **Biographical** | I was born on 10 October 1930 in Menin (Menen in Flemish) in western Flanders, on the border between Belgium and France. My parents were French. To be more precise, they were not only both from the Tours region, but also descended from long-established families in the little village of Beaumont-la-Ronce. I used to spend my holidays there in my grandparents’ large family house, with my numerous cousins. When I die, I am going to be buried in the village cemetery. My grandmother was fond of painting and playing the piano. She had been given lessons by Emmanuel Chabrier, who used to spend the summer months in nearby Membrolle. He said in his correspondence that he did not much care for his pupils on the whole and my grandmother found him very strict. Most of my ancestors were small farmers. My father was an electrical engineer. After three years of military service and quite a difficult time in the First World War, he was sent by the company that had taken him on after his demobilisation to Ypres and then Menin, to work on rebuilding (building) the electricity network in this war-ravaged province. I remember him always being very motivated and working very long hours. He was sent to war again in 1939 and taken prisoner. There were 5 brothers and sisters in the family and we had quite a strict upbringing. From my bedroom, I looked out over our large garden (roses and vegetables) and the Lys river, which at that particular point separates France from Belgium and was where the flax was retted in tanks then dried in little bundles in a field (what a foul smell!). I watched the barges go past, towed by horses or even by men. It was a fascinating sight: the man pulling the rope remained bent over and unmoving for several minutes before the barge started to move. I also remember Vauban’s fortifications in this land of invasions, and the smell of roasted chicory … I still have many paintings of Flanders that my father bought from contemporary painters – somewhat classical, but not devoid of charm. I went to pre-school in Flanders and then the French primary school, which meant that I crossed the border every day. I then continued my secondary and higher education in various towns. During the war, I managed to come through the bombings unscathed, though sometimes only just. The war taught me to eat what there was; I am still not a fussy eater, although I do enjoy good food. To be perfectly truthful, I was not a very brilliant student, even at chemistry school. I chose chemistry rather by chance, because I firmly believed (and still do) that you can become passionately involved in your work whatever it is. Various circumstances, mainly to do with my military service, prevented me from doing a PhD and I have often regretted it, though you do need to choose the “right” supervisor in the “right” discipline – no easy task when you are totally inexperienced.  So I took a job in industry, but the fact that process development consisted primarily of copying what already existed, with no possibility of exploring other fields, prompted me to resign. Furthermore, I discovered that this was a very common attitude among managers. They are afraid of anything new: “Do what everyone else does and change as little as possible: at least we know it will work.” It is the opposite of my way of thinking, which, I must admit, is a bit of an obsession! I have often got into arguments about it. My motto is more, “If you want to find something new, look for something new!” There is a certain amount of risk in this attitude, as even the slightest failure tends to be resounding, but you are so happy when you succeed that it is worth taking the risk.  The whole contradiction of research (whether applied or fundamental) generally lies in the fact that we have to start out with the knowledge handed down by our predecessors, but be able to depart from it “at the right time.”  I joined Institut Français du Pétrole in 1960 and managed to focus my work on what I thought would be most interesting. I got married the same year and over the course of time we had two sons and five grandsons.  The oil industry essentially uses heterogeneous catalysis: cracking, reforming, hydrodesulphurization, hydrogenation, etc., but that was not what interested me. I have always tried to avoid areas that have been perfected with time. At the time, nothing much was being done in France on coordination chemistry, organometallics or homogeneous catalysis by transition metals and I was fascinated by the achievements in Italy ([G. Natta](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1963/index.html)), Great Britain (J. Chatt), Germany (at the Max-Planck-Institute in Mülheim) and the United States. As a result, I unwittingly became the French specialist in these disciplines, which brought me into contact with both the positive and the unwieldy aspects of the various commissions at the CNRS. I spent the best part of my time on applied chemistry, which was what I had been employed for and which I was quite happy about. This was how I came to develop two homogeneous catalysis processes. The first one, which uses a nickel-based catalyst, was called “Dimersol” and exists in 2 basic versions.    The “gasoline” version (Figure 1) consists of dimerising propene to high-octane isohexenes. There is, quite often, an excess of propene, especially in oil refineries that do not have petrochemicals, as in the United States. There are currently 35 plants in operation (including 18 in the USA ), with a combined annual output of 3.5 million tonnes. It was the first and only time that coordination catalysis had been used in refining.    The “chemical” version of the process (Figure 2) consists of dimerising n-butenes to isooctenes, basic inputs for plasticizers, using the “oxo” reaction. Current production levels stand at 400,000 tonnes a year.    The second process I developed, and which uses a titanium-based catalyst, was called “Alphabutol.” It consists of dimerising ethylene to 1-butene (Figure 3), the co-monomer of low-density linear polyethylene. The benefits of such a process were not evident to begin with and stem from a number of causes. There are currently 20 plants operating worldwide, with a combined output of 400,000 tonnes a year. However, others are under construction, which will take total output to over 0.5 million tonnes a year.    While there are obvious drawbacks to not having done a PhD (especially when you supervise them!), the advantage is that at least your mind is free to focus on whatever presents itself. At the time, I was working on batteries and, in particular, the non-aqueous electrolytes used to extend their electrochemical window. I thought it would be a good idea to try to use these electrolytes, which belong to the class of ionic liquids, as catalyst solvents. These liquids feature very low vapour pressure and virtual non-solubility in hydrocarbons, paving the way for a biphasic catalysis. The mixture of alkylimidazolium chloride and aluminium chloride forms a liquid with a very low melting point (below ambient temperature) (Figure 4). It proved to be a first-rate solvent for nickel-based dimerisation catalysts (“Dimersol” catalysts). The diagram for this process, called “Difasol,” is shown in Figure 5. The reaction volume required for a biphasic system is 10 times smaller than for a homogeneous system (important for safety: refineries do not like to have large volumes in reaction because they are potential “bombs,” especially at start-up); likewise for nickel consumption. This new process, dealt with in a PhD project in 1990, will see the light of day thanks to the inventiveness and determination of Hélène Olivier-Bourbigou, who took over from me in the laboratory.  What applied chemistry has taught me is the need for absolute solidarity between the research laboratory and the “downstream” side (pilot testing, marketing, setting up industrial plant): same enthusiasm, same determination, especially when everything goes wrong!  There is no difference between fundamental research and applied research. Although this is my view, based on personal taste and the areas I have worked in, it is not necessarily true for others. The PhD either led to, or were derived from processes. I have spoken so much about “processes” because they took up about three-quarters of my working time. However, I also took an interest in other aspects of coordination chemistry, such as palladium catalysis, rhodium catalysis, asymmetric amino-acid synthesis, and so on. After retiring in 1995, I was invited to work in J.-M. Basset’s laboratory in Lyon, which allows me to pursue a reasonable level of activity. |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** | – Âllo.  – Hello. Is this Yves Chauvin?  – Yes.  – Hello. My name is Joanna Rose. I am calling from Nobelprize.org which is the official site of the Nobel Foundation. My congratulations to the Nobel Prize.  – Thank you very much.  – How are you feeling about that?  -Oh, more or less …  [Telephone answering service interruption]  – I am making a recording for our website for a few minutes, can you speak to me?  -Yes, but I speak … not fluent English. You cannot speak French, not?  – Maybe you can answer in French, if you prefer that.  – Yes.  – Do you understand the questions?  – I hope so.  – So … How does it feel?  – Je me sens plutôt embarrassé. /- I find it embarrassing, above all./  – Ah … Pourquoi? /- Why so?/  – Eh bien, parce que je n’avais pas l’habitude de la célébrité. Et la célébrité, c’est lourd à porter. Voilà. /- Because I am not used to fame, and fame is heavy to bear./  – Are you totally surprised?  – Yes, yes, sure, certainly very surprised.  – And you did not expect to receive the Prize.  – No, not at all.  – Do you know the other Prize-winners?  -Ah, oui, je les ai rencontrés; j’ai lu beaucoup leurs travaux. J’ai beaucoup lu leurs travaux. Donc je connais bien ce qu’ils ont fait, mais je les ai vus deux ou trois fois dans les congrès, quoi? Voilà. Je n’ai pas de relation directe avec eux. /- Yes, I have met them and I have read their works a lot. So I’m well-acquainted with their work, but we have only met a few times at conferences, I do not have a direct relationship to them./  – What does this Prize mean to you?  – Oh …! It is difficult to say. No, I … It is difficult for me, to manage this situation …  – Vous pouvez parler français. /- Please speak French if you wish./  – Oui, oui. C’est difficile pour moi de manager cette situation. Je n’ai pas l’habitude des … disons … de la célébrité; et c’est quand même une célébrité, et je n’ai pas l’habitude. Donc je ne suis pas bien – je ne suis pas très à l’aise. Vous comprennez? Je ne suis pas à l’aise. Donc je ne peux pas dire que ça me remplit de joie. Bien sur, c’est une fierté, mais je suis plus gêné que … enthousiaste. Voilà. /- It is difficult for me to manage this situation, since I am not used to, let’s say, fame; and this is nevertheless fame and I am not used to it. So I am not comfortable, I don’t feel at ease, you see? I don’t feel at ease. So I cannot say that this fills me with joy. Of course, it is something to feel pride in. I feel more embarrassed than enthusiastic./  – Will you celebrate the Prize now?  – No, no! Quelle genre de célébrations … Quelle genre de gens? Non, rien de spécial, non. /- No, no. What kind of celebrating … What kind of people …? Nothing special, no./  – I’ve been trying to call you all day, but the phone was busy all the time.  – Yes! Ça … Il y a une foule de journalistes. Il y a beaucoup de journalistes qui sont déjà venus et on me telephone très souvent et je ne leur ai pas répondu, parce qu’il y avait un journaliste dans mon appartement. Voilà. Donc c’est pas facile. /- Yes, there’s a whole crowd of journalists that have already turned up and people are constantly phoning me, but I have not answered because there was a journalist in my apartment, so it’s not easy./  – I understand. But I hope that you are planning to go to Stockholm in December?  – Perhaps. Je pense. Je ne sais pas. Mais, on est obligé de faire un discours? Non? On est obligé de faire une … /- Perhaps. I think so, I don’t know. – Is one obliged to give a …/  – Nobel Lecture.  – A Nobel Lecture, on est obligé? /- A Nobel Lecture – is it obligatory?/  – Well, it’s usual that people do it.  – Parce que … on est trois, et il y en a deux qui peuvent faire un “speech”, une lecture. Et puis, moi pas. Parce que je n’ai pas beaucoup à raconter. Parce que, si, j’étais le premier, et après j’ai abondonné assez rapidement ce domaine. /- Because there are the three of us, and two of us could hold a speech. But me, no, because I don’t have much to tell you. Because yes, I was first, but then I left that field pretty soon. /  – Ah …  – Oui, j’étais le premier et c’est pour ça que l’on m’a donné un prix parce qu’on a dit “Oui, c’est le premier qui l’a fait.” Et puis voilà. Mais, depuis, je n’ai pas tellement travaillé dans ce domaine. Donc je n’ai pas beaucoup de choses à dire. Voilà. / Yes, I was first and that is why they gave me a prize, but since then I have not worked much within that field, so I do not have much to relate./  – But do you remember how it was when you did the work?  – Yes, yes. Sure.  – So you can tell this story.  – C’était un dimanche après-midi, dans mon appartement; il faisait mauvais temps. Et d’un seul coup j’ai dis “Ah, oui – c’est évident.” Voilà. Aussi simple que ça. Mais ça arrive à beaucoup d’autres scientifiques que c’est dans les périodes de repos qu’on peut avoir de bonnes idées, quoi. Voilà. /- It was a Sunday afternoon in my apartment, the weather was bad, and all of a sudden I said – Oh, yes, it’s obvious. Voilà, as simple as that. But that happens to lots of others in science, that it is while you are resting that great ideas come to you, see? There you are./  – Are you engaged in environmental issues?  – Non. Je suis intéressé, mais pas engagé. Bien sur, je suis préoccupé, mais pas engagé. /- No. I am very interested, but not involved. Of course I’m worried, but I’m not involved./  – I would like to say that I am looking forward to meeting you in Stockholm in December; I hope really that you can come.  – Oui. /Yes./  – Did you think about what you might do with the Prize money?  – Ah, no. I don’t … Je ne sais pas combien je vais toucher. Je ne sais pas combien. Je donnerai ça à mes enfants. /- No, I don’t know how much it is, I don’t know how much. I’ll give it to my children./  – Thank you very much for taking your time.  – Je vous en prie. /You are welcome./ |
| **Interview** |  |

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| **Chemistry\_2024-2000** | |
| **ID** | 0349 |
| **Biographical** | I was born at home in rural Kentucky in 1942, in a house that my father, Howard, had built. He did most of the construction himself and built it on land that his father had given him when he married my mother Faye. In some places, my birthplace is listed as Calvert City and in others Possum Trot. I was actually born between the two, so either one really is correct. Both of my parents were from small farm families in western Kentucky where most people stayed close to their homes. My many aunts, uncles and cousins formed a very supportive environment during my childhood. Although my grandmother spent her years working on the farm, she was very well educated and set a high standard that has resulted in many of her grandchildren becoming teachers and educators. She always read, told us stories and maintained an intellectual level that was unusual in rural Kentucky at that time. My mother was one of six surviving children of my grandmother and grandfather, a strawberry farmer. Because she was often sick when she was young and of little help on the farm, she was sent to college, where she received her teaching certificate after two years. She subsequently taught school for over 35 years as she moved from a one room school house teaching all grades, to a two room school teaching lower grades and finally to an elementary school where she taught first grade. Some of my early memories are of going to school with her when the baby sitter was not available and going to night and weekend classes with her while she finished her BA degree. It took her 28 years, but she finished her degree. She and my grandmother provided great role models for the value of education. Although my father did not attend college, he was a very gifted mechanic and a practical engineer. I grew up helping him to rebuild car engines, to install plumbing, to build houses and to work on my uncles’ farms. After my father returned from serving two years in the US army in Europe during WW II, we moved into Paducah where he took night classes to become a diesel mechanic. He then spent many years working for the Tennessee Valley Authority, (TVA), operating and maintaining heavy equipment that was used in the construction of the extensive series of dams in Kentucky and Tennessee. The academic model of my mother and grandmother and the very practical, mechanical training from my father turned out to be perfect training for organic chemical research. I was the middle child between two sisters. My older sister became a teacher and has been heavily involved in art and painting. My younger sister became the first female journeyman electrician in western Kentucky and has spent a number of years working for the TVA.  As a child I was always interested in building things. Instead of buying candy, I would purchase nails which I used to construct things out of scrap wood. My mother always claimed that my spending my money on nails instead of on candy was why I was so skinny as a kid. As I grew older, farms in Kentucky provided me with many jobs in hauling hay and in cutting tobacco. In addition to helping fund my college years, these jobs helped me to meet an array of very interesting and amazing men and women.  My interest in science started in Junior High School where an outstanding science teacher, Mrs. Baumgardner, introduced me to the joys of science. In the 50’s there were many excellent scientists in Paducah, Kentucky, who had settled there to become teachers after working in what we called the “Atomic Plant”. This was a major uranium refining facility that was located in western Kentucky to take advantage of the power and production facilities resulting from the TVA construction in the area.  Since I had grown up with parents who had started life on farms in rural Kentucky and I had spent many hours working on farms, it was natural that I started college at the University of Florida as an Agricultural Chemistry major. This field combined my interests in science and agriculture. One of my summer jobs in college was in an animal nutrition laboratory where I analyzed steer feces all summer long. Fortunately, one of my friends was working in an organic laboratory for the summer and invited me to help him at night. He was working for Merle Battiste, a new faculty member at the University of Florida. I found that organic chemicals smelled much better than steer feces and that there was great joy in making new molecules. Battiste started me on the chemical journey and saved me from a life of analyzing animal matter. Shortly after joining his group, I read an organic text, *Mechanisms and Structure in Organic Chemistry*by E.S. Gould on reaction mechanisms which explained how chemical reactions take place. I was fascinated by being able to do rather simple chemical transformations to learn about the details of how organic compounds reacted at the molecular level. This direct coupling of simple observations with fundamental chemical reactions is the power of organic chemistry. Also, building new molecules was even more fun than building houses. The reactions of cyclopropenes served as the basis for most of my work in the Battiste group, and many years later a similar reaction of cyclopropenes opened the way to the synthesis of our first generation of catalysts. Battiste not only introduced me to organic research, but after he had trained me to be a productive researcher, he told me that I would have to leave his group. Although it would have been best for him for me to stay in his laboratory to finish my degree, he encouraged me to move on to a different group in a different part of the US to receive broader training. He encouraged me to go to Columbia University in New York City where I worked for Ron Breslow. Battiste had been Breslow’s first PhD student. Just before going to Columbia, I heard a young Australian chemist, Rolli Pettit, who worked at the University of Texas, lecture at Florida. He talked about the stabilization of unstable molecules by coordination to transition metals. Rolli, who unfortunately died much too young, was an inspirational scientist who helped to direct me toward the use of metals in organic chemistry. For my graduate work, I initially chose a project related to the Pettit work and finished studying the anti-aromaticity of cyclobutadiene. It was an exciting time in the Breslow group. A number of students and postdoctoral fellows who have since gone on to stellar academic careers worked in the group at that time and, along with Breslow, provided an amazingly stimulating environment. Working on projects involving metals confirmed my desire to turn my research toward transition metal organometallic chemistry and I obtained an NIH fellowship to work with Jim Collman who had just moved to Stanford. At that time organometallic chemistry was in its infancy and it provided a fertile field for a mechanistic chemist. There appeared to be an incredible array of important catalytic processes emerging in the field while little was known about the fundamental transformation involved. Collman had developed a systematic method of discussing reaction types that provided a basis for starting to understand the steps in Catalytic processes. One of the most exciting of these processes was olefin metathesis. It turned out that completely new fundamental steps were required to understand this reaction.  In 1969, as I finished my fellowship with Collman, Michigan State University, (MSU), was the only school that offered me a position in which to start my independent academic career. Harold Hart, Mike Karabatsos, Gene LeGoff, Don Farnum, Bill Reusch and Pete Wagner served as my early mentors at MSU and provided a very supportive environment for a starting faculty member. After nine very productive years at MSU where I started my work in olefin metathesis and a number of other areas of catalysis, I was offered a position at Caltech in 1978. Numerous outstanding graduate students contributed to my program at MSU. One postdoctoral fellow, however, played a major role in developing my research program. Dr. Akira Miyashita, who died in 2004, brought a number of new techniques to the group as well as an exemplary work ethic. He moved with me to Caltech in 1978 where he helped to reestablish the group in California.  The faculty at Caltech had created a rich environment for the training of outstanding graduate students, and these students, along with creative postdoctoral fellows and new faculty colleagues allowed my program to grow in many directions to take advantage of the growing field of organometallic catalysts. Bob Ireland and Dave Evans helped me to return to organic synthesis and to the development of new synthetic processes based on transition metals, and Peter Dervan and Dennis Dougherty, who provided guidance in physical organic chemistry as well as friendship over many years. John Bercaw and Harry Gray kept me honest in inorganic chemistry. Shortly after I arrived at Caltech, Fred Tebbe, a DuPont chemist, reported the structure and reactions of the complex that we later named the “Tebbe Reagent.” Working with Dave Evans and Stan Pine on sabbatical from CSULA, we demonstrated that this reagent provided the first general route for the conversion of esters to vinyl ethers. This work also provided the basis for our mechanistic work that resulted in the synthesis of the first metathesis active metallacyclobutane. Many of the lessons learned with the Tebbe reagent were important in later developments. We discovered that it was important to develop a commercial source of this organometallic reagent so that other researchers could try the reaction without making a major investment of time in developing the techniques for making the reagent. The utility of the reagent was always limited by its instability under normal laboratory conditions. It required special air and water free conditions for its use. The desire for ease of use drove the early development of the ruthenium catalysts. We pursued the ruthenium based catalysts since they did not suffer many of the instability problems that had limited the use of the earlier tungsten and molybdenum based catalysts. We also developed early commercial sources and later commercially viable methods for the production of the well defined ruthenium based catalysts. In my lecture I discussed many of the developments from this point that let to the discovery of the family of ruthenium based metathesis catalysts and I named key members of the group who contributed directly to their development. Surrounding the group who made the key discoveries were others who made equally significant contributions that served as the basis for the specifically listed advances.  The olefin metathesis mechanism was one of my first projects at MSU and my group explored various aspects of this reaction throughout my career. In addition, we explored other mechanistic questions. An early project returned me to my interest in cyclobutadiene and we designed a mechanistic study to determine if cyclobutadiene was really formed from the decomposition of the Pettit iron tricarbonyl complexes. Other studies explored the mechanism of the Ziegler catalysts in the polymerization of ethylene and propylene. Using isotopes and stereochemistry, while working along with Mike Steigerwald, we developed a method that determined the critical steps in this reaction. Other work involved the study of metallacyclopentanes, a class of complexes we had become interested in from our early mechanistic studies of metathesis. Although metallacyclopentanes are not important in olefin metathesis, they have been found to be important in a variety of other olefin dimerization reactions. In a similar way, the discoveries in olefin metathesis have led to new processes that can benefit from detailed mechanistic explorations. Many of our advances in ruthenium catalyst development were the result of applying the techniques developed earlier in our group in the study of other complex catalytic processes.  One of the important developments in the group was the growth of research in polymer chemistry. Many of the students and postdoctoral fellows who helped to develop our polymer program have moved on to outstanding careers and have helped to establish polymer chemistry in other universities. The polymer program has opened many new opportunities and has led the group in a number of directions from biomedical applications to the synthesis of new membranes and barrier films. Although ring opening olefin metathesis polymerization, (ROMP), provided the path into polymer science, the techniques learned have opened possibilities outside of olefin metathesis. For example, they have resulted in the development of a new material that has found applications in light adjustable interocular lenses.  In the present commercial environment, it is difficult for fundamental discoveries to be transitioned into large companies. After a number of early frustrations that resulted from attempts to move our work directly into major companies, we were involved in the creation of a company to aid in the transition of technology from discovery to product. Mike Giardello, in addition to developing the first commercially viable route to a ruthenium metathesis catalyst, has played a major role in establishing Materia, Inc., where many of the commercial applications of the ruthenium technology – and other metathesis based products – were developed.  It has been very pleasing that a process that we started to study from pure intellectual curiosity has resulted in new processes which have very practical applications. I hope the success of the process has been a sufficient reward for the patience of the granting agencies who have allowed me to follow the metathesis reaction on the wandering path that has resulted from many chance and unanticipated discoveries. There are still many turns left on the metathesis path.  During my career, over 200 students and postdoctoral fellows have worked in my research group. They have all left their mark. I thank them all for their hard work, for their creative contributions and for making chemistry fun.  During my second year at Columbia, I met a wonderful lady from Brooklyn, Helen O’Kane. She has been my companion and best friend since that time. I thank her and our three children, Barney, now a Professor of Chemistry at Dartmouth, Brendan, an MD resident at USC and Kathleen, a PhD in Clinical Psychology program at University of Hawaii, who have supported me professionally as well as personally during this chemical quest. |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** | – Hello.  – Hello. Dr Grubbs?  – Yes.  – This is Joanna Rose from Nobelprize.org …  – Okay …  – … the official site of the Nobel Foundation.  – Yes?  – I wanted just to record some questions and answers from you, about the Prize.  – Okay.  – Congratulations to the Prize.  – Thank you.  – How did you receive this message?  – I was … at home, recovering from a lecture tour in New Zealand and at home I have … They put us up in Christchurch; I’m in Christchurch as an Erskine Fellow, giving a lecture course. And I’m just sitting in my home; it’s now 11.30 at night, so I … the end of a long day.  – When did you get the message?  – Just a few minutes ago, a short time ago.  – Did you expect it in any way?  – No. You know, it’s one of the things no one ever expects to happen, not usually. But you never expect it.  – It never occurred to you that you could be a Nobel Prize-winner?  – No. You know, that’s not one of the things that I’d even …  – Do you think it will change your future research, or …?  – I hope not, of course. It’s still too early, but I don’t think so. I’ve been enjoying doing what I’m doing for a very long time, so I see no reason to change.  – Do you think that this means some new responsibilities, becoming a Nobel Prize-winner?  – It probably does. But I haven’t thought about those yet. I guess so. It’s so soon and … I’m sure that will happen over the next little while.  – I see. Do you have any idea what you will do with the Prize money?  – No, I haven’t thought about that. I’m sure we’ll find some interesting things to do.  – Are you going to celebrate the Prize now?  – Well, as I say, I’m pretty exhausted and so I will probably have a few drinks and try to get some sleep tonight.  – Thank you very much for being with us tonight.  – Okay. Thanks.  – Goodbye.  – Bye. |
| **Interview** |  |
| Q9 | **Two months have gone since you got the message from Stockholm, what happened during this time, Dr Grubbs?** |
|  | Robert Grubbs: It seems like it’s been a very long time, many things have happened with many interviews and many events. The other fun thing has been many people who I’ve lost track with over the years have gotten back in touch with me, and so we’ve re-established a lot of friendships which we’ve lost over the years. |
| Q9 | **Could you pursue your work after that?** |
|  | Robert Grubbs: Yes, it changed a bit but not much. I did return back to California and started teaching a course there and I’ve kept my research group going and written papers and so life goes on. It just adds a few extra things. |
| Q2 | **How did you become involved in science if you go back?** |
|  | Robert Grubbs: For me it was probably goes back to a teacher in junior high, middle school, who was an outstanding teacher and who started challenging me and getting me interested in science, and so it continued from there. It took many different variations along the way until I arrived at chemistry, but it was still always a science emphasis. |
| Q6 | **Are you the kind of nerds that do just nothing but science?** |
|  | Robert Grubbs: I don’t know about that, we do many things. I know Dick has many hobbies as do I, other than chemistry. |
| Q6 | **Did you do walking in New Zealand?** |
|  | Robert Grubbs: I did walking yes, that was a part of the reason I went to New Zealand, was to walk, I didn’t walk as much I’d like but it was still very good. |
| Q2 | **Did you start to work together then? Or you knew each other before?** |
|  | Robert Grubbs: We knew each other long before.  Richard Schrock: We knew each other since the early 1970s I would say.  Robert Grubbs: Early -70’s, yes. |
| Q2 | **So this is what you do at conferences?** |
|  | Robert Grubbs: Yes, we decided we should never do that again.  Richard Schrock: So Bob did do a lot of further studies with these and similar molybdenum catalysts. I made more variations probably, since I’m an inorganic chemist, so I work more with making and designing catalysts and Bob with applying that chemistry to make polymers, and then really set his sights on organic chemistry. He was the first to really see the possibilities, since he’s an organic chemist, that one could influence organic chemistry powerfully. |
| Q15 | **What is the relation between applied science and fundamental science? Can you comment on that?** |
|  | Robert Grubbs: I think they naturally sort of flow together, at least for me it’s been. We started out doing very fundamental work, we still do very fundamental work, but you also have to keep an eye for where it might be useful and then point it in that direction. Then once you get it going in the right direction there’s lots of people who will take that then and use it to make things and do the applied stuff. I try to do the fundamental and then point people in the direction that the applied stuff can happen and then there’s all kinds of wonderful people around who takes that and does nice things with it.  Richard Schrock: And the main idea is to control these catalysts and what they do and then you control it by making different catalysts and you know everything about them in a fundamental way, and then you can apply that knowledge to making a polymer of a certain type or doing a certain type of organic reaction. Then you can apply what you know with these catalysts, but it all begins with fundamentals. |
| Q2 | **And they are started by academics?** |
|  | Robert Grubbs: In many cases by academics yes.  Richard Schrock: Like him for example. |
| Q10 | **So you work with a company and in academia?** |
|  | Robert Grubbs: Yes. My job is in academia, but part of getting the technology, the fundamental stuff, we’ve developed two applications which after all one loves to see your stuff used and done. It was essential to build up this middle part and the only way to do that is to be involved in starting a company that is involved in that transition work. I tried doing it lots of other ways but it’s the only real way that I found to do it now. Dick’s also involved in the company too.  Richard Schrock: Yes, but not to such an extent. But they’re trying to get all of metathesis under their roof, I would say, and push it, which is good. And they will try to apply this reaction for pharmaceutical companies or for whoever wants to use it because it’s so universal in the sense that you can go in many directions. It’s a fundamental reaction, you can do many different things with it, and many companies might see some reaction that they could do in fact, and then they would license for example the possibility to do that from this company.  Robert Grubbs: But you need someone there who, as I say, that middle piece is missing, I mean for example DuPont used to do a lot of the fundamental work but they also could do the transition into the very applied stuff. But that’s all missing now. So I think that’s going to be the next generation of the way the technology develops. |
| Q4 | **There is also a question on going another way. How do you get information about what are the problems in the industry to solve in academia?** |
|  | Robert Grubbs: Yes, that’s hard, but you don’t have to do that. What I’m finding now is that if you generally go around and you talk about the fundamentals, you talk about the places where the chemistry can be applied. The places where industrial chemists find applications always astounds me, you know, it becomes important and commercially viable, not for some fundamental chemical reason but for some small business reason which I have no idea about. It’s just been really fascinating to watch this happen, and there’s no way you can predict it or even think about it, and so you just put the science out there and get it to the point where people can understand it and use it and then they just find amazing applications. |
| Q10 | **Can you see it with your students? People who come to the universities?** |
|  | Robert Grubbs: I don’t, not in our students, I mean we’re both at institutes of technology which have probably the two highest standards for admission in the US and so our students come in interested in science, wanting to do science, and so for our students that we work with everyday it’s not an issue. It’s outside of that group you see it.  Richard Schrock: And you see it through the funding agencies and the money they get which has, fortunately this year I think increased, but there have been some difficult years, and well, the government statements, our government and any government has positions, and sometimes they are not, shall we say, scientifically what we would like them to be. And that’s something that is very visible and it’s very distressing to see things said that are just not true or certainly debatable at best.  Robert Grubbs: The other thing is when we started out there was a great emphasis on doing fundamental science and over the last number of years … it’s not a bad thing but it’s a different thing, which is that even at the agencies that support fundamental work one has to say where this can be used, the applied end, and see it, and if we’d been starting out that way we’d have never started our work because there was no way in the world one could have imagined where this would go, it was just a fascinating reaction to look at.  Richard Schrock: And now you have to say how is this going to benefit mankind before you even know basically what you are going to discover or develop. We know now what this reaction has done but you cannot predict the future, and to say where it’s going to actually benefit mankind at a point where it’s fundamental research is impossible really.  Robert Grubbs: I mean after 35 years now working on this reaction I still get shocked very often about new thing it can do and new directions it would go in, so it’s a … I hope it stays for a few more years. |

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| **Chemistry\_2024-2000** | |
| **ID** | 0350 |
| **Biographical** | I was born in Berne, a northeast Indiana farming community proud of its Swiss heritage. Life was not easy for my parents, Noah J. Schrock, the second of six children, and Martha A. Habegger, the second of ten children. They married in 1933 during the Depression. My oldest brother, Luther, was born in 1934, Theodore in 1939. A few months after I appeared in 1945, the family moved to Decatur, about 13 miles north of Berne, where we lived until the summer after my fifth birthday. My most lasting memory of our first home is its proximity to the city swimming pool where I spent many happy summer days.  We moved into an old house on the west side of South 13th Street in 1950. The house required a good deal of work, but my father, who had been a carpenter for fifteen years, accomplished the renovation over a period of several years. The house was located on what seemed to me to be an enormous plot of land (one acre); the backyard took forever to mow on a steamy summer day and the vegetable garden produced quantities of corn, strawberries, melons, tomatoes, and raspberries. A large vacant lot extended south toward a small railroad that dove beneath the highway on its way east to a mill where tiles were made from the clay dug on the west side of the road. The process of mining the clay created ponds, which I explored along with the surrounding woods at length. In the summer I would fish, catch snakes and frogs, and build simple huts in the woods, which probably were the first indications of my love for designing and building, and for the outdoors. In the winter I learned how to ice skate and often (so it seemed) would come close to actually freezing toes and fingers. We never had much money, but the house was comfortable (except during the first, and especially cold, winter) and the food (fresh in the summer, canned in the winter) was plentiful for the five of us.  My father built a woodworking shop in the two car garage at the rear of the house where I also spent much time discovering, among other things, that it is not easy to drive nails into maple. I was not allowed to operate power tools at a young age, but my father introduced me to several as I became older, except his prize 1941 Delta table saw, which I eventually inherited when he died of leukemia in 1980 at age 69. He was a patient teacher even though I did not fully appreciate the difference between a chisel and a screwdriver or clear pine and a prized piece of birds eye maple when I was young. I learned many things by trial and error but nevertheless grew to appreciate what one can do with wood and the right tools used the right way. I maintain that interest to this day. Like most young Hoosier men at that time, I played on the school basketball, baseball, and football teams. Although I did not continue to play organized sports beyond age ten or eleven, sports provided me with a respect and need for physical exercise that I still have.  My curiosity and love of building things played into the hand of my older brother Theodore who presented me with the proverbial chemistry set on my eighth birthday. He was thirteen at the time and beginning to appreciate the beauties of science. His interest in chemistry continued through his college years but he eventually studied medicine instead and became a highly successful surgeon. I was hooked. I created a small laboratory at the end of a storage area for canned goods and used my budding woodworking skills to build shelves for the ever expanding collection of test tubes, beakers, and flasks. I obtained most of my equipment through a mail order supply house with money earned from an early morning paper route. I carried out simple experiments (combining acids and bases to make salts, making pleasant smelling esters, etc.) following the directions in chemistry laboratory texts handed down to me. When I reached the age of thirteen, Harry Dailey, the high school chemistry teacher, stoked my interest in chemistry with more textbooks and discarded equipment. I thought all equipment wonderful to behold. As I became aware of the power of burning natural gas, the lowly alcohol burner was replaced by the common Bunsen burner, and the Bunsen burner ultimately by a high tech broad-headed model capable of putting out a good deal of heat, enough to melt metals in a porcelain crucible and even sodium chloride.  After we moved to a house on Jackson Street in 1958, my laboratory grew in size, diversity, and complexity. I now had at my disposal relatively sophisticated and, if misused, dangerous substances in a small room in the basement. I was often interested in testing recipes for mixtures of oxidizing agents and oxidizeable materials as well as nitrating common household substances. Thankfully, there were no serious mishaps, although my mother tells stories that belie that statement, including one in which the local fire department was called to our home; fortunately only a small rug was burning, not the house. At least I also was quick to think and act.  My father went to San Diego, California, in the fall of 1958 to work in the construction industry with his brother, Clarence, and to explore the feasibility of moving west. In 1959 my mother and I joined him. She drove and I navigated cross country with my laboratory carefully packed in the trunk of the car. By the time I finished Mission Bay High School in 1963, both my parents had also fulfilled their dreams of finishing high school, something they had not been allowed to do in their youth. My interest in chemistry expanded in San Diego. I found a laboratory supply house where I could buy classic equipment (a 250 mL retort was coveted and purchased) and a drugstore where I could buy basic chemicals with some adult help of course. I discovered many wonderful things such as how to make bromine from KBr and sulfuric acid, how to make sodium (and chlorine) by electrolizing molten sodium chloride, and how to analyze for metals by making sulfides with brilliant and characteristic colors. I took up surfing and skin diving, and continued my interest in woodworking by designing, making, and selling fins for surfboards. I entered a regional science fair with a project that concerned osmotic processes in sea urchin eggs and managed to win a prize for it. I collected the sea urchins at low tide and harvested the eggs myself. That, and dissection of a sheep’s brain (which I greatly enjoyed) in physiological psychology later in college, was the closest I would come to following my brother into medicine.  I always assumed I would attend college and study chemistry. The only financially viable option was the University of California. I was accepted at Berkeley but chose to attend Riverside, a relatively new campus about 90 miles north of San Diego, because I thought that a smaller school might allow me to do more independent research earlier in my career. That proved to be the case. After the first exam in my first chemistry course at UCR, I was approached by Professor James Pitts who asked if I wanted a summer job. I agreed and began research in what broadly could be called atmospheric chemistry, a hot topic in the smog ridden Los Angeles basin and surrounding area at that time. In actuality, I spent my time learning to blow glass and construct vacuum lines, and to measure low concentrations of photolysis products using a temperamental, delicate, almost impossible to align, multi-pass Perkin-Elmer IR machine connected to a vacuum line. (Fourier Transform machines were not yet known.) A paper entitled “The Detection of Ethylketen and enol-Crotonaldehyde in the Vapour-phase Photolysis of *trans*-Crotonaldehyde” reported some of my work in 1968 after I had moved on to graduate school. I also worked “up the hill” with Dr. E.A. (Ed) Schuck and in 1966 found my name on a paper entitled “Rate Constant Ratios During Nitrogen Dioxide Photolysis.” I learned many things, scientific and otherwise, that need not be detailed here. One that I might mention was the joy (and sometimes discomfort) of hiking in the Sierra Nevada Mountains. I still enjoy mountain hiking, although the frequency has decreased considerably. I capitalized on my knowledge of IR spectroscopy during a summer of research at Dow in Midland, Michigan, where my oldest brother Luther was an engineer.  At Riverside I was influenced by a talented and enthusiastic teacher in physical chemistry named Jerry Bell. Jerry decided that I had enough ability to attend Harvard University for graduate study where he had received his Ph.D. I liked the idea, applied, and was accepted. I celebrated by listening to Rachmaninoff’s second piano concerto played by Byron Janis, loudly, through a Fischer amplifier and large home built speakers, each with a volume approaching 12 cubic feet; an arts in western civilization course at UCR had boosted my interest in music that I had acquired in high school. During the last semester at UCR I took an inorganic chemistry course taught by Fred Hawthorne who appropriately spent a good deal of time discussing boron compounds. Although I enjoyed organic chemistry, the possibility of exploring the chemistry of all elements in the periodic table was fascinating to me. Yet for some reason I still regarded myself as a physical chemist.  When I arrived at Harvard, I was scheduled to live in Perkins Hall, a graduate student dormitory. I was offered several possible roommates, among them David Swickard, a childhood friend from Decatur, who unknown to me was beginning graduate school in political science. Needless to say, he was surprised to find me in the dorm room when he arrived. I lived in Perkins for the first year and then moved to an apartment with several other friends near Central Square in Cambridge. The apartment was adequately furnished, convenient to Harvard, and cheap. I spent most of my time in the lab anyway. I was one of the constant residents in the apartment for the next three years, although from time to time I was uncertain how many roommates I actually had.  I had not visited Harvard or researched the faculty before arriving and had no plan concerning the kind of physical chemistry I wanted to pursue. My desire to permute compositions of matter did not seem to fit with the physical chemistry being done at Harvard at that time. Perhaps I had the wrong impression of what I wanted to do or what “physical chemistry” was. Therefore picking a research supervisor proved problematic. One day while walking dejectedly down the main hall of Mallinckrodt Laboratory I passed a long office/lab (in fashion in years past) where a recently arrived assistant professor sat at the desk. I entered and talked with John Osborn, who told me about transition metal chemistry, about the excitement of creating new, colorful, crystalline compounds, and about catalysis by transition metal species such as the rhodium catalysts he had developed as part of his doctoral study with Geoffrey Wilkinson at Imperial College. That sounded like what I wanted to do, make new compounds with potential uses, so I signed on. I am not sure John was totally pleased that I chose to work on rhodium since he may have felt that it was too close to his own doctoral work, although in the end the cationic complexes that I discovered turned out to be quite useful for asymmetric hydrogenation, at least those that contained the appropriate enantiomerically pure phosphine ligand. I also met [Ryoji Noyori](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/2001/index.html) who was exploring catalysis by transition metal species in [E.J. Corey’s](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1990/index.html) group, and Mike Strem, who had started Strem Chemicals and for whom I made a sample of deuterated Zeise’s salt for the fantastic wage of $100, half a month’s pay at that time.  The late sixties were wild in Cambridge as in other university areas, with the Vietnam war escalating, and rebellions seething, or actually erupting. I decided I needed a break and had to see the world. I informed John that I would be traveling abroad for fifteen weeks during the summer of 1968 on a grand European tour. The mantra was $5 a day. I think I almost achieved that goal. Hitchhiking was still acceptable and helped the budget greatly, as did youth hostels and a diet of bread and cheese. I could not believe I actually was in Europe, visiting all the famous museums and practicing my high school Spanish and college German. My success with French was more modest. While I am eager to learn other languages, I do not have the special talent required to achieve that goal without actually having lived abroad.  In November of 1969, the 16th I believe, I meandered to a party near Davis Square where I met a tall blond school teacher named Nancy Carlson. She not only was beautiful but also bright and seemed attracted to me, which I found refreshing. We saw each other regularly that year and most of the next, and married in August of 1971, shortly after I finished and defended my Ph.D. thesis and she completed a master’s degree in library science. Only one job was available in 1971, for which there were several hundred applicants, so I considered myself fortunate to obtain a postdoctoral fellowship from the National Science Foundation to work at Cambridge University in the laboratory of Jack Lewis, later Lord Lewis. The year in England was the beginning of a long relationship with England that continues today. Our present house is graced by a brass rubbing of Roger de Trumpington (gold and silver wax on black paper), one of the oldest brasses in England. It took some time to rub a brass that size, and the church in the village of Trumpington south of Cambridge around Christmas time was unrelentingly cold. I discovered a great deal about the relative heat capacity of my body versus a stone floor. We rubbed other brasses, but that particular event remains in my memory because of the cold and the boy’s choir practicing their Christmas program in the background. I returned to the U.S. in the winter to look for permanent employment. Job offerings were still relatively meager, although I garnered a couple of offers. Upon returning to Cambridge I met Earl Muetterties, an associate director at the DuPont Experimental Station in Wilmington, Delaware, who was on a sabbatical at Cambridge, which was unusual for a nonacademic. He interviewed me and ultimately gave me an offer to work at the Central Research Department, which I accepted. At that time CRD was an academic department in an industrial setting; nothing close to it exists today. Nancy and I moved to Wilmington in August of 1972 with two bicycles purchased in England. I still have mine and ride it occasionally.  At DuPont I shared a lab with the remarkable Fred Tebbe, who was studying, among other things, reactions of ethyl aluminum reagents with titanocene dichloride. His most important and surprising discovery was what has become known as Tebbe’s reagent, a species made through the reaction of titanocene dichloride with trimethylaluminum. The most remarkable feature of Tebbe’s reagent is a methylene group bridging between titanium and aluminum, which could replace the oxygen in a carbonyl group in a Wittig-like reaction. I dabbled in cyclooctatetraene chemistry and synthesized compounds such as the anion of triscyclooctatetraene niobium, and blue Ta(C8H8)Me3, prepared through addition of the dianion of cyclooctatetraene to tantalum trimethyldichloride, the only known alkyl of tantalum, which had been reported by G. L. Juvinall in 1964. I found TaMe3Cl2 to be easy to prepare on a large scale from TaCl5 and dimethylzinc, which at that time could be purchased neat in large quantities. I became interested in the possibility of preparing other tantalum alkyl complexes. I was heavily influenced by [G. Wilkinson’s](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1973/index.html) synthesis of hexamethyltungsten. Wilkinson was a consultant for DuPont at the time. On a trip to DuPont in the spring of 1973 he told us about the synthesis and properties of that remarkable compound. I subsequently concentrated on the synthesis of tantalum pentaalkyl complexes and soon had made highly volatile and highly unstable pentamethyltantalum by treating TaMe3Cl2 with methyllithium. By July the attempted synthesis of pentaneopentyltantalum led to trineopentylneopentylidenetantalum, Ta[CHC(CH3)3] [CH2C(CH3)3]3 instead. That compound marked the beginning of high oxidation state carbene, or alkylidene chemistry, as stated in a book by Bill Nugent and Jim Mayer (*Metal-Ligand Multiple Bonds*, 1988) in which the actual DuPont notebook page which describes that discovery was reproduced. (Fortunately, that particular page also was an example of how to keep a proper notebook.) Shortly thereafter I prepared the first isolable terminal methylene complex, the structure of which was solved by Lloyd Guggenberger. George Parshall, my group leader, allowed me to do what I thought interesting and to work after normal hours, which greatly increased my productivity. In the fall of 1972 I first heard the term “olefin metathesis” from Earl Muetterties, who remained interested in the subject after he moved to Cornell in the summer of 1973. I started to follow the metathesis literature and began to suspect that the new alkylidene complexes that I discovered in 1973 might be relevant to that process, even though tantalum was not a known catalyst for olefin metathesis.  I was impressed by the high oxidation state chemistry of osmium imido complexes being carried out by [K. Barry Sharpless](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/2001/index.html) at MIT and invited him to DuPont to give a talk, probably in late 1974. He was excited about the potential of the new alkylidene compounds I had discovered. He and several others at MIT pushed for an offer from MIT, which came in the spring of 1975. I accepted, even though I took a cut in salary. I do not recall salary being much of an issue. MIT fulfilled my dream of obtaining an academic position at a top institution. I looked forward to exploring tantalum chemistry further and teaching. Nancy and I moved to Brighton (part of Boston) in August of 1975. While I pushed ahead with research at MIT, Nancy added a master’s degree in art history to her graduate degree in library science and learned bookbinding through an apprenticeship.  I was fortunate to obtain support from the National Science Foundation early in my career at MIT and to build a group of ten students by the end of my third year. I could not have been happier. High oxidation state organometallic chemistry developed rapidly, thanks to the talented students and support for them from the National Science Foundation. By 1980 we had transferred the principles behind tantalum chemistry to tungsten, molybdenum, and rhenium, and had shown what type of tungsten species would metathesize olefins. By the mid 1980’s we had developed what I call well-defined catalysts for both the olefin and acetylene metathesis reactions that contained sterically protecting imido and/or alkoxide ligands. I became interested in dinitrogen chemistry around 1980, and polymer chemistry (first ring-opening metathesis polymerization and later olefin and acetylene polymerization) a few years after that. In the mid 1990’s I began a fruitful collaboration with Amir H. Hoveyda on asymmetric metathesis reactions and their applications to organic chemistry, which was and still is supported by the National Institutes of Health. With support of the NIH I also was able to achieve in 2003 a long sought goal for hundreds of researchers over a period of 40 years, the catalytic reduction of dinitrogen with protons and electrons at room temperature and pressure. It turns out that a single molybdenum center within a properly designed protective ligand is sufficient. Time will tell whether these findings are relevant to how dinitrogen is reduced to ammonia in nature on a huge scale by nitrogenase enzymes.  My son Andrew was born in 1978 and Eric in 1981. The family became too large for the house in Brighton so in 1983 we moved to Winchester, Massachusetts, where we slowly renovated a 1904 Arts and Crafts style house. A bindery on the third floor allowed Nancy to practice book conservation while our sons were growing up. Half the basement became my woodworking shop; the other half became at various stages a cub scout den, a teenage getaway, and later a finishing room for items built in my shop.  In 1997 Nancy accepted a position as the Chief Collections Conservator of the Harvard College Libraries in Widener Library at Harvard University; in the summer of 2006 she will return to the MIT Libraries as the Thomas F. Peterson, Jr., Conservator of the Special Collections. With the children on their own we enlarged the kitchen/living area in 2000 and in the process expanded the basement, adding another room for woodworking and a small wine cellar. We enjoy cooking together in the new kitchen and gardening on our manageable 1/4 acre lot.  As of 2006 I have published approximately 425 papers and have trained ~65 graduate students and ~75 postdoctoral students. I still find the process of unlocking nature’s secrets an enormously satisfying profession and hope to be fortunate enough to continue to practice it for some time. |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** | – Hello.  – Hello. My name is Joanna Rose and I’m calling from Nobelprize.org …  – Okay.  – … which is the official site of the Nobel Foundation.  – Okay.  – And we are making a recording now for our website.  – Okay, thank you.  – My congratulations on the Prize, to begin with.  – Thank you very much.  – How does it feel?  – Er … It feels wonderful! It feels wonderful, really the culmination of an entire life’s work, for me.  – I see. How did you receive the message?  – I received the message at 5.30 in the morning from the Nobel Committee and other representatives, and I had gotten up at 5 a.m. – I tend to get up early – and was having some coffee when the call arrived at 5.30.  – I see. Did you expect it, the call?  – I think “expected” is not the right word, because …  – Did you hope for it?  – You never expect these things. You know, I could have, maybe, gone on for ever without receiving a Nobel Prize, but there are rumours and so, if the phone rings at 5.30 in the morning, that’s pretty unusual. So … It crossed my mind, yes.  – Did you think about the Nobel Prize the previous years?  – Sometimes, a bit, but usually not a lot, no. And I never thought that, of course, I would actually be worthy of that sort of honour. But eventually I realised that a lot of other people think that I was worthy of it. So … that’s what counts.  – Yes, great. What does the Prize mean to you?  – I … To me, it is really an opportunity to say something about science in general, in the US, about chemistry, I would say, more specifically and about, really, what we should be doing in the future in terms of funding for chemistry and what we should do as far as basic research is concerned, because what we accomplished, Bob Grubbs and I, came through basic research without really knowing exactly how we were proceeding; we ultimately came to realise, step by step, that our basic research was leading to something really useful. And that is very, very pleasing to me; and I think that’s what the Nobel Prize is all about: to do work that turns out to be useful to society in some way and certainly other fields in science. So I hope that I can be a spokesman for the future and what chemistry of the future will be.  – So, somehow, the Prize puts new responsibilities on you.  – It definitely changes one’s life, yes. And I’m still young enough that I think I have some time to take advantage of that change.  – Are you planning to pursue studies as well?  – Well, I continue – or will continue, I hope – to have an active research group of about fifteen co-workers and to write papers and certainly to do basic research; that’s my greatest love. And what we are doing now is, much of it, a continuation of what I’ve been doing for thirty years. But also other new and wonderful things are happening that I’m excited about and that I will continue to work on.  – And my last question is maybe: do you have any idea what you will do with the Prize money?  – Well, I think I’ll put it in a safe place, like a bank, for example. Ultimately, I don’t know at this point what I will do. But certainly that will be on my mind and I will be thinking about it.  – Dr Schrock, thank you so much for taking your time, and I’m looking forward to meeting you in Stockholm in December.  – I’m very much looking forward to it too. Thank you.  – Thank you. Bye-bye.  – Okay. Bye-bye. |
| **Interview** |  |
| Q2 | **Did you start to work together then? Or you knew each other before?** |
|  | Robert Grubbs: We knew each other long before.  Richard Schrock: We knew each other since the early 1970s I would say.  Robert Grubbs: Early -70’s, yes. |
| Q2 | **So this is what you do at conferences?** |
|  | Robert Grubbs: Yes, we decided we should never do that again.  Richard Schrock: So Bob did do a lot of further studies with these and similar molybdenum catalysts. I made more variations probably, since I’m an inorganic chemist, so I work more with making and designing catalysts and Bob with applying that chemistry to make polymers, and then really set his sights on organic chemistry. He was the first to really see the possibilities, since he’s an organic chemist, that one could influence organic chemistry powerfully. |
| Q15 | **What is the relation between applied science and fundamental science? Can you comment on that?** |
|  | Robert Grubbs: I think they naturally sort of flow together, at least for me it’s been. We started out doing very fundamental work, we still do very fundamental work, but you also have to keep an eye for where it might be useful and then point it in that direction. Then once you get it going in the right direction there’s lots of people who will take that then and use it to make things and do the applied stuff. I try to do the fundamental and then point people in the direction that the applied stuff can happen and then there’s all kinds of wonderful people around who takes that and does nice things with it.  Richard Schrock: And the main idea is to control these catalysts and what they do and then you control it by making different catalysts and you know everything about them in a fundamental way, and then you can apply that knowledge to making a polymer of a certain type or doing a certain type of organic reaction. Then you can apply what you know with these catalysts, but it all begins with fundamentals. |
| Q2 | **And they are started by academics?** |
|  | Robert Grubbs: In many cases by academics yes.  Richard Schrock: Like him for example. |
| Q10 | **So you work with a company and in academia?** |
|  | Robert Grubbs: Yes. My job is in academia, but part of getting the technology, the fundamental stuff, we’ve developed two applications which after all one loves to see your stuff used and done. It was essential to build up this middle part and the only way to do that is to be involved in starting a company that is involved in that transition work. I tried doing it lots of other ways but it’s the only real way that I found to do it now. Dick’s also involved in the company too.  Richard Schrock: Yes, but not to such an extent. But they’re trying to get all of metathesis under their roof, I would say, and push it, which is good. And they will try to apply this reaction for pharmaceutical companies or for whoever wants to use it because it’s so universal in the sense that you can go in many directions. It’s a fundamental reaction, you can do many different things with it, and many companies might see some reaction that they could do in fact, and then they would license for example the possibility to do that from this company.  Robert Grubbs: But you need someone there who, as I say, that middle piece is missing, I mean for example DuPont used to do a lot of the fundamental work but they also could do the transition into the very applied stuff. But that’s all missing now. So I think that’s going to be the next generation of the way the technology develops. |
| Q10 | **Can you see it with your students? People who come to the universities?** |
|  | Robert Grubbs: I don’t, not in our students, I mean we’re both at institutes of technology which have probably the two highest standards for admission in the US and so our students come in interested in science, wanting to do science, and so for our students that we work with everyday it’s not an issue. It’s outside of that group you see it.  Richard Schrock: And you see it through the funding agencies and the money they get which has, fortunately this year I think increased, but there have been some difficult years, and well, the government statements, our government and any government has positions, and sometimes they are not, shall we say, scientifically what we would like them to be. And that’s something that is very visible and it’s very distressing to see things said that are just not true or certainly debatable at best.  Robert Grubbs: The other thing is when we started out there was a great emphasis on doing fundamental science and over the last number of years … it’s not a bad thing but it’s a different thing, which is that even at the agencies that support fundamental work one has to say where this can be used, the applied end, and see it, and if we’d been starting out that way we’d have never started our work because there was no way in the world one could have imagined where this would go, it was just a fascinating reaction to look at.  Richard Schrock: And now you have to say how is this going to benefit mankind before you even know basically what you are going to discover or develop. We know now what this reaction has done but you cannot predict the future, and to say where it’s going to actually benefit mankind at a point where it’s fundamental research is impossible really.  Robert Grubbs: I mean after 35 years now working on this reaction I still get shocked very often about new thing it can do and new directions it would go in, so it’s a … I hope it stays for a few more years. |

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| **Biographical** | The formative years – childhood in the newly born state of IsraelI was born in Haifa, a port city in the northern part of Israel, in October 1947, one month before Israel was recognized by the [United Nations](https://www.nobelprize.org/nobel_prizes/peace/laureates/2001/index.html) (UN) as an independent state. It took several additional months to establish the necessary institutions and for the British to leave, and on May 15th 1948, David Ben-Gurion, the founding father of the modern Jewish state and its first Prime Minister, made Israel a fact and declared its establishment as a democratic state and a home for every Jew in the world. The neighboring, but even more distant Arab countries, along with powerful Arab parties from within, did not accept the UN resolution and deliberately decided to alter it by force. A bloody and costly war erupted. It lasted a year, and more than 1% of the population of the newly born and defenseless state sacrificed their lives on its defense. I assume that the first two years of my life (1947-1949) were extremely difficult for my parents, Bluma (nee Lubashevsky) and Yitzhak, who immigrated from Poland with their families as adolescents in the mid-1920s. Why did their families leave Poland – their “homeland” – their houses, working places, property, relatives and friends, and decided to make their new home in a place with a vague, if any, clear future, that was part of the British Empire? They were idealists who enthusiastically followed the call of the Zionist movement that was established at the turn of the century by Benjamin Ze’ev Herzel – the seer of the Jewish State – to settle the land and make it – after two thousand years in the Diaspora, since the destruction of the temple in Jerusalem – a home for the Jews. Following the Jewish Congress in Basel (Switzerland) in 1896, Herzel declared: “In Basel I founded the Jewish State”. At that time Israel was part of the Ottoman Empire and became in 1917 part of the British Empire. My parents came from religious families, and the move, I believe, had also religious roots: Jews, throughout their lives in the Diaspora, have not stopped dreaming of having their own country, with Jerusalem as its capital, a dream that was driven by a biblical decree and prophecy: *“Thus saith the Lord GOD: Behold, I will take the children of Israel from among the nations, whither they are gone, and will gather them on every side, and bring them into their own land” (Ezekiel 37:21); “And they shall dwell in the land that I have given unto Jacob my servant, wherein your fathers dwelt; and they shall dwell therein, they, and their children, and their children’s children, for ever” (Ezekiel 37:25); “And I will rejoice in Jerusalem, and joy in my people; and the voice of weeping shall be no more heard in her, nor the voice of crying” (Isaiah 65:19); “And they shall build houses, and inhabit them; and they shall plant vineyards, and eat the fruit of them” (Isaiah 65:21).*  The question of timing was an important one, as despite centuries of continuous persecution and discrimination in Europe, the initial idea to establish a Jewish State had been the dream of a few. Only small groups of Jews settled in Israel during the 18th, 19th, and the beginning of the 20th century. It was only towards the end of the 19th century, with the ideas of Herzel and the moves that led to the Balfour declaration (the British Minister of Foreign Affairs, who declared in 1917 the recognition in the need for a Jewish homeland), that an active Zionist movement and institutions were established, resulting in the translation of the dream into reality. Yet, it took an enormous amount of courage and daring by these European Jews to materialize this dream and try to establish, with almost no resources or support, a homeland in a place they had dreamt of for two thousand years, but that was not theirs at the time. The process was clearly accelerated by the heavy clouds that then covered the skies of Europe and that ended with the Holocaust. Many members of my parents’ families immigrated to Israel before the Holocaust, but those who remained in Poland were perished by the murderous German and their loyal Polish collaborators. The conversion of this movement into a State at that particular time (1947-1948) was no doubt the direct historical result of the holocaust, and symbolized the rise of the Jewish Nation from ash.  My father was a clerk in a law firm (later – along with my brother – he studied law and became a lawyer), and my mother was a housewife and English teacher. My brother, Joseph (Yossi), who is 14 years older then me, was already on his national military compulsory service when I was 4 years old, the age from which I remember myself. I grew up in Haifa and enjoyed the wonderful beaches and Mount Carmel that rolls into the Mediterranean Sea. From my early days at home I remember a strong encouragement to study. My father worked hard to make sure we obtained the best possible education, and at the same time he was a member in the “Hagannah” (defense), one of the pre-state military organizations that fought the British for an independent Jewish State. Working in a law firm in the Arab section of the city, he risked his life daily going to work during the pre independence war hostilities and then the war time. My brother told me the family was waiting daily on the balcony to see him returning home safely. At home he used every free minute to delve into classic literature, Jewish religious law (Mishnah and Talmud) and modern law books. An important part of the education at home involved Judaism and Zionism. On the Jewish side we obtained a liberal modern orthodox education. We attended services in the synagogue every Saturday and during holidays, and celebrated at home all Jewish feasts. Needless to say that my mother kept a kosher kitchen. It was extremely important for my parents to educate us as a new breed of proud Israeli Jews in their own independent country. My father inherited me with his love of Jewish studies and cultural life. To this very day, along with several physicians and scientists colleagues, I take regular lessons taught by a rabbinical scholar, on how the Jewish law views moral and ethical problems related to modern medicine and science. Jewish cantorial music reflecting prayers of Jews along many centuries has become my favorite music, and I avidly search for this vanishing vocal expression of Jewish culture in flea markets, used records stores, and auctions all over. Also, different Judaica artifacts decorate my study. In parallel, my parents made sure we should receive an excellent general education. My father spoke fluently several languages, Hebrew, Polish, Arabic, French, English, German and Yiddish, and wanted me to acquire his strong love for books: while our home was not a rich one, we had a huge library. My parents also loved classical music, so we had a great collection of 78 rpm, and later 33 rpm records. I remember that Bizet’s Carmen occupied more than twenty, double-sided, RCA (His Master’s Voice) 78 rpm bakelite records. The apparently peaceful life of our family in Israel (although under the British Crown) during the years of the Holocaust in Europe (1939-1945) were overshadowed by the murder of their family members and of many families of their relatives and friends that did not escape Europe in time. For my parents, the establishment of the State of Israel as an independent and sovereign Jewish State was a direct historical result of the Holocaust in Europe and a clear statement of “*Never Massadah shall fall again*” (Massadah was one of the last strongholds of Jews during the Roman Empire. It fell into Roman hands after a long curfew during which all its defenders committed suicide in order not to fall as prisoners in Roman hands. While aspiring for freedom, they lost their land and lives. They were not ready to live anywhere or under any circumstances, but as free people in their own land). They left us with the idea that the Jewish State will not only protect us as a free people, but will allow us to develop our own unique culture in a more general national context, rather than as minorities scattered in different countries in the Diaspora.  **Falling in love with biology** From early days I remember my strong inclination towards biology, though it has taken different directions at different times. I remember collecting flowers on Mount Carmel and drying them in the heavy Babylonian Talmud of my brother. I will never forget his rage at discovering my love of nature hidden among the pages of the old Jewish tracts. Then came the turtles and the lizards, and extracting chlorophyll from leaves with alcohol, and the first microscope my brother bought me from his trip to England when I was 11 years old. With this microscope I discovered cells (in the thin onion epithelium) and did my first experiment in osmosis, when I followed the alteration in the volume of the cells after immersing the epithelium in salt solutions of different strengths. With friends we tried to launch a self propelled rocket. The flowers collection kept growing, now in special dedicated albums, and with it, a small collection of skeletons of different animals – fish, frog, snake, turtle, and even some human bones I received from an older friend who was a medical student. After several years of amateurish flirting with biology, I decided to formalize my knowledge and love of biology, and to major in biology in high school. While my years in elementary (1953-1959) and junior high school (1959-1963) were mostly uneventful and passed without any thoughts on my future, the last two years in “Hugim” (circles) high school in Haifa (1963-1965) were not. I had wonderful and inspiring teachers in biology (Naomi Nof), chemistry (Na’ama Greenspon), and physics and mathematics (Harry Amitay) who revealed to me a little of these different and exciting disciplines. Yet, I felt that twice as much was still concealed. Biology at that time was largely a descriptive area. While we studied the mechanism of conversion of glucose to H2O and CO2 and the production of energy in yeast and mammals (and the opposite process occurring during photosynthesis in plants), and became acquainted with simple graphic descriptions of mitotic and meiotic cell divisions, most of our studies were devoted to detailed descriptions of the flora and fauna in our region, to comparative zoology (I remember well the efforts invested in memorizing the twelve differences between the frog and the toad, or between the circulatory systems and skeletal structure of the cat and dog), and to basic descriptive human anatomy and physiology (e.g. how the human skeleton structure enables posture on two limbs). Pathogenetic mechanisms of diseases had not been taught, and the structure of DNA and the genetic code had entered our textbooks only towards the end of our high school studies, in 1964/5. On the other hand, chemistry and physics appeared to me, maybe naively, strong mechanistic disciplines built on solid mathematical foundations. As a result, I had a deep feeling that the future somehow resided in biology, in deciphering basic mechanisms, as so little was then known. Yet, the complexity of biological and pathological processes looked to me enormous, almost beyond our ability to grasp, and I was intimidated: while I was clearly attracted to the secrets of biology, I was afraid to get lost. Importantly, I had nobody around, close enough, to consult, to clarify my thoughts. While deliberating between the largely unknown in biology and what I naively thought were the already well founded physics and chemistry, medicine emerged as a compromise: it appeared to me as representing a balanced mixture of physics, chemistry, basic biology and physiology, along with interesting pathology and social sciences.  Adding to this complexity was that during these years I lost both of my parents: my mother died in 1958 and my father in 1964. After the death of my mother, I was left with my father who took wonderful care of me. When my father died several years later, my late aunt Miriam (Wishniak; my mother’s sister), with the help of my brother and sister-in-law, Atara, took me to her home in Haifa, enabling me to seamlessly complete my high school studies in the same class and along with my friends – without interruption. The other option was to move to Tel Aviv, to my brother’s home, but this would have been much more complicated. So I spent the weekdays with my aunt in Haifa, studying, and the weekends and holidays with my brother and sister-in-law, in Tel Aviv. Their help was a true miracle, as thinking of it retrospectively, being left alone without parents at the age of sixteen, the distance to youth delinquency was shorter than the one to the high school class. Yet, with the help of these wonderful family members, I managed to continue.  **How my love of biology evolved to become a career** Towards graduation from high school I had to make a decision. The regular track would have taken me, like most Israelis, to national compulsory service in the Israeli Defense Forces, IDF, a duty we were all eager to fulfill. In addition to the regular service, the army encourages certain high school graduates to postpone their service and first obtain a university education, particularly in areas that are relevant to the military, such as medicine and different disciplines in engineering and sciences. Lacking any financial support, I thought it would be better to acquire a practical profession I could make a living from as soon as I could. As I mentioned, medicine emerged as a compromise between the complexity and mysteries of biological mechanisms to what I thought are the already well founded physics and chemistry. Not less important, medicine has traditionally been the ultimate in “Jewish” professions, the dream of every Jewish mother and family. What also attracted me to medicine is that I was under the impression that diseases can be cured: as children, we may have been influenced by short, self-limiting diseases that affected us, like influenza and measles, and were not directly aware of the major killers that left physicians and scientists alike helpless (much like these days), such as malignancies, vascular diseases and neuro-degenerative disorders: I had not appreciated at the time how far more descriptive medicine is, much more than biology. Practically and not less important (which helped solve my dilemma), was the fact that biology was not an option in this military-supported service postponement program. Last but not least, it was a practical choice, a profession one can make a living on. So, after a fierce competition I was accepted into the only medical school in Israel at that time, that of the Hebrew University and “Hadassah” in Jerusalem (1965). The first four years (1965-1969) were exciting. We studied basic and clinical sciences, and I started to seriously entertain the idea of broadening my knowledge base in biochemistry or pharmacology. Towards the end of the 4th year, once we started to examine patients, serious doubts had begun to arise whether I made the right choice and truly want to become a practicing physician. The imbalance between phenomenology and pathogenetic mechanisms of diseases on one hand, and the lack of any mechanism-based treatment for most of the major killers on the other hand, made me seriously think that I was on the wrong trail. I felt restless and started to realize how little we know, how descriptive is our understanding of disease mechanisms and pathology, and as a consequence how most treatments are symptomatic in nature rather then causative. The statement “with God’s help” that I heard so frequently from patients that were praying for cure and health, took on a real meaning. I had a feeling clinical medicine was going to bore me, and decided to take one year off in order to “taste” true and “wet” basic research. The Faculty of Medicine had a special, one year program for the few who elected to broaden their knowledge in basic research, and I decided to major in biochemistry. I had to convince my brother that this was the right thing to do, as I needed his help to further postpone my military service by one year. This was not easy, as he too had a “dream” – to see me independent with a profession from which I could make a living, and which in the traditional Jewish spirit was nothing else but practical medicine. Following our parents’ death, he felt he was responsible for my future and well being, and wanted to see me professionally and financially independent as soon as he could. I nevertheless managed to convince him, and during that year (1969-1970), under the guidance of excellent biochemists, Jacob Bar-Tana and Benjamin Shapira, I investigated mechanisms of CCl4-induced fatty liver in a rat model, and discovered that it may be caused, at least partially, by an increased activity of phosphatidic acid phosphatase, a key enzyme involved in di- and triglycerides biosynthesis. Completing this research year (and obtaining a M.Sc. degree), I knew I had found a new love – biochemistry. Jacob and Benjamin walked me through the exciting maze of biochemical pathways, and I was mystified. Yet, the consummation was still far away. Being loyal to the promise I made to my brother, and also to my commitment to the Israeli army, I completed the clinical years (1970-1972) and graduated from Medical School.  To obtain my medical license, I still had to complete one additional year of rotating internship. At that time, colleagues told me that a young talented biochemist, Dr. Avram Hershko, had just completed his post-doctoral training with Gordon Tomkins at the University of California in San Francisco (UCSF) and was recruited by the Dean and founder of the newly established Faculty of Medicine at the Technion in Haifa, the late Professor David Ehrlich, to establish a Unit of Biochemistry. I wrote to Avram, with the intention to relocate to Haifa, to carry out my rotating internship there, and to use this year to complete my M.D. research thesis under his supervision. This was a small thesis I had to submit to the Medical School in partial fulfillment of the requirements for graduation. Typically for this thesis, most medical students are evaluating statistically on-going treatments/procedures, but I decided to return to the laboratory and touch on yet another research project in biochemistry. Avram agreed to accept me as an M.D. research student, and in October 1972 we started our more than three decades voyage. Avram was still not certain about his own main research direction, and we discussed two possibilities for my M.D. thesis. One was obviously to further dissect the tyrosine aminotransferase (TAT) ATP-dependent proteolytic pathway: Avram started his own trip into the world of intracellular proteolysis with Gordon and discovered that the degradation of the gluconeogenetic enzyme TAT in cells requires energy. This was a corroboration of earlier findings of Simpson who demonstrated in the early 1950s that the degradation of the entire population of cellular proteins in liver slices requires energy. Yet, the mechanism(s) of this thermodynamically paradoxical requirement had remained elusive. The other possibility was to study the mechanism(s) involved in the cell’s “pleiotropic response” – the immediate response of serum-starved, G0 synchronized cells to the addition of serum. During his post-doctoral studies with Gordon, Avram found that among the many stimulated processes that follow the addition of serum, are rapid uptake of nucleotides, amino acids, and phosphate. As during my studies on fatty liver I acquired experience in analyzing lipids, and since Avram felt the elucidation of the TAT proteolytic mechanism may be a too difficult undertaking for a limited-in-scope M.D. thesis, we decided to add one additional layer to the study on the “pleiotropic response” and to analyze the effect of serum on synthesis of phospholipids. We assumed that following serum addition, cell membranes undergo major changes that will be reflected in phospholipid metabolism. Indeed, a few minutes after serum addition, we were able to detect a dramatic increase in the turnover of the phospho-inositol moiety on the diglycerol skeleton. A review of the literature revealed a similar effect in different target cells in response to a broad array of stimuli, including parasympathetic secretory cells responding to acetylcholine and thyroid gland cells to their cognate hormones, thyrotropin (TSH). The year (1972-1973) I spent in the laboratory (it was not a real year but rather moon lighting, as a significant part of the time I was busy in the hospital, rotating among the different clinical departments, completing my internship and duties towards graduation. I worked in the laboratory in my free evenings, nights, weekends and holidays) finally convinced me to pursue a career in Biochemistry. But I still had three years of military service ahead of me (1973-1976)  **My military service and professional career – have they collided with one another?** Following graduation, it was time to repay my national debt and serve in the IDF. I served for three years (1973-1976) and did it gladly. Serving in the army has always been regarded as an integral and important part of Israeli life, and an entry card to its society, giving one the feeling of sharing – everyone takes part in protecting this land and its inhabitants. In addition, the service itself was extremely interesting, technically, but also socially and historically. Technically, since I served in interesting units. Socially, since the military service is a wonderful humane experience, the best melting pot one can go through, generating true friendships during hard times, friendships that are therefore deep, true and lasting. Historically, it spanned an interesting period. Initially I served in the navy, as a physician in the missile boats fleet. The year was 1973, immediately after the October Day of Atonement (Yom Kippur) war, and Israel faced a problem of protecting its southern gates, the Red Sea and the marine entry to its port in Eilat. Marine transportation through the southern gates of the Red Sea, Bab-el-Mandeb strait, and the narrow Tiran (Sharm-a- Sheikh) strait were threatened by the Arab countries that neighbored the water way, mostly Saudi Arabia and Egypt, but also Yemen and Somalia, and Israel had to stretch its marine arm. To do so, it was necessary to transfer missile boats from the main naval bases in the Mediterranean to the Red Sea. At that time Israel did not have diplomatic relations with Egypt, and the Suez Canal was blocked by ships sunk by the Egyptians during the June 1967 Six Day War. Thus, the decision was to bring the boats from Haifa to Eilat, sailing via the Mediterranean Sea, the Gibraltar strait and around the West and then East coasts of Africa. I was the physician on the “Reshef”, one of the two modern Israeli missile boats that were built in the Haifa naval shipyard. One can imagine that for small missile boats, such a long, several weeks voyage, a large part of it in the open Oceans, is rather complicated, and for many reasons also risky. Beyond fuelling and provision of supplies and spare parts to the crews and boats, one has to think of sailing in waterways surrounded by hostile countries, many miles away from home and a long flight distance for the Israeli Air Force. Another problem was obviously medical, how one treats emergencies, from possible gunshot wounds through “simple” daily problems like appendicitis, in a small ship, far from any medical facility and with limited diagnostic and treatment capabilities. I was particularly concerned, as I was a young physician with almost no clinical experience. I assume this would have been a challenge for more experienced physicians as well. Luckily, the voyage was smooth. The remaining part of my three-year service was also interesting. I spent that time in the Research and Development (R & D) unit of the Medical Corps, developing a broad array of sophisticated devices for the soldier in the battlefield. Because of the broad range of experiences acquired, the military service has been my ever best school for real life “sciences”. During all these years (1973-1976) I maintained tight connections with Avram and fulfilled my duties as an “external” department member: during vacations from the military, and along with other members of the department that grew meanwhile, I taught continuously the course in Clinical Biochemistry to 3rd year medical students. I should mention in particular Michael (Mickey; see also below) Fry, with whom I have remained a good friend to the very present. Also, in 1975, during the military service, I married Menucha, a physician and a graduate of Tel Aviv University School of Medicine. Menucha was a resident in internal medicine in Tel Aviv Municipal Hospital, and we built our first home in this city. Marrying Menucha brought my wanderings to an end, and I felt I had again a family and a home. During all the years since the death of my father (1963-1975), I did not have a real stable home, and I wandered between the homes of my brother and sister-in-law in Tel Aviv and of my aunt in Haifa. They were truly wonderful, but I needed a base, and Menucha, with her quiet approach and warm acceptance, along with our beautiful apartment, provided me with this, so much needed, shelter.  **Discovery of the ubiquitin system – graduate studies** Towards the end of the military service, I had to make what I assume has been the most important decision in my career: to start a residency in clinical medicine, in surgery, which was my favorite choice, or to enroll into graduate school and start a career in scientific research. It was clear to me that I was heading for graduate school. My disillusionment from clinical medicine that diseases can be cured based on understanding their pathogenetic mechanisms, along with a magical and enchanting attraction to biochemistry made the decision easy. I received a strong support and encouragement from my wife Menucha, who started to realize she was married to a student in sciences with no clear future rather than to the physician with a bright career and broad financial horizons that she thought she had married. So in November of 1976, after my discharge from the national military service and a two-month driving trip across the USA, I started my graduate studies with Avram Hershko. At that time his group focused mostly on studying intracellular proteolysis, and I learnt from him that he had given up on trying to identify the mediator(s) and mechanism(s) involved in serum-induced “pleiotropic response”. The model system that was chosen to study proteolysis was degradation of abnormal hemoglobin in the reticulocyte which is the terminally differentiating red blood cell. The reason for the selection of the reticulocyte as a model system was that we were looking for a non-lysosomal and energyrequiring proteolytic system, as from many studies it had become clear that regulated proteolysis of intracellular proteins is non-lysosomal (see the accompanying Nobel Lecture), and the reticulocyte no longer contains lysosomes which are removed during the final stages of its maturation (see below) before its release into the circulation. Interestingly, in the summer of 1978, during a Gordon Conference on Lysosomes, I met Dr. Alex Novikoff from Yeshiva University School of Medicine in New York. Alex, along with Dr. [Christian de Duve](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1974/index.html), was one of the pioneers of the lysosome research field. When I told him we were working on the reticulocyte because this cell does not have lysosomes, he angrily dismissed this argument, telling me that he characterized morphologically acid phosphatase-positive organelles in reticulocytes. He even gave me the relevant paper he published on the subject, though it was not clear that these are proteolytically functional organelles. Another reason for the choice of the reticulocyte as a model for studying intracellular proteolysis was that in its final stages of maturation in the bone marrow and prior to entering the peripheral circulation, a massive proteolytic burst destroys most of its machineries, making it clear that the cell is equipped with an efficient proteolytic system. Earlier studies by Rabinovitz and Fisher demonstrated that the reticulocyte degrades abnormal, amino acid analogue-containing hemoglobin, yet the mechanisms had remained elusive. We assumed that the same mechanism that is involved in differentiation and maturation of the reticulocyte is also involved in the removal of “naturally occurring” mutant abnormal hemoglobins that are synthesized in different hemoglobinopathies, such as thalassemias and sickle cell anemia, and also in the destruction of the amino acid analogs – containing abnormal hemoglobins. We wanted to believe and hoped that this mechanism would turn out to be “universal”, and involved in degradation of normal proteins in all cells. Years later this assumption turned out to be correct. Thus, this important piece of information – the existence of a non-lysosomal proteolytic system, made the choice of the reticulocyte an obvious one. It was still necessary to demonstrate that the process requires energy, and indeed, following our initial characterization of degradation of abnormal hemoglobin in the intact cell, we showed that the process required energy (was published in 1978 in the proceedings of a proteolysis meeting held in Buffalo, NY), and felt that the time was ripe to break the cell open and isolate and characterize the non-lysosomal and ATP-dependent proteolytic enzyme(s). Shortly before, in 1977, Dr. Alfred Goldberg and his post-doctoral fellow Dr. Joseph Etlinger at Harvard Medical School characterized, for the first time, a cell-free proteolytic system from reticulocyte, which was exactly the point where we wanted to start our own march, so we basically adopted their system.  I will not describe here the detailed history of the discovery of the ubiquitin system, but rather highlight two important points along the five years of my exciting graduate studies (1976-1981) with Avram and Irwin A. Rose (Ernie) that led to the discovery of the system. The more detailed history can be found in several review articles written on the system at that time (most notable is Hershko, A. and Ciechanover, A. (1982). Mechanisms of Intracellullar Protein Breakdown. *Annual Review of Biochemistry*, **51**, 335-364.) and later, and in the accompanying Nobel Lecture.  (1) The first point relates to the multiplicity of enzymatic components of the system: Our first aim along the purification process of the ATP-dependent “protease” was to remove hemoglobin, the major protein in the crude extract. Towards that end, we resolved the extract on an anion exchange resin, where we encountered already the first exciting finding. The proteolytic activity could not be found neither in the non-adsorbed material which we denoted Fraction I, nor in the high salt eluted material (denoted Fraction II). Rather, we recovered the activity following reconstitution of the two Fractions. We learnt two important lessons from this experiment which was published in 1978 in *Biochemical and Biophysical Research Communications* (BBRC; in my opinion the first paper in the long historical trail of the ubiquitin system) and which I regard as one of two or three key publications in the field. We learnt two lessons from this experiment: (i) The first was that the protease we were after was not a “classical” single enzyme that degrades its substrate, but had at least two components. This was already a digression from the paradigm in the field at that time that proteolytic substrates, almost without exception, can be cleared, at least partially, by single proteases with limited, yet defined specificities. Now, following the unraveling of the human genome and the discovery of important common structural domains within several groups of enzymes of the system, we know that the number of components of the ubiquitin system exceeds one thousand, but the first hint was already there; once one is left without a paradigm, all possibilities are open. (ii) The second lesson was a methodological one. Each time we lost activity during purification of any of the components we were characterizing, we “returned” to the chromatographical column fractions and tried to reconstitute it via complementation: “classical” biochemistry at its best was on our side. Standing at a crossroad, we – luckily but thoughtfully – decided to start first with purification and characterization of the active component in Fraction I. We decided so because Fraction I was the hemoglobin-containing fraction that did not adsorb to the resin, and since many proteins do absorb, we thought that this fraction should not contain too many additional proteins beyond hemoglobin, and it would be easy to purify the active component. Ten months after I started my studies (summer of 1977), Avram started his sabbatical with Ernie at the Fox Chase Cancer Center in Philadelphia, PA, USA, and left me with the task to purify the active component from Fraction I. After many unsuccessful trials along with another graduate student of Avram, Yaacov Hod, my colleague Mickey Fry, who was appointed as my substitute thesis advisor for this year (1977-1978), came with the “crazy” idea to heat Fraction I and see if the active component is heat-stable, and indeed it was. He did so as all our attempts to resolve the activity – despite the large difference in the molecular mass between the active protein (~10 kDa) and hemoglobin, the other major protein in Fraction I (65 kDa) – failed: hemoglobin, that is so abundant, “contaminated” the entire resolution span of each column in every single resolution method we used. Following 5-10 min at 90°C, the hemoglobin in crude Fraction I was “cooked” and precipitated like mud, and the activity remained soluble in the supernatant. It was hard to believe it was a protein, but Mickey remembered several other heat-stable proteins. Immediately after, we showed directly that the activity in Fraction I was also a protein: it was sensitive to trypsin and precipitable with ammonium sulfate. Further characterization revealed that the protein had a molecular mass of ~8,500 Da, and we called it ATP-dependent Proteolysis Factor-1, APF-1, to denote that this was the first component in the system that we characterized. All along the way I corresponded with Avram, sent him my results, and during his sabbatical we wrote the BBRC paper.  (2) The second key finding was also discovered in Haifa during the winter of 1978-1979. We purified APF-1 to homogeneity and labeled it with radioactive iodine. When the radio-labeled protein was incubated in crude reticulocyte Fraction II in the presence of ATP, we observed a dramatic increase in its molecular weight: it now migrated as a sharp peak in the void volume of the gel filtration chromatographical column. For several months we tried to elucidate the mechanism that underlies the change in the molecular weight of APF-1, hypothesizing, for example, that APF-1 could be an activator of a protease that must generate a binary complex with the proteolytic enzyme in order to activate it, but to no avail. An important breakthrough occurred during our 1979 summer stay of several months in the laboratory of Ernie. Through a series of extremely elegant, yet simple, experiments, in the design of which the broad knowledge of Ernie in protein chemistry and enzymology played a critical role, we found that APF-1 is covalently attached to the substrate through a bond that had all the characteristics of a peptide bond. Furthermore, we found that multiple moieties of APF-1 are attached to each substrate molecule, and that the reaction is reversible: APF-1 can be removed from the substrate or its degradation products and recycled, though not via reversal of the conjugation reaction. Accordingly, we hypothesized that covalent attachment of multiple moieties of APF-1 to the target substrate is necessary to render it susceptible to degradation by a downstream protease that recognizes only tagged but not untagged proteins, followed by the release of free and reusable APF-1.  The APF-1 cycle predicted the existence of three, entirely novel activities: (i) APF-1 conjugating enzyme(s), (ii) a protease that recognizes specifically the tagged substrates and degrades them, and (iii) APF-1-recycling enzymes. All these activities were identified later by us (the three conjugating enzymes, E1, E2, and E3) and by others (the conjugates degrading protease known as the 26S proteasome complex, and the ubiquitin recycling enzymes, the isopeptidases; see the accompanying Nobel Lecture). The findings describing the covalent tagging of the target substrate by APF-1 as a degradation signal, along with the first model of the newly discovered proteolytic system, were published in 1980 in two manuscripts that appeared in the *Proceedings of the National Academy of Sciences of the USA* (PNAS).  Another important development also occurred during our stay in Ernie’s laboratory, and I am not sure whether it was sheer luck or serendipity, probably both. We were not aware of any other precedent of a modification of a protein by another protein. The neighboring laboratories of Martin Nemer, Alfred Zweidler, and Leonard Cohen studied dynamics of variants of different histones during sea urchin development. They drew our attention to a protein called A24 (uH2A) which was discovered earlier by Ira Goldknopf and Harris Busch, and that was a covalent conjugate between two proteins – a small, ~8.5 kDa protein called ubiquitin, and histone 2A (H2A). Goldknopf and Busch, and in parallel Margaret Dayhoff, identified the nature of the bond between the two protein moieties in the conjugate. They found that the ubiquitinhistone bond was an isopeptide/bifurcated bond between the C-terminal Gly76 residue in the ubiquitin moiety, and the e-NH2 group of Lys119 in the histone moiety of the conjugate. The role of this conjugate was not clear at the time, though its level was found to be dynamic and change during differentiation, when the histone moiety is subjected to ubiquitination and de-ubiquitination. This information on the ubiquitin-histone adduct along with the striking similarities we found between APF-1 and ubiquitin in their general characteristics such as molecular mass and amino acid composition, led Keith Wilkinson and his colleague Arthur (Art) Haas who were post-doctoral fellows in the laboratory of Ernie, along with Michael Urban from Zweidler’s laboratory, to carry out a series of direct experiments, showing unequivocally that APF-1 is indeed ubiquitin. Our study on the characterization of APF-1 and its possible similarity to ubiquitin, and Wilkinson’s study (along with Urban and Haas) on the identification of APF-1 as ubiquitin, led to the convergence of two fields, that of histone research and of proteolysis. More important, they suggested that the bond between ubiquitin and the target proteolytic substrate might be identical to that between ubiquitin and histone, which turned out later to be true. The two studies were published in tandem in 1980 in the *Journal of Biological Chemistry* (JBC; see the accompanying Nobel Lecture). The identification of the nature and structure of the bond clearly paved the road to the later purification and characterization of the conjugating enzymes and their mode of action.  As for ubiquitin, the protein was identified in the 1970s by Gideon Goldstein (in the Memorial Sloan-Kettering Cancer Center in New York City) as a small, 76 residue thymic polypeptide hormone that stimulates T cell differentiation via activation of adenylate cyclase. Additional studies by Gideon Goldstein had suggested that it was universally distributed in both prokaryotes and eukaryotes, thus giving rise to its name (coined by Gideon Goldstein). Later studies by Allan Goldstein showed that the thymopoietic activity was due to an endotoxin contamination in the protein preparation, and not to ubiquitin. Using functional assays, it was found in my laboratory (and I believe that in several others as well) that ubiquitin was limited to eukaryotes, and its apparent presence in bacteria was due to the contamination of the bacterial extract with the yeast extract in which the bacteria were grown: growing the bacteria in a synthetic medium containing carbon (glucose) and nitrogen (ammonium chloride) sources and vitamins resulted in “disappearance” of ubiquitin from the preparation. The later unraveling of the bacterial genome demonstrated unequivocally that the ubiquitin tagging system does not exist in prokaryotes, though there is some similarity between the proteasome and certain bacterial proteolytic complexes. Thus, in a relatively short period of time, ubiquitin was converted from a ubiquitous thymopoietic hormone to a eukaryotic proteolytic marker. While it appeared that the term ubiquitin was not justified anymore, as it is clearly not ubiquitous, we stopped using the term APF-1 and adopted the term ubiquitin for the modifying protein in the newly discovered proteolytic system. At times habits and tradition are stronger than the scientific validity and/or the logic in nomenclature. Accordingly, we adopted a general policy to use in our terminology the name/term that was first coined by the discoverer of any novel protein.  From that point on, the road was relatively short to the identification and characterization of the conjugation mechanism and the three enzymes involved in this process. En route we followed partially, with great admiration, the footsteps of Dr. [Fritz Lipmann](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1953/index.html), the great biochemist from the Rockefeller University (who was awarded the 1953 Nobel Prize in Physiology or Medicine for the discovery of Coenzyme A). Lipmann continued to contribute enormously to our understanding of basic biochemical processes. Among his many discoveries was the mechanism of non-ribosomal (and hence non-genetically encoded) peptide bond formation that is involved in the biosynthesis of bacterial oligopeptides such as Gramicidin S. We learnt that the basic biochemical principles, such as generation of high-energy intermediates involved in peptide bond formation, were preserved along evolution regardless of whether the bond is encoded genetically or not, or whether it links two amino acids, or two proteins, or an amino acid to the elongoting polypeptide chain. Initially, we identified the general mechanism of activation of ubiquitin in crude extract. Later, using “covalent” affinity chromatography over immobilized ubiquitin and a stepwise elution (that was based on the general mechanism we deciphered earlier), we purified the three conjugating enzymes that act successively, in a cascade-like mechanism, and catalyze this unique process: (1) the ubiquitin-activating enzyme, E1, the first enzyme in the ubiquitin system cascade, (2) the ubiquitin-carrier protein, E2, to which the activated ubiquitin is transferred from E1, and (3) the ubiquitin-protein ligase, E3, the last and critical component in the three step conjugation mechanism that specifically recognizes the target substrate and conjugates it with ubiquitin. The E3 was also adsorbed to the immobilized ubiquitin, although via a yet unknown mechanism, distinct from that of E1 and E2: the binding of these two enzymes was mediated by the activation mechanism. Later studies by Avram in the late 1980s revealed that the E3 adsorbed by the column was E3a that recognizes substrates via their N-terminal residue. At this point, however, unknowingly and unintentionally, we were extremely lucky when we used as model substrates commercial proteins such as BSA, lysozyme and RNase, that were all recognized (as we learnt later) by this ligase and via a similar targeting motif – their N-terminal residue. Had we used other substrates, such as globin, the protein we used in our initial experiments, the E3 adsorbed to the column would have probably escaped our attention, as E3s do not typically adsorb to ubiquitin. Independently, and in parallel to the later characterization of the enzyme by Avram, I also used this enzyme in order to characterize a distinct subset of proteins recognized via this signal (see below). Lastly, using antibodies that we raised against ubiquitin with the help of Arthur Haas, we found that the ubiquitin system is involved in degradation of abnormal, short-lived proteins in hepatoma cells, demonstrating that the system is not limited to the terminally differentiating reticulocyte, but is probably distributed “universally” in nucleated mammalian cells, playing an important role in maintaining the cell’s quality control, by removing abnormal proteins. During my graduate studies at Avram’s laboratory, I collaborated with Hannah Heller, an extremely talented and knowledgeable research associate (who also joined us for some of our summer stays in the laboratory of Ernie in Philadelphia), and with Yaacov Hod, who was also a graduate student with Avram at that time. Other colleagues in the laboratory provided me with a lot of help during this period, including Dvorah Ganoth, Sarah Elias, and Esther Eythan who were research associates with Avram, and Clara Segal and Bruria Rosenberg, two dedicated technicians.  **The interaction with Irwin Rose** As noted, I spent an important part of my graduate studies in Ernie’s laboratory. Avram spent a sabbatical in his laboratory in 1977-1978, and I joined him for the first time for several months in the summer of 1978, after I completed the initial characterization of APF-1 in Haifa. I returned to Ernie’s laboratory during the summers of 1979, 1980, and 1981. As noted, during our summer stay in 1979, we resolved the problem of the nature of the high molecular mass “compound” generated when APF-1 was incubated with Fraction II in the presence of ATP. This change in the molecular mass of APF-1 was discovered several months earlier in Haifa. However, we were not able to unravel the nature of the “compound”; this had to await the knowledge and wisdom of Ernie. In a breakthrough discovery, we found that the target substrate is covalently modified by multiple moieties of APF-1, a reversible modification that renders the protein substrate susceptible to degradation. This was a novel type of post-translational modification (see, however, above for the modification of histone H2A by ubiquitin) and clearly a new biological paradigm, that the elucidation of which required – as I feel today in retrospect – a different type of knowledge in biology and enzymology, and an original experimental approach. Elucidation of this modification would not have been possible without Ernie’s advice that was based on his immense knowledge in enzymology and protein chemistry, accompanied by his unbiased original thinking and approach to problem resolving. This discovery, along with the discovery in 1980 that APF-1 is ubiquitin, made Ernie and his fellows critically important partners in the historical trail of the discovery of the ubiquitin system. Interestingly, Ernie studied proteolysis before Avram joined him first, but had never published in the field before.  **Post-graduate training at MIT and how I continued my studies on the ubiquitin system independently** The five years in graduate school had a significant impact on my future career. Not only because I played an active part in the discovery of such an important pathway, but maybe more important, because I learnt several basic and key principles on how to approach a scientific problem. From my mentors I learnt two principles: first, to select an important biological problem, preferably an unobvious one and not in the mainstream, and second, to make sure that there are appropriate research tools to approach it experimentally. I also learnt to become a long books author rather than a short story writer: I learnt not to be opportunistic but rather to adhere to a project, to dig deeply into a problem, to resolve it mechanistically, to unravel complex mazes – peeling them like an onion, not to be tempted to be dragged after fashions. I learnt to pay attention to small details, to carefully examine hints, as the important findings are not always obvious from the apparent results. I learnt to be stubborn, to fight difficulties uphill, but most importantly, to be critical: I believe I developed good senses that enable me to distinguish false from truth, and artifacts from meaningful findings. Interestingly, I learnt all these principles not in frontal lessons or formal presentations, but as an apprentice, following my mentors’ own attitude and way of thinking. At the same time I also learnt to question, to doubt, to ask, and to discuss, to follow my own gut feeling when it was necessary, not to always take advice and direction for granted, and to trust myself too. It did help in many occasions along the way. Thus, at times I found myself swimming alone against the stream. Altogether, these principles generated an important philosophy and shaped my approach to science, something I try to instill in my own students, as I strongly believe it is the only way one can make an impact, leave an imprint behind.  Towards graduation I had to think of the next step – post-doctoral training and planning of my future career as an independent scientist. I was in a dilemma. On the one hand, I knew it was important to obtain training somewhere else, under different mentorship, in a different environment, being exposed to a different culture of science. On the other hand, I knew for certain that the ubiquitin system was extremely important and that we were seeing only the tip of its iceberg. I therefore wanted to continue my studies in a related field, learning more on regulated proteolysis, but also to continue my own studies on ubiquitin. I had several ideas in mind on where to go, but the choice was quite narrow and also risky, as I did not have any idea of how much independence I could have as a post-doctoral fellow. Searching for a mentor, and with the advice of my colleague Mickey Fry, I looked for scientists whose work was related to regulated proteolysis. I wrote to [Günter Blobel](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1999/index.html) in the Rockefeller University, who worked at that time on translocation of proteins across the endoplasmic reticulum (ER) membrane, a process that involves cleavage of the leader peptide by signal peptidase, to Jeffrey Roberts in Cornell University who worked on *E. coli* RecA protein-directed cleavage of phage l repressor and its requirement for polynucleotide, and to Harvey Lodish at the M.I.T. who worked, among other subjects, on processing of viral polyproteins. I am not sure Harvey was that impressed with the ubiquitin system at that time, but he was the only one to respond positively. Typical of his etiquette (as I learnt later), his response was prompt and direct, and he invited me for an interview after which he accepted me. Günter was kind enough to let me know he did not have space in his laboratory at that time, and Jeffrey never responded.  With two fellowships, one from the Leukemia Society of America and one from the Israel Cancer Research Fund, ICRF, I started a period of three wonderful years (1981-1984) in Harvey’s laboratory in the Department of Biology at M.I.T. Harvey gave me complete freedom to choose my research subjects. What I had in mind was to take advantage of the exceptional strength of the laboratory and Harvey’s unique expertise in cell biology, but in parallel, to continue my own studies on the ubiquitin system. I realized that Harvey was no longer interested in viral proteins processing, and along with Alan Schwartz who was a visiting scientist (from Harvard Medical School) in the laboratory, we started to characterize the transferrin receptor on a human hepatoma cell line with the aim of disseding the dynamics of the receptor and iron delivery into cells. This collaboration led us, along with another fellow in the laboratory, Alice Dautry-Varsat (from the Pasteur Institute) who joined us later, to the discovery of a fascinating mechanism of how iron is delivered into cells, a process mediated by the transferrin receptor: In the neutral pH of the growth medium, the iron-loaded holo-transferrin binds to its receptor with a high affinity and is endocytosed into the cell. At the low endosomal pH, the affinity between iron and transferrin is weakened dramatically. As a result, the iron cation is released, but the apo-transferrin, which has high affinity for the receptor at acidic pH, remains bound strongly. Along with the receptor, the apo-transferrin recycles to the cell surface. At the neutral pH of the growth medium, the apo-transferrin loses its high affinity to the receptor and is released into the neutral pH extracellular fluid. There, it binds iron with high affinity, rebinds to its receptor and the hololigand is endocytosed again. The transferrin-transferrin receptor pH- and iron loadingdependent cycle has become a “classic” in the field of receptor mediatedendocytosis. Based on this mechanism, other phenomena related to receptor and ligand recycling to the cell surface or targeting to the lysosome could be explained, which are also due to the pH difference between the external environment and the interior of the endocytic pathway vesicles. However, throughout this time, I lived under the strong feeling that the ubiquitin system had barely started to emerge, with only the basic principles unraveled: I felt compelled to get back and work on it. So gradually I started to “crawl” and return to my alma mater’s research subject.  On one fascinating subject I worked on my own, continuing to explore a mysterious finding I discovered during my graduate training and which I did not pursue at the time: When we purified APF-1/ubiquitin in Haifa, we noticed a large discrepancy between its dry weight and its Lowry or 280 nm protein quantitative measurements. We hypothesized that the protein can be a ribonucleoprotein, RNP, and the remaining mass is that of the nucleic acid component. To test this hypothesis, I added DNase to the crude extract in which we monitored ATP- and ubiquitin-dependent degradation of BSA, that was used as one of our model substrates. The enzyme had no effect. We then added RNase A, and to our surprise proteolysis was completely inhibited, even with an extremely small amount – mere few nanograms – of the enzyme added: it looked as if the enzyme exerted its effect via catalysis – RNA degradation. Avram suggested to test the RNase effect also on lysozyme, a protein that was used as our second model substrate. Here we got no effect, which was kind of a surprise, as proteolysis of the two substrates, BSA and lysozyme, behaved in an identical manner all along the way: ATP as well as all the different factors we resolved from the crude extract, were all required for the degradation of both proteins. Avram suspected that the RNase effect could be an artifact. Meanwhile APF-1 was identified by Keith Wilkinson and his colleagues as ubiquitin (see above), and the amino acid sequence/composition of ubiquitin disclosed the “secret” of the dry weight/protein measurement discrepancy – the molecule has a single tyrosine residue. So we decided not to pursue this subject, and the selective inhibitory effect of RNase A on BSA degradation had remained an unsolved mystery – for the time being.  I had not stopped suspecting, however, that the findings must represent some true biological phenomenon, and used the opportunity of my independence at Harvey’s laboratory to pull out the late 1970s results from my notebook and start dissecting the RNase effect in a systematic manner. With some advice from Alexander Varshavsky (Alex; M.I.T.), and a lot of help and reagents from Joan Steitz (Yale), Harvey Lodish and Uttam RajBhandary (M.I.T.), I managed to make some progress. I discovered that the degradation of BSA was completely dependent on specific tRNAs, that of Arg and His, and that the destruction of the tRNA led to inhibition of the reaction. The nature of the mechanism of action of the tRNAs and the problem of why the degradation of lysozyme was insensitive to RNase had remained a mystery at that time, which was resolved only when I returned to Israel and established my own laboratory (see below).  The other ubiquitin subject I was studying involved a collaboration with Alex Varshavsky and his then graduate student, Daniel Finley – Dan. At that time Alex was studying the role of mono-ubiquitination of histones (for the histone-ubiquitin adduct H2A known also as protein A24 or uH2A, see above). Alex noted a series of publications on a temperature sensitive cell cycle arrest mouse mutant cell, ts85, that was generated and described by the group of M. Yamada. These researchers reported that at the non-permissive temperature, the cell lost the histone H2A-ubiquitin adduct. With the ubiquitin cycle unraveled we surmised that this loss could be due to one of two defects: (i) loss of ubiquitination, or (ii) activated de-ubiquitination. Planning our experimental approach, we thought that the defect in these cells is more likely due to loss rather then to gain of function, and we set to dissect the defect. The idea was that the same defect in monoubiquitination of the histone may affect also protein degradation which involves polyubiquitination, though it was clear that the single modification of the histone molecule by ubiquitin does not lead to its targeting to proteolysis. Identification of the biochemical defect in the cells was not too difficult, as we used the isolation technique of the conjugating enzymes developed in Haifa and demonstrated that the defect results from a temperature-sensitive ubiquitin-activating enzyme, E1, the first enzyme in the ubiquitin system cascade (see above). Importantly, inactivation of the enzyme led to inhibition of ubiquitin conjugation to the general population of cellular proteins and was not confined to inhibition of conjugation of histone H2A. Consequently, degradation of both abnormal and normal shortlived proteins was also inhibited, demonstrating that the same enzyme that is involved in ubiquitin activation for histone modification, is also involved in activation of ubiquitin for modification of substrates destined for degradation. We were very lucky in the sense, as if the defect would have been more specific, involving an E3 that targets several substrates, or “worse”, a specific histone E3, we could not have possibly detected an effect on the degradation of the general population of cell proteins: only a defect in a key enzyme such as E1 could have resulted in such a dramatic effect. Identification and characterization of the cell defect further corroborated our earlier general hypothesis that ubiquitination signals proteins for degradation, and that it also occurs in nucleated cells, a finding we had already demonstrated in Haifa, albeit indirectly (using anti-bodies raised against ubiquitin and monitoring the level and dynamics of ubiquitin-protein adducts under conditions of basal and accelerated proteolysis in hepotoma cells; see above). Since the ts85 cell was also a cell cycle arrest mutant, we hypothesized, but did not show at the time experimentally, that the system may be involved in regulating the cell cycle, an hypothesis that later turned out to be correct.  **The return to Israel – independent research career** After three years at M.I.T. (1981-1984), it was time to seek for an independent academic position. After many deliberations and despite attractive offers and a strong temptation to stay in the US, I decided to return home, to Israel. With the help of Avram, I obtained an independent academic position in the Department of Biochemistry at the Faculty of Medicine of the Technion (where I graduated), and returned home towards the end of 1984, after a productive post-doctoral period. Importantly, I already had a research subject I wanted to pursue, the effect of RNase on ubiquitin-mediated proteolysis.  The years that followed the post-doctoral fellowship (1984-present) have been extremely rewarding. I was happy to return to Israel, to my family and friends, to a place I felt I belong. I established my own independent research group and laboratory, obtained extramural competitive funding, and continued my research on the ubiquitin system. I have been lucky to have, along the years, a group of extremely talented graduate students and post-doctoral fellows. In our first series of studies we elucidated the role of tRNA in the proteolytic process, a subject I discovered as a graduate student and continued to study independently while at the M.I.T. (see above). Along with one of my first graduate students, Sarah Ferber, we demonstrated that proteins with acidic N-termini, Asp or Glu, undergo arginylation at the N-terminus, converting the acidic, negatively charged residue at this site to a positively charged residue. The reaction is catalyzed by Arg tRNA-protein transferase, a known protein with an hitherto unknown function. The enzyme uses charged tRNAArg as a source of activated Arg. Therefore, digestion of the cell extract RNA with RNase A inhibits this reaction. This finding explained the selectivity of the RNase effect to BSA and not to lysozyme: BSA has an Asp residue in the N-terminus, while lysozyme has lysine in this position. Interestingly, the ligase involved in BSA ubiquitination is E3a that was discovered during my graduate studies. As described later by Avram and his gradute student Yuval Reiss, the ligase recognizes several groups of substrates, among them proteins with basic but not with acidic N-termini. Thus, what appeared initially as an artifact turned out to be part of the first specific recognition signal in a target substrate (see below). Parallel to our work on the RNase effect, Avram and Yuval characterized the enzyme and identified on it three distinct substrate binding sites for: (i) basic (the one involved in recognition of basic and Arg-modified acidic Ntermini) and (ii) bulky-hydrophobic N-termini, but also for (iii) larger, yet still undefined “body” sites that reside downstream to the N-terminal residue. Because the enzyme recognized certain substrates at their N(a)-terminal residue, it was termed E3a. In parallel and using a systematic genetic approach in the yeast *S. cerevisiae*, Alex Varshavsky and his colleagues formulated a general rule (‘N-end rule’) for recognition of all 20 different amino acid residues at the N-terminal site.  Research in the laboratory has evolved also in other directions. We have shown that N-a-acetylated proteins are also targeted by the ubiquitin system. This important finding demonstrated that this N-terminally modified “family” of proteins, a group that constitutes a large proportion of cellular proteins, must be targeted by signals that are distinct from the N-terminal residue and reside downstream to it: since they do not have free N-termini, they cannot be recognized by this residue. Along with the discovery of the “body” site in E3a, we felt that N-terminal recognition involves only a small and limited set of proteins, and the mode of recognition of the numerous substrates of the ubiquitin system must be broad and diverse: they must be recognized by multiple and distinct targeting motifs. At that point, the end of the 1980s, we felt it was time to move from studying model substrates to investigating the fate of specific native cellular substrates. We have shown that an important group of cell regulators – tumor suppressors (e.g. p53) and growth promoters (c-Myc) are targeted by the ubiquitin cell free system. We strongly believed that this must be also true for targeting of these substrates *in vivo*, which later, through the work of many others and our own, turned out to be the case. We continued and demonstrated that, unlike the paradigm in the field until that time, that degradation of proteins in the lysosome proceeds independently from the ubiquitin system – the two proteolytic pathways are actually linked to one another, and ubiquitination is required for stress-induced lysosomal degradation of cellular proteins. This area has later evolved in a dramatic manner, and engulfed involvement of the ubiquitin system in receptor-mediated endocytosis and autophagy. Other studies involved elucidation of some of the mechanisms involved in the two step ubiquitin-mediated proteolytic activation of the centrally important transcriptional regulator NF-KB, demonstration of a role for heat shock proteins in targeting certain protein substrates, and identification of a novel site of ubiquitination – the N-terminal residue of the protein substrate. This modification is clearly different and distinct from recognition of the substrate by E3a at the N-terminal residue. In the latter case, the ligase binds to the N-terminal residue while ubiquitination occurs on an internal lysine residue(s). In N-terminal ubiquitination, modification occurs at the N-terminal residue, while the ligase binds, most probably, to an internal sequence in the protein target molecule. This subject has evolved in a surprising manner and changed another paradigm in the field that ubiquitination is limited to internal lysine(s) of the target substrate; we, and later others, have shown that the phenomenon is not limited to the one protein we identified initially – the muscle-specific transcriptional regulator MyoD, and identified a large group of proteins that undergo N-terminal ubiquitination. This group of proteins contain many that have internal lysine(s), but that from some reason(s) cannot be targeted, but interestingly, also a large group of proteins (such as p16INK4a that plays an important role in cell cycle regulation), that are devoid of any lysine residue. To be degraded by the ubiquitin system, these proteins must undergo N-terminal ubiquitination.  These years have not been simple, however. The Technion has traditionally been a school of engineering, and life sciences and biomedicine have been foreign to many of its senior leaders, faculty members and policy planners: we were treated in many ways like step children, and thoughts of closing the medical school have been aired at times. This deeply rooted philosophy, which only now starts slowly to change, has severely hampered development in these fields and had left the body of researchers and infrastructure in these areas small and battling for survival. Unlike leaders in other schools of engineering like M.I.T. and Caltech, the Technion’s leaders failed to forsee the upcoming revolution in biology and medicine and its huge impact on modern technology. However, through a network of wonderful colleagues all over the world (important among them is my friend Alan Schwartz who is currently at Washington University in St. Louis, but was then at Harvard Medical School; see above for the beginning of our collaboration at the M.I.T.), and fruitful collaborations, I was able to establish an active research group and carry out what I believe was a good and original research program, even under less than optimal, and at times impossible conditions. This was important in balancing my desire to live in Israel, but at the same time to remain at the forefront of the ubiquitin research field that has grown in its importance to become an extremely exciting, yet a highly competitive, area.  **Unpaid debts** Last but not least, I owe a huge debt, which I doubt I shall ever be able to repay, to several people who helped me cross critical stormy waterways along my life. My aunt, Miriam, who took me to her house after the death of my father and made her home a new home for me, enabling me to complete seamlessly my high school studies without any interruption. My brother Yossi (Joseph) and my sister-in-law Atara, who opened their home to me during the fragile times of my high school and medical studies, and made sure I would not collapse along the way, emotionally, but also economically. And last, my wonderful wife Menucha and my son Tzachi (Yitzhak, Isaac; called after my late father). They engulfed me with love, care, and deep understanding of my needs, and were always there for me when I was flying high on the wings of my dreams, not always seeing or listening to them or being with them, physically and emotionally. Without all these wonderful life partners, I could not have achieved anything.  I also owe special thanks to all my mentors, who each contributed in his own way to my upbringing as a scientist. I owe a big debt to Jacob Bar-Tana and the late Benjamin Shapira from the Hebrew University in Jerusalem, who opened for me the gates to the wonderful maze of metabolic pathways, enabling me fall in love with biochemistry. Their enthusiasm and wisdom convinced me, at a critical stage of my development, to pursue a career in biological sciences. Deep thanks to Avram Hershko, with whom I have come a long way in discovering the ubiquitin system, and from whom I learnt the very basic principles of how to approach a scientific problem. I owe special thanks to Ernie Rose for showing me that methodic thinking is not always necessary in science, and is even interfering at times, and that being erratic and disordered, even absent minded, thinking in a most unconventional manner, can yield wonderful ideas and results. The interaction with Ernie is unique, as it gives one a feeling of instability, casting doubt in one’s basic knowledge and beliefs. The real challenge is to select Ernie’s correct idea, which then takes you high above any traditional, step wise approach. Lastly, I owe a huge debt to Harvey Lodish, who is not only a great cell biologist, but a wonderful spiritual mentor in a different way we tend to think of mentors. He gave me complete freedom to choose my own way, but did not let me fall. He always listened carefully and helped me to analyze my results, and with his deep insight was able to find in the ocean of my numbers and graphic data new routes and pathways that I could have never seen or thought of. He used to gently comment on my approach when he felt I got derailed, and helped redirect me. Yet, he was never imposing: Harvey’s active passive educational approach is truly unique. I owe many thanks to all my colleagues, in particular Alan Schwartz, Iasha Sznajder, Yinon Ben-Neriah, and Kazuhiro Iwai, who helped me in many ways along this long voyage. I must also mention my laboratory research associates, initially Sarah Elias (who also helped me in the initial studies) and then Hedva Gonen and Beatrice Bercovich, who have become my eyes and hands since I established my own laboratory. I should mention the major contribution of Hannah Heller, an extremely talented technician of Avram, who was an integral part of our “voyage” and discovery. Dvorah Ganoth and Esther Eythan also helped us along the way, and Clara Segal and Bruvia Rosenberg provided us with skillful technical help. Last but not least, my wonderful graduate students, fellows and visiting scientists, with whom I made new and exciting ways in the rapidly evolving and exciting ubiquitin field. |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** | – Hello.  – Hello. Is this Aaron Ciechanover?  – Speaking. Yes.  – Yes. My name is Joanna rose and I’m calling from Nobelprize.org, which is the official website of the Nobel Foundation.  – Yes.  – My congratulations to the prize.  – Thank you very much.  – How does it feel now?  – Exhausting. Still hard to digest. Overwhelming. I don’t have words. I’m speechless.  – You are. I hope you can tell us something. Did you expect the message?  – No. Not at all. I was on my way out and my son picked up the telephone and, it was like, it was a complete surprise. I was … certainly not in chemistry. I had some thought of medicine. I’m a physician by education and biochemistry. If I thought of it ever, it was in the direction of medicine and physiology, if at all. Chemistry, total surprise. Absolutely. I was on my way out. If I wouldn’t have been caught within the minute, I would have been out driving my car to some last … it’s the evening of the holiday now in Israel … last arrangements for the holiday.  – Oh, I see. So, what was your first reaction?  – I cannot tell you even. I have to ask my son and my wife that were with me in the room because I came to say ”hello,” that I’m leaving. And, I was caught in total surprise. It’s wonderful. What can I tell you? Obviously, it’s wonderful. That’s the climax that every scientist can ever dream of. I will not deny that I am proud for me, for this science, for the state of Israel, for my family, for everybody. It’s wonderful. But, I’m still digesting it. It’s still not … the word ”Nobel” still doesn’t stick to me.  – I understand. So, can you imagine how this prize is going to affect your future work?  – I truly hope that there will be no effect. Because I love my lab. I love my students. I love my science. I’m in the middle of wonderful work now. There are many more discoveries coming. I’ll try to do my best that there will be no effect whatsoever. So, I believe it will be a little bit of a havoc in the next few months. But I’ll try to quiet it, to silence it as fast as I can.  – Do you have any students that maybe can become Nobel Prize winners in the future?  – I cannot tell you. I have excellent students, and I love them. And I love my technicians. And I love my post-doc fellows, and I love my science.  – Do you have any advice for the young students how to become excellent in science?  – I don’t know. I don’t know how many lessons one can learn from our own one, because it has many ramifications. I think that one is to ask an important question, and in Israel … you know Israel is doing science in a different way than in the United States and even now in Europe. We are a very small country and now involved also in some political chaos in the area, and budgets are limited and science is not first priority … budgeting science. And the Americans are tough competitors. So, it’s so for ourselves, when I was a graduate student with Avram Hershko, the other laureate, and then with Ernie Rose, we saw something that wasn’t in the main focus of science. It was protein degradation. Everybody looked into protein synthesis … into DNA and how the genome is being translated into the proteome. And we said, ”No. Maybe there is something on the other side.” Not that we expected. But, we knew that it must be important. There were some hints that it’s important. And we knew that nobody’s busy with it. So, first of all, we were original I think, in choosing the subject. We didn’t run into the mainstream. So this is one idea. Also, for Israelis … I mean if you want to be competitive, don’t run into the mainstream, because you are doomed to lose. And then, ask something that is important, some major problem that is important. But the idea is to choose something original … for the Israelis, maybe a little bit of a niche. And drive it. And just believe in yourself and do it.  – Do you still cooperate with your colleague, Avram Hershko?  – Not now anymore. But we are in the same building. We are in the same faculty, and we are independent scientists. Actually, it’s even typically unusual that people are coming back to the same institute, because I graduated with him. I was his graduate student. And then I returned to the same institute and it was a problem for me. Because, you know, the problem of identification, how shall I build my own independence? But we managed. But, I’m completely independent. I’m running my own group, my own budget, my own everything. And we write reviews from time to time together.  – Thank you very much and I wish you a nice holiday evening.  – Thank you very much to you too.  – Bye bye.  – Bye bye. |
| **Interview** |  |
| Q5 | **When I say the word mentorship, what does that conjure up?** |
|  | Aaron Ciechanover: For me it was very important in particular because in my case at least I shared the prize with my own supervisor. And so it means a lot. I was lucky to have an excellent mentor. I don’t know if the word luck is proper here because I picked him by purpose, not because I knew that one day both of us were going to share the Nobel Prize, but I really searched around. And I had the privilege of searching around because I was a physician already, a practising physician and I had my own career, basically paved, or at least I could see where I was heading. But then I decided to change direction and to go to research. I did it already in medical school but then I went back to medicine and I kind of flipped back and forth, back and forth. And I hadn’t made my mind yet.  And then I decided never the less to try science and I went around and explored the possibilities with several potential mentors. And each of them was very clear about his ideas. Let’s do that and let’s do that, and I did that and you know whatever is left here. And Avram was a young investigator, just came back from a post doctoral fellowship, I mean he himself … And there he started to work on protein degradation, basically just corroborated previous findings from the past, some paradoxical findings that protein degradation requires metabolic energy, typically it’s the opposite. When you synthesise proteins you need energy. Why invest energy if you are taking high energy compounds and degrade them into low energy ingredients, which are amino acids? And Avram told me: I don’t know what I am going to do. All I know that I want to identify the system that degrades into solo proteins. I don’t know how to do it, I don’t know where it is, I don’t know how it’s going to look like.  So he had some ideas and for me I said: Wow, that’s wonderful, this risky way. And he said: Let’s take it for two or three years and see, you know, if we are going to bump to the wall, I’ll go back to the OR, to the operations theatre. I had in my mind to be a surgeon. And if I get excited, even if we don’t get results, I mean if I get excited about it I’ll stay. And it was wonderful. Avram is an excellent biochemist, and after a short time we realised that we had something very unusual at hand. And then it continued. I learnt a lot from him. But you know it was kind of a dialogue, an active dialogue. I thought that good mentors, I don’t want to be proud, they need also maybe good students. Certain interaction. But Avram certainly had the idea to work on the system, though he didn’t know what’s behind the corner. |
| Q5 | **And do you think you provide good mentorship for your students? Do you follow those principles?** |
|  | Aaron Ciechanover: I hope so, I hope so. I am different. You know, we are different people. I think that Avram was a little bit more tight, but that’s okay, I mean that’s his nature. I give them freedom, so I let them drown. I learnt more from my American mentor about mentorship than from him. I let them drown and if they feel that they have taken too much water into the lungs then they know that my door is always open. And so I never turn them down but I want them to evolve you know more independent.  But it’s a matter of taste, of how you go about them. I don’t let them die by drowning, I just let them drown. And I give them all freedom. But it’s a matter of personal style. I encourage them to, I never turn them down by telling them: Oh, you know, you shouldn’t have done it. I always let them do mistakes. But then we analyse the mistakes. I refer them to the literature in the entire lab. Whenever I read something, I refer them to the literature. Many journal’s club, you know, what’s the mistakes? It’s not just reporting on the journal. So it’s maybe a little bit different mentorship but I take, I think, don’t know if good, whether it’s good or bad, you have to ask them, but at least intensive care. |
| Q5 | **And critical reading of the literature?** |
|  | Aaron Ciechanover: And critical reading and critical evaluation of their own results. And they have to write their own papers. For example, I didn’t write my own papers. Avram wrote them, wrote them mostly. I let them write and then we’ll discuss, you know. We read them together and obviously I have the final touch. But, you know, we said: No this figure should be first because this is really the one that was the important and led us into this. And we develop it by logic, figure one, figure two, so we make a story, we make an alphabet out of the paper. And then the discussion. I put a lot of emphasis on the discussion. How did we think about it? What’s, what we still have to find out?  So it’s kind of a more dynamic, of a very dynamic interaction. I feel it a little bit more dynamic than I had with Avram but I think that it’s a matter of taste. I mean it’s not something principle. Altogether I was extremely lucky to have two excellent mentors. One is Avram, with him we found the system. And another one is Harvey Lodish at MIT with whom I post doc-ed. And he gave me, he is a mentor of my own style. I mean he said: Do that but he didn’t go into the details. But then when I came to him with a problem he knew always how to, you know, when he felt that I am derailed he was able to just put me back on by a slight tap on my shoulder and not a push. Just a hint of what to do. And I think that I adapted more his style. But never the less, mentorship is extremely important. |
| Q7 | **When you come to choose a student what do you look for in the student?** |
|  | Aaron Ciechanover: First of all I want him to have the background of what I do. I don’t want students to knock on my door and to say whether I have a spot. So the first question that I ask them is: Why me, why not my next door neighbour or my next floor neighbour or whatever. Why me? And then he said: Well, I read about you. I said what did you read? And then he comes and he tells me what did he read. And then I said: What do you think, what shall we do? I mean are there still open questions? I’m not asking them to give me, to come right there with a project. I want to identify the structure motif in the Myc onco protein. I mean we are not going to there. But what do you think about it? And somehow from time to time they’re very naïve about it. I mean they want to develop drugs, but I take it in their proper context. I mean I don’t take this naivety against them. As long as I’m convinced that they’ve read, they know why they picked me, they know the problems in the field, what is still there.  And then I never take a student, I never promise them studentship. I say I take you for a trial. Start work, I’ll pay you, as a technician, super technician, for three or four months. And then I assign them to another student or a post doc, and then I follow them myself, and with them I really carry out a very extensive dialogue along these three months. And then at the end of the three months all the group consults together about first and foremost about the scientific skills. Then also about social skills. We want the lab to be not homogenous but we want people to be good departmental citizens, you know. I very much care about the good atmosphere in the lab. And then we don’t vote but I get the sense and I myself know the candidate and so it’s a process. |
| Q10 | **What kind of environment do you encourage? How physically do you organise the lab?** |
|  | Aaron Ciechanover: Oh the lab is, first of all it’s very well equipped. We are very sophisticated. We have everything that we need almost on the floor, except obviously for proteomics and mass spectrometers. We have all the microscopes and everything that we need, time lapse, fluorescence, ConfoCor, whatever we need we have. And so the lab is very well equipped. My two research associates take care of everything. Cleanliness, orders, badgets, everything, so that’s beyond me. But we’re organised in clusters. So we are working, we are about 15 or 14 people and we are working about three or four projects. So three or four students, typically one post doc and two or three students are working on the same project. But it’s the same by title. They don’t compete against one another. I hate it. They study different aspects of the same problem. |
| Q10 | **Is it common that people do get their students to compete over the same project do you think?** |
|  | Aaron Ciechanover: I heard so. I don’t want to comment. But yes I know so. But again I’m not, it’s for me inhumane in the worst sense of the word. So for example now we are studying polycomb complexes, repressive complexes, and they have many components. So one studies one component, the other studies one, and then they can talk to one another and then they share probs. And since the lab is entirely ubiquitin lab, so even between the clusters they can share in the group because everybody understands the language. So one group is working on meek degradation, another group is working on NF-KB, another group is working on polycomb, another group is working on apoptosis. So basically that’s it. Now we have four clusters, about three to four in each. And so it’s mostly kind of collaboration. Collaborative efforts but never the less very distinct individual projects. |
| Q7 | **And are there are any tricks you use in the way you organise the space to get them to collaborate more than they would otherwise?** |
|  | Aaron Ciechanover: They are in bays. I mean the lab is very spacious. We designed it. You know it was an empty floor and we designed it to our needs. We were working against the architects for a year and a half and it’s a very unique lab. |
| Q10 | **How many people are there in the lab in total?** |
|  | Aaron Ciechanover: About 15, we are between 12 and 15 all the time. I keep it this size. I don’t want to go higher because then I lose control, I don’t know what they do and in group meetings I really want to know what they are doing. And don’t go much lower than ten because then we lose projects. It happens, you know, it fluctuates, but it’s about that number all the time. |
| Q9 | **That was fascinating. Thank you. If we turn to your own scientific beginnings, in your Nobel autobiography you write very elegantly and at considerable length about where you came from as a scientist. And you describe that section as falling in love with biology. What was the beginning of the love affair? What got you going?** |
|  | Aaron Ciechanover: Almost from day one it’s like, but at that time obviously you remember or you know, it was very different biology you know. So I grew up in a city that is in the mountains and much of the city wasn’t settled and the mountain was just open and wild. And I asked my brother. So initially it was simple taxonomy. I collected flowers and dried them out. I think that I wrote in my biography that I dried them out in the Jewish scholarly books, in the Jewish Talmud of my brother, and then he exploded and he got a fit. You know, I took the holiness of the holiness of the Jewish faith and smashed flowers. |
| Q2 | **Where did you get the idea from?** |
|  | Aaron Ciechanover: I got it from books and I read about it and then I pinched my finger and took blood and smeared it over a cover glass. So I just was looking, I was curious, there was no DNA at that time, nothing. I directed myself. But then I didn’t know what’s biology really, even in high school. And then I had to go to the army and then I said Well I don’t know about science. And the army gave us opportunity, the Israeli army, to go and study first and then serve in the Israeli army in our profession. But you couldn’t go to biology because they were not interested in biologists. They were interested in physicians. |
| Q6 | **Was it strange studying in a medical school that was the only medical school in Israel at the time?** |
|  | Aaron Ciechanover: Israel was at that time a small country of three or four million people. So that’s what we had. Now we have four. And I became restless again and then I decided to take fresh air for one year and I went to do my master’s degree in science. But then I decided never the less to finish because I still have to serve in the army. And it was like flip flopping for a long time. So I finished, I did my master’s degree in biochemistry, fell in love with biochemistry but then went to complete my medical studies.  And then I had to return my service to serve in the Israeli army. I was a combat physician for three years. And then I still didn’t know so I started surgery. I had a short stint in surgery but then I gave up. I said No, I cannot take care of patients and do the same. And then Avram just came back from his post doc fellowship and I was his second, well, we started together, graduate students. I mean I started immediately with a young post-doctoral fellow that just came back and started his own lab. |
| Q12 | **I mean these days it’s very unusual for people to take three years out to go to the army before doing a PhD. So it would be interesting to know what that gave you. Did it improve?** |
|  | Aaron Ciechanover: The army gives one I think, it’s a difficult service but I don’t know if it improves you, but it matures you. You take things in proportion, especially that this was the ’73 war, 1973. I served in the army between ’73 and ’76. I started my military service with the Day of Atonement War and fights and wounded and so on and so forth. So it matures you. And then you learn to live with other people of different educational levels because they just came from destroyed homes. It’s an excellent melting pot.  You know, with the khaki uniform you don’t know who is the man behind unless you know him. And then you get to know him and the people are just wonderful. You know, people that hardly can write or read they all of a sudden became your brothers and you would cook together and it’s very pressed. I was in a missile boat, I was a physician on an Israeli missile boat, and it’s crowded, it’s the hot bed system, you don’t have your own bed. Well, I had because I was an officer but, and then you learn, you don’t want to be above them, you want to be with them. So I took a short course and I was standing near the steering wheel of the …, and I was broadcasting the news that came from the shore every day and I became their friend. And then they cook … I mean it’s like, it’s a wonderful melting pot. It matured me. I wouldn’t have given it up. Also nation wise, you’re entering exam into the nation, it’s something, wonderful experience. |
| Q13 | **And students coming into your lab now have in general also done military service?** |
|  | Aaron Ciechanover: Except to the Israeli Arabs. They don’t serve in the military. And I take a lot of Arabs into my lab because I think education, research science is also an important platform for peace, for attenuating religious extremism. And so there are always some Arab Muslim students in my lab. Currently I have two. |
| Q4 | **Coming to that in a second. As you were working through these discoveries which would take you further and further away from the known universe so to speak, were you not worried that other people, bigger labs, would pick up on what you were publishing and just take it away faster than you could keep up?** |
|  | Aaron Ciechanover: You always worry about competition. And there we saw, actually without mentioning names because they are good friends now, we saw them failing around us. Actually we were not the first, if we really probe the history into the date and publication, we were not the first to find the in vitro proteolytic system. Obviously we were the first to fractionate it. There was another good friend, one very famous university in the United States, probably number one university in the United States, huge, starts with H. And he was on, and we were a little bit concerned. But then the beauty of it is, I think, again it’s, you know, we have to be very careful. It’s a retrospective, retroactive analysis.  You cannot, it’s like saying Okay, work on something important that nobody works. I mean this is kind of this type of definition that are non-existing in my mind. But when I analyse it retrospectively why did he fail and he is a good guy, very good guy, I think that he was a proteolysis guy. We worked in parallel. We didn’t take anything from him, absolutely. We were our own. But he was faster or whatever and he published the reticulocytelysate system that we were working on and he was the first to come out. And then he was, we were on the starting line, actually he was ahead of us on the starting line, because he was more … But I think that he was captured with emotion and that tells you how, you cannot be prejudiced and maybe our background … Fred was a proteolysis guy for decades. That’s what he did for life. And I think that he was occupied with a notion that for that this marriage you need only two for this tango. You need a protease and a subscript. He knew that it’s ATP-dependent. But the idea /- – -/ substrate, chymotrypsin substrate.  And he said Well I have something which is ATP-dependent, so it’s some crazy protein, it’s unlike trypsin and chymotrypsin. But never the less it’s still the same door to the tango idea. And whenever he put his protease or extract on a column and fractionated it by whatever method, he lost it because the ubiquitin going this way, he went this way, the protease went this way. And he thought Well I lose it because it’s such a gentle complex or maybe I wrap it up with DTT. And DTT was not sufficient and wrap it up with glycerol and this and that. And while he was wrapping up his gentle elusive protease we were fractionating it. And I think the reason, and then we opened the gap of two to three years that he could never close any more. We came out, we poured papers to the literature at a pace of one every two months or every three months. So he just couldn’t keep. And he didn’t believe us as a matter of fact, which was good. He was the only serious contender or competitor at that time. And all the rest, Bob Shimki, they left the field. There were no real serious competitors at that time.  And I think that our luck compared to his was not, you can say we were better, I don’t know, I don’t like this, I don’t compare myself to anybody. I think that we were not preoccupied with any idea because we were not proteolysis people. We were in awe to the field. We never proteolysed the problem, we were never preoccupied with any idea about the system. We lost activity we said well maybe we split it into two, let’s take the two parts, put it together, wow, it worked. And then we took each factor and we took the other one and we further fractionated it and then we skin it again. It was like a puzzle. And at the time that I left the lab there were ten of fifteen E1, E2, E3 and some of them were unnamed. We knew that we knew them but we didn’t know what they are. So we were simple minded elegant biochemists, not occupied with any idea and I think that in this competition he lost, I think, because he was … |
| Q6 | **Was it nice to be in that period of almost a decade of working fairly much alone or did you actually want more input after a while? Did you hope that more people would join you?** |
|  | Aaron Ciechanover: Retroactively I mean it was very nice. People told us you’ll lose your career but that’s minor. I mean you fail you do something again, maybe not important but unique, very nouvelle. So you don’t think of prizes, you don’t want to cure cancer, you think of what you do in the lab and it was nice. And it became complex and we discovered E1 and E2 and E3 and several histories and recognition of substrates. So we had a lot to do. So this was very interesting. I think that it’s very rare these days for such a system, I can compare it for example to SARNE which is a wonderful discovery and unbelievable. But it’s a system, it’s several enzymes that do what they do, /- – -/. We discovered I think, and again I don’t compare importance, don’t misunderstand me for a minute, I don’t say – there is nothing that is more or less important in biology, phosphorylation, but we discovered I think something, a huge iceberg. I mean that was still underneath.  And nobody could have predicted that this system, we discovered a system that has now almost 2,000 components, 1,500 components. It is involved everywhere and it’s not only in proteolysis. Ubiquitin like proteins say, routing of proteins to different subcellular destinations, to the nuclear por complex to the, from the cell membrane. And quality control, the whole quality control, /- – -/ the ubiquitin cell cycle and division, beautiful work of Tim Hunt, the cycle that goes up, it’s ubiquitin. I mean it’s only ubiquitin. Ubiquitin is everywhere and it’s not only for degradation. For me if I would have been asked a few years ago what’s ubiquitin, I would have said it’s a degradation signal. Now if somebody will ask me what’s ubiquitin I say it’s a passport. What’s a passport? Passport is a document that allows you to go to different countries. So if it ubiquitin certain way you go toward, you enter the country of the protozome. If ubiquitin another way you go to the world of the country of lysozome If ubiquitin /- – -/ you go to … it’s a very rich platform because you have several likes and many ubiquitin like proteins. So it’s very, it’s dynamic and it’s very flexible. You can use the same molecule to send different signals to different molecules to fulfil different functions.  So it’s first, now it’s extremely exciting to be there. I mean it’s, we are still competitive, we are doing very original work I believe in my lab. But it’s nice to know that you created a field, a humming field with 100,000 papers and laboratories and drug companies and thousands of researchers and conferences that you cannot even go any more. There are so many ubiquitin meetings, Cold Spring Harbour, Fasser, Embo, it’s endless, books, monographs, it’s a world of itself. But it’s rare, the fact that it was silent at the beginning basically let us lay down the entire system, not the system as we know it now, but the principles, conjugation, degradation … conjugation, recognition, degradation. And it’s an entirety. I mean we published 12 papers that are masterpieces that take you from A almost to Z. I mean the rest are as much as important as it is, genetics, the diseases, the drugs, are additional details that were added on it. But the core is in the paper. Now if people, you know, they’re RNA or let’s say reverse transcription, it’s an enzyme, that’s it. So it’s important but once you discover it that’s it, that’s the enzyme. Here it’s a huge thing that was hidden and I think that if people would have sensed that there is something important they would have jumped on it right there. So luckily they let us do it on our own and to really deploy and lay out the entire principles of the system, not the system. And that’s very nice.  So I think that retroactively looking at it I think that we were extremely lucky that people were sceptical so that we are in the, either in the back yard of the back quarters of biology or even worse, having an artefact people also said, well that’s just an artefact. And I remember we sent the first paper to, not the first paper, the first conjugation paper to sell and there’d been /- – -/ round it and he said that he will consider publishing it if we will tell him what’s 1, 2, 3, 4, all the steps. 1,2 3 protozome /- – -/ And then Irwin Rose who was our co-/- – -/ sent it to PA, just communicated, and in a few days it was in. And people simply didn’t believe us. And that allowed us to really lay out the entire system which I believe will not happen today any more. I mean if people will sense that something is important they’ll jump on it. So it’s our time. As I told you, from ’78, basically from ’76, but our first paper came in ’78, the next important paper on ubiquitin system came only in ’84, I’m with Alex Varshavsky, the two, we had a back to back sell paper, some of the first ubiquitin. So this was the next one. So you can imagine six successive years of silence in the field. Can you imagine these days this will happen? No way, no, absolutely no way.  But another, now that just comes to my mind about the disbelief, came I think from Marc Kirschner, well he believed us from the very beginning. But that work on cyclins and degradation of cell cyclin, Avram also joined the field later. And Marc told me that he always saw the high molecular way junk at the top of the gel but he looked only into cyclin. And he thought that this high molecular way is the real junk, I mean it’s garbage. ‘Schmutz’ as he called it, it’s a ‘German schmutz’. And then he realised that this was ubiquitin cyclin and it’s gold basically, the ultimate gold. So it took him years to just get it. So I think the attitude obviously changed, but I think the people left us alone for a wonderful period of silence that I really cherish in retrospect. |
| Q5 | **Do you still teach your students that the series of 12 papers? Do you make them go back through it?** |
|  | Aaron Ciechanover: Actually what we do when I teach advanced course, graduate course, the first two hours are reading plus my lecture about, not all the 12 of them, but the milestones among them. I think it is awfully important. And what I do more, which I’m going also tomorrow in my talk, I tell my students, and also tomorrow’s audience and every audience that I feel that I need to educate, that once you start a project it’s not you and me and I and me and I. What you do you look around you into the field and you see milestones. And then you try to connect them. You said what’s known now about proteolysis? Is the lysozyme /- – -/? What about energy? Who found that and who found that? Who cast now that it’s not the lysosome? And then you collect it.  And there are many people to which we should pay tribute. I mean we were not isolated. You don’t start a problem by just, you’re not floating in a vacuum. There was Bob Shimkin, Rudolph Shemheimer and Fred Goldberg and others that laid the ground that convinced us, yes, there is something that is still hidden, let’s find it. So I think that the beauty is the threads that leads from different milestones into a conclusion that ignites the process. I mean you don’t ignite a process without having a car that has a gas tank, wheels, steering wheel, whatever. It all feeds into one, into the final pushing the button. And in our case or in the case of new discovery it’s a button that has never been pushed but never the less this button is always fed by whatever your predecessors put before you.  And I think that’s very important because students today, maybe even me, I don’t remember myself, thinks that science is being born with them and will die with them and they start something completely new. And I think that it’s awfully important, not only to give credit because it’s morally right, but to give credit as a lesson of how to approach science and how to build on past knowledge. It’s critically important and I do it repeatedly day in and day out, go to papers from 1935 and 1940, we take the JBC out and we just telling the history repeatedly. Because there is so much into it. |
| Q5 | **You alluded to the fact earlier that your PhD experience made you approach your post doc in a particularly different way. What was it that you took from the Hershko experience?** |
|  | Aaron Ciechanover: Well, when you go to a post doc and I remember coming to Harvey’s lab at MIT, and I consulted with Harvey. I wrote my post doc fellowship on something else. And then Harvey said, Harvey himself didn’t appreciate the ubiquitin system at that time and we are very good friends, and he said It’s very healthy that you’ll detach yourself from your past and start something new and then, from the ubiquitin whatever, do something else. Receptor /- – -/. And I started with it. It’s a matter of time. And I started, we did beautiful work on it that is classic now. It’s in Harvey’s text book of cell biology, cited a thousand times, on how the transferrin receptor releases iron into the cell transport – beautiful classic.  But then I became restless. I mean in a year into it, actually beforehand I became extremely restless and I said it must be stupid, I left behind such a beautiful system that is hardly the tip of the iceberg. I must go back. And luckily I had my own fellowship so I didn’t, you know, you feel more independent if somebody pays you out of his MIAge one. That’s one.  Second, Harvey is a terrific mentor. I mean he’s so liberal and so open and he’s not imposing. And he doesn’t care that people will do their own, I mean that’s very unique. And I said to him I want to go back to the ubiquitin system. He said Okay but keep a little bit on small fire what you did now because it’s so beautiful. All right, I flipped around day and night, whatever, weekends. And I went back to the ubiquitin system and then collaborated with Alex Varshavsky and he came with his ideas about, that was his entry to the field, and he came with wonderful ideas. But I worked on my own also. I published on my own as a post doc on the ubiquitin system, on the recognition motifs that later turned out to be part of the N-end rule that Alex worked but we needed biochemically, it doesn’t matter. |
| Q11 | **In general, how does Israeli science fare these days? What challenges does Israeli science face?** |
|  | Aaron Ciechanover: I think that we are doing quite well. I mean we are a small country of six, seven million people with leading universities, the Weizmann Institute that you all know and you can point out to achievements. Let’s leave alone the ubiquitin system. Drug development, multiple sclerosis, Copaxon that came from the Weizmann Institute, Alzheimer drug, very successful and it came from. You can go not only to biology. You can go to the condensation of information that led later on to the development of the fax and computers and so on. It’s the Lempel-Ziv algorithm, something that was never patented but it came from the Technion. So Israel is very, you know we are exporting $20 billion a year of high tech. We don’t export oil, we are not Saudi Arabia, we don’t have one drop of our own oil. So all that we export.  Initially we were a farm land, we exported oranges. And now we export knowledge. And it’s all a result of our educational system. The future I cannot tell you. I am a little bit more pessimistic. So to be realistic I am a little bit more pessimistic because the government cut some high education. Maybe they say we are successful and there are other needs and we are succumbing also to political settlements. Again I’m not expressing my opinion for or against but I say that different religious parties, I mean they are different sources, different channels to which the budget goes that should or shouldn’t go doesn’t matter, but never the less you are using budget for that. And the government is not that supportive as it should be in my opinion of high education. Also the very best scientists, we are still absorbed, we recruit the best scientists back. But some are already raising doubts whether they want to leave there because of the security, because of economy and so on and so forth. I think that we are doing good. We are okay now. I cannot predict for the future.  I mean there is a brain drain for different reasons, mostly, I don’t know if mostly, but security is clearly one of them. The instability in the area. Just a year ago we were bombarded with Hizbollah missiles. So I think that there is a place for concern about the future of science in Israel. But I think that learning and scholarly has always been a Jewish trait and in that sense I think I am not concerned, it will continue. Whether it will be in Israel I hope so and I will support it with all my power and spirit. I was born in this country and will die there, there is no doubt about it and will live the rest of my life in this place. Because for me it’s more than a country, it’s much more than a country and a place of living. |
| Q9 | **The Nobel Prize has many effects on many people, but what in particular has it done for you?** |
|  | Aaron Ciechanover: Well, it had the same many effects like on many other people. It keeps me busy travelling all over the world. But I think that there is something that is, I don’t know if maybe unique to me, and the fact that I’m Jewish and Israel. And it opened the door for me to Jewish communities all over the world. And there are Jewish communities which are very diverse. I mean there are very rich Jewish communities and affluent and well to do in the United States. But on the other hand there are very small Jewish communities that you know cling to the walls and hardly survive, and never the less want to remain as they are. In Athens in Greece; Greece had half a million Jews, they were all exterminated in the holocaust. Now there are less than 5,000. Peru, 3,000. Paraguay, Ecuador, Uruguay. And there are two things about it that made me so excited about it. And the issue is extremely important to me. As we talk Israel is my country, it’s not Israel as a nation, it’s the Jewish state, and the country was born after the holocaust in Europe because during the holocaust Jews were persecuted and murdered in Europe. So the timing of the establishment of the state of Israel is not just a random date. It’s a very particular date, ’47 and so on. And so the whole thing is very important for me. And I come to these Jewish – and I’ll tell you in a minute a story that is really important – I come to these Jewish communities and you see that you blow an unbelievable wind in themselves, you fill them with pride. There are many Jews who won Nobel Prizes, let’s don’t analyse numbers and reasons for it, it’s a unique phenomenon by itself. But an Israeli that speaks Hebrew, that’s served in the battle field, that was born in the year that the country was born, ’47, for them it’s something else.  And you see the cheerfulness, the joyfulness, the pride. I mean for me I feel like an ambassador of not only of my own country, without being an ambassador, and you see how important it is to them. And let me just end up with again one Jewish note. It was Saturday afternoon, I was invited to a meeting in Tomar, Portugal. It is a city 120 kilometres north-east of Lisbon. And I had to give a key note in a stress meeting, protein stress. It was the International Heat Check Society. And we drove from north of Spain we drove into Portugal, we arrived early and my son was with me. And we walked in the city, the city of Tomar, and we walked in the city and it’s a typically open city you know, the big square, the church, the city hall. And all of a sudden we see a small note saying synagogue, a small sign said synagogue. I said synagogue, let’s go and see the synagogue. So we start to crawl in back alleys and we get to the synagogue. And the synagogue is a very small room and nicely refurbished but completely erratic in its furniture. So you see that the chairs were brought from homes and on the walls there was some posters of El-Al which is Israel Airlines, with pictures of Jerusalem. But the walls were very nicely re-done.  And we looked around and we said yes and we read some sign about the history of the place. And the history was very interesting. It was established in 1430s and was closed sixty years later in the 1490s by a decree of King Emanuel I, the King of Portugal that married the daughter of Ferdinand and Isabel of Spain, and the condition for the marriage was obviously the enforcement of the inquisition laws in Portugal. And the Jews were forced to either leave the country or convert. And the synagogue was closed. And for 500 years it was offices, prison, whatever, belonged to the government. And in ’75, 1975, 500 years later it was re-opened once Salazar the dictator of Portugal was deposed and Portugal became democracy a few years after Spain. For 500 years these Jews that were converted became Iramos, they became crypted Jews, so they lived as Jews under the ground. To the eyes of the neighbours they were Christians. They went to the church, whatever. But at home in the most hidden way they kept a thin thread of Judaism.  So they didn’t keep it in full. They didn’t marry, they didn’t keep their Saturday, whatever, they just you know on Friday night they lighted the candles but they didn’t say any blessing. And it went from mother to daughter to son. I mean they never were told that they were Jews or anything. On Passover they did some residual ceremony and that’s it. No books, no nothing. And they kept their Judaism hidden. And all of a sudden in 1975 they floated up again and they became ultra-Orthodox Jews. Now the synagogue, we came to the synagogue and we read the history and they said it was closed because of this and that, and then we signed our name in the guest book. And the guy who was the guard of the synagogue saw that we were writing in Hebrew and we said We bless you for opening the synagogue. He said Are you from Israel? We said Yes we are from Israel. So all of a sudden we became … so he said to us I want to tell my story and his story is indeed the story.  He belonged to a Catholic family for 500 years, he grew up as Catholic, and in 1975 he’s 75 years old, all of a sudden he was converted to Judaism and became an ultra-Orthodox Jew. There are only two families in the city that were left, he and his friend, old friend, and they were appointed by the Portuguese government to guard the synagogue. And the Portuguese government takes very good care of them now because they want to revive Jewish life or at least the rich Jewish history. That’s just the beginning of the story but I’ll end it up with two very shortly and you’ll see how exciting and then you’ll understand why I’m so … So he said to me, You know it’s Saturday, why won’t you come tomorrow afternoon to the synagogue. I said You know Jews pray on Saturday, why should I come on Sunday? Sunday belongs as far as I can remember to the Christians, they go to church. He said, so he said to me There will be ceremony tomorrow afternoon, a ceremonial prayer in the synagogue. I said Ceremonial prayer in the synagogue, why on Sunday? He said You know tomorrow the first ever Israeli scientist that won a Nobel Prize is going to be our guest.  Wow! I said to him and I looked at my son and, you know, typically you come to these conferences and you are so busy, they load you with your schedule and you never look at it. And get up in the morning and my wife will say what shall we do? I said don’t worry, people will take us around, just don’t worry. We have a plan, let’s don’t worry about it. So it was on my schedule that I have to be in the synagogue for some ceremonial prayer and I didn’t look at it. So I look at my son and I said to the guy I suspect that you’re talking on me. And he couldn’t believe it. He just couldn’t believe it. And there was a silence in the room for a minute and then he fell on my shoulder with tears. And you know it was an unbelievable moment. We were the three of us alone in the synagogue, him, my son and myself, and for him it was the ultimate Jewish experience. I mean that here for the first time, you know, there are no Jews to pray there. You know they’re going to pray ceremonially celebrating the victory of science, whatever, with an Israeli Nobel Laureate and for him he was waiting for this ceremony. And all of a sudden somebody walks from the street, just at random, and we started to talk. So for him it was such an intimate moment. And me myself I broke in tears. And then the next day we came, the Israeli ambassador, I mean it was a very nice prayer, they kind of, Jews came, cryptic Jews came from all the villages around because the whole area was scattered with them, there was a huge Jewish community in Portugal at that time. And we celebrated but this moment on Saturday afternoon I understood to the tiniest last smallest detail what I mean for these Jews. I mean it’s unbelievable. And I said If I’m going ever to live in the state of Israel, it’s for him. So I mean that’s the Nobel Prize because without the Nobel Prize it would never have occurred, I would never have been invited. So the Nobel people don’t know about it at all what they did to my country, to me, to the Jewish community, it’s unbelievable experience. |

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| **Biographical** | I was born on December 31, 1937, in Karcag, Hungary. Karcag is a small town of around 25,000 inhabitants, about 150 kilometers east of Budapest. It had a Jewish community of nearly one thousand people. My father, Moshe Hershko, was a schoolteacher in the Jewish elementary school in Karcag; most of the Jewish children in that town were his students. His former students from Hungary, and later from Israel, described him with admiration as an inspiring teacher and a role model educator. My mother Shoshana/Margit (“Manci”) was an educated and musically gifted woman. She gave some English and piano lessons to children in Karcag. My older brother, Chaim, was born in 1936, less than two years before me. My mother wanted very much to have also a baby girl, but the times were at the eve of World War II, Hitler’s screams could be frequently heard on the radio, my parents became apprehensive of the future and thus did not try to have more children. Still, my recollections of my early childhood are of very happy times, with loving and supporting parents, growing up in a nice house with a beautiful garden, created by my father who was also an amateur (but avid) gardener. A family picture from these times, with my parents, my brother and I as an infant, shows well the warmth of my family.  This early paradise was lost rapidly and brutally. World War II broke out, and soon Hungary joined in as an ally of Nazi Germany. In 1942, my father was taken by the Hungarian Army to serve as a forced laborer, in the company of other Jewish men. They were sent to the Russian front, where most of them perished. Luckily for my father, the Soviet Army advanced so rapidly after Stalingrad that he was captured by the Soviets before the Nazis could kill him. Then, he was used by the Soviets as a forced laborer. He was released only in 1946, so we did not know for four years whether or not he was alive.  In the spring of 1944, Hungary’s dictator Horthy understood that Germany was loosing the war, and planned to desert. The Germans sensed this and quickly occupied Hungary. This was followed by the rapid extermination of much of the Jewish population of Hungary. In May-June 1944, most Jewish people were concentrated in ghettos and then transported to death camps in Poland. I was six years old at that time. We were in a ghetto at the outskirts of Karcag for a couple of weeks and then were transferred to a terribly crowded ghetto in Szolnok, which is a larger city in the same district. From there, Jews from the entire district were transported further on freight-trains. They were told that they were sent to work, but after the war we learned that most of the trains were headed for Auschwitz. By some random event, my family and I were put on one of the few trains that headed for Austria, where Jews were actually used for labor. This group included my mother with us two children, my paternal grandparents and my three aunts. In Austria we were in a small village near Vienna, where adults worked in the fields and in a factory. We were liberated by the Soviet Army on the spring of 1945. My maternal grandparents perished in the Holocaust, along with 360,000 Hungarian Jews and almost two-thirds of the Jewish people of Karcag. Following our reunion with my father in 1946, the family lived for three years in Budapest, where my father found job as a schoolteacher. The family emigrated to Israel in 1950.  In Israel we settled in Jerusalem and I started a new and very different life. Of course, there were initial difficulties of being new immigrants. We had to learn a new language, Hebrew. This was not too difficult for children (I was less than 13 at that time), but it was more difficult for my parents. Still, my father studied Hebrew and soon started to work, again as a schoolteacher. (Later he taught in at a teachers’ seminary and authored mathematics textbooks, which were very popular in Israel). As always, education of their children was my parents’ highest priority. Although we were quite poor immigrants at that time, my brother and I were sent to an expensive private school in Jerusalem. I suspect that most of the salary of my father was spent on our tuition fees.  At school I was received well by the other children. These were times of massive immigration to Israel, so a new immigrant child with a Hungarian accent did not stand out too much (I am told that I still have some Hungarian accent, especially in English, though my Hungarian language is quite poor now). I was a good student, and learned easily different subjects, such as mathematics, physics, literature, history and even Talmud! That became a problem when I finished high school. I was interested in too many subjects, so it was difficult for me to decide how to continue. I chose to study medicine, probably by default, because my brother Chaim was already a medical student, so I could inherit his books for free! Chaim always wanted to be a physician, and he is now a very well-known hematologist and an authority on iron metabolism.  In 1956, I started to study at the Hebrew University – Hadassah Medical School in Jerusalem, which was the only medical school in Israel at that time (there are now four). In the basic science part of my medical studies, I fell in love with biochemistry. I studied biochemistry in three different courses: organic chemistry, basic biochemistry and a course called “physiological chemistry”, which was medically oriented biochemistry. I was very fortunate to have outstanding teachers in all three courses. Organic chemistry was taught by Yeshayahu Leibowitz, a legendary person in Israel, a highly original thinker whose knowledge encompassed philosophy, political science, the Bible, Talmud, medicine, chemistry and more. He was probably my best teacher, it was an intellectual feast to listen to him. Leibowitz loved biochemistry, and he sneaked biochemistry into his lectures on organic chemistry whenever he could, which was often. Basic biochemistry was taught by Shlomo Hestrin, also an inspiring teacher who had a special talent of transferring his enthusiasm for science to the students. Physiological chemistry was taught by Ernst Wertheimer, a professor of German Jewish origin whom we had some difficulty to understand because of his heavy German accent, but who had an excellent perspective of integration of metabolism at the level of the total body and of physiological contexts of biochemistry. Another part of the same course was taught by Jacob Mager. Mager was an outstanding biochemist and a man of encyclopedic knowledge. However, he was very shy and quite a bad classroom teacher (though an excellent teacher in the laboratory, as I learned later). Most of his lectures were delivered while he was writing whole metabolic pathways on the blackboard, without any notes, with his face to the blackboard and his back directed to the class. Still, I was so much impressed by the depth and breadth of his knowledge of biochemistry that I decided to ask Mager to do some research in his laboratory.  I started to work in Mager’s laboratory in 1960. At that time, there was no formal M.D.-Ph.D. program at the Hebrew University, but it was possible to do a year of research between the preclinical and the clinical years of medical studies. I did that, and although I completed medical studies later on, I already knew by the end of that year that I was going to do research, rather than clinical practice. I was very fortunate to have had Jacob Mager as my mentor and tutor of biochemical research. He was a scientist with incredible scope of interests and knowledge. He was interested in every subject in biomedicine, he knew almost everything about every subject and he worked simultaneously on 3-4 completely different research projects. This undoubtedly caused fragmentation of his contributions to science, but provided his students with a broad experience in different areas of biochemistry in a single, relatively small laboratory. In a period of a few years I worked with Mager on subjects as different as the effects of polyamines on protein synthesis *in vitro*, glucose-6-hosphate dehydrogenase deficiency and a variety of aspects of purine nucleotide metabolism, including enzymology and regulation. During this time, I also finished my medical studies, did my military service as a physician (1965-1967) and then returned for two more years to Mager’s laboratory to finish my Ph.D. thesis (1967-69). I received not just a broad view of biochemistry from Mager, but also a very solid base. He was a very rigorous experimentalist, every experiment had to be done with all possible positive and negative controls, all experiments were carried out in the duplicate, and every significant new finding had to be repeated several times to make it sufficiently credible. I owe a lot to Jacob Mager for a strong background of rigorous biochemistry.  I met Judith (née Leibowitz) in 1963, and we married at the end of the same year. Judy was born and raised in Switzerland. After her studies in biology, she decided to spend a year in Israel. During this year, she worked in the hematology laboratory of the Hadassah hospital in Jerusalem. One day, I walked over to the hematology laboratory to get a blood sample that I needed for my research, and we literarily bumped into each other. This collision caused her to stay in Israel for more than one year, and now we are married for over 41 years. We have three sons: Dan (1964), Yair (1968) and Oded (1975). Dan is a surgeon, Yair is a computer engineer and Oded is a medical student. We have now six grandchildren: Maya (1994), Lee (1997), Roni (1998), Ela (2000), Ori (2002) and Shahar (2004). Needless to say, both Judy and I are crazy about all our grandchildren. During all our years together, I got tremendous support from Judy. Although she came from one of the world’s most peaceful countries to one of the least, and from a very comfortable and pampering environment to quite primitive surroundings, she stood her ground with a lot of energy, courage and cheerful optimism. She always took care of all my possible needs, as well as the needs of our children and grandchildren. Judy is not only a very beautiful woman, but she also radiates a lot of caring, love and compassion. In addition to providing so much support at home, she also helped me a lot in the laboratory over a period of more than 15 years. The ubiquitin system was helped by Judy in more than one way.  In 1969-71 I was a post-doctoral fellow with Gordon Tomkins at the Department of Biochemistry and Biophysics of the University of California in San Francisco. I met Gordon the previous year, when he gave some lectures in Israel. He was very different from Mager: outgoing, vivacious, bursting with original ideas. Unlike Mager, Gordon did not care much about controls or experimental detail, but he was a volcano of a man, constantly erupting with great ideas and he was a wonderful stimulator of many other researchers’ work as well. Many distinguished scientists who knew Gordon Tomkins at that time (unfortunately, he died at an early age) are still speaking of him with great admiration. He exuded a great personal charm and I liked him instantly. I thought that Gordon may add some new dimensions to my development in science and this indeed was the case. I got a lot of stimulation and biological perspective from Gordon, while I continued to use what I learned from Mager about rigorous controls. As described in the accompanying lecture, I learned about protein degradation and got fascinated with this process while I was working with Gordon Tomkins.  I returned from San Francisco to Israel in 1971. Originally, I planned to return to the Hebrew University in Jerusalem, but a new medical school opened in Haifa and I was offered to be its Chairman of Biochemistry. This sounded very challenging and I agreed, but later it turned out to be a very minute Unit of Biochemistry in a very small Faculty of Medicine of the Technion, so at the beginning I chaired mainly myself. One initial reason for its being so small was that there was not enough space to house much faculty. The whole Faculty of Medicine was housed, on a temporary basis, in an old two-floor monastery. This “temporary” situation lasted for more than 15 years, until the new building of the Faculty of Medicine was completed in 1987. However, I had great times in that old monastery, and much of the discovery of the ubiquitin system was done right there. Isolation may at times lead to creativity, since one is not bothered by what others are doing and does not feel compelled to work on currently popular, “fashionable” subjects. I was very fortunate to assemble there a highly devoted research team, that included at the beginning Hanna Heller and Dvora Ganoth, and later, at different times, Ety Eytan, my wife Judy, Sarah Elias and Clara Segal. Dvora and Ety still work with me. My first graduate students were David Epstein, Yaacov Hod and Michael Aviram. For a number of years, we tried to establish a cell-free system that reproduces energy-dependent protein degradation in the test tube, essential for the biochemical analysis of this system. For this purpose, we tried different sources, such as liver homogenates and extracts from cultured cells and even from bacteria. We did not have any success in all these attempts. I remember that a biochemist friend from Jerusalem visited my laboratory and at the end of the visit she told me that I should not have most of my laboratory working on a hopeless subject. However, I was very obstinate and was obsessed with the idea that it would be possible to find out how proteins are degraded only with a biochemically analyzable cell-free system. Maybe I was lucky to work in such a remote and small place; in a larger institution, my graduate students and research assistants may have deserted me for some less frustrating research. Finally we used for biochemical fractionation the reticulocyte cell-free system established in the Goldberg laboratory (see Lecture). At that time, Aaron Ciechanover joined my laboratory for a D. Sc. thesis, after completing his medical studies and army service. Aaron was the most incredibly hard-working graduate student that I ever had. With his huge energies, he contributed a lot to the discovery of the ubiquitin system. He was also a natural manager, even as a graduate student. I recall that at the end of my sabbatical year in Philadelphia in 1978 (see below), after telling Ernie Rose how small the Israeli research grants were, Ernie suggested that I should apply for a foreign research grant from the NIH to support my work in Israel. I was inclined to do a couple of more experiments instead of writing a grant application, but Aaron pushed me into a chair and commanded: “now write the NIH grant application!” I wrote it and got the grant, the first of five consecutive grant periods supported by the NIH. It saved the situation in the Haifa lab at a very critical time. I am very grateful to the NIH for supporting my work and also to Aaron for forcing me to write the initial grant application.  The story of the discovery of the ubiquitin system is described in my lecture, and here I add only some anecdotal episodes from these times. The fractionation of reticulocyte lysates to Fractions 1 and 2 was based on a trick that I learned from Mager in the purification of enzymes of purine nucleotide metabolism from erythrocytes. Hemoglobin constitutes about 80-90% of total protein of erythrocytes and reticulocytes, and therefore the first task in the purification of any enzyme from these cells is to get rid of the great mass of hemoglobin. This is most conveniently done by using the anion exchange resin DEAE-cellulose, which binds most non-hemoglobin proteins, but not hemoglobin. In our case, this procedure resulted in loss of activity, which could be recovered by adding back Fraction 1 that contained not only hemoglobin but also ubiquitin. In fact, in our laboratory jargon we called ubiquitin for some time “Red”, because of the red color of hemoglobin in this fraction. After we found that the factor in this fraction (i.e., ubiquitin) remains active after boiling for 30 minutes, we consulted a protein expert at the Technion who told us that our factor cannot be a protein. We found, however, that it is a protein, based on its sensitivity to the action of proteinases. Maybe the lesson from this story is that it is dangerous to consult experts.  After working for 6 years at the Technion, I had a sabbatical year due in 1977-78. I had a problem in choosing a person with whom I would spend my sabbatical year. I knew the people in the (then) small protein degradation field, and I was not very enthusiastic. Many people in the field had their pet theories about the cause for the high selectivity of intracellular protein degradation, without much (or any) experimental evidence. Once again, I was lucky. In 1976, I attended a Fogarty meeting on a quite general subject at the National Institutes of Health. Irwin Rose also attended this meeting, and one morning I joined him at the breakfast table. Ernie was well known for his work on enzyme mechanisms. In the course of our conversation, I asked Ernie in what else was he interested, and his reply was: “protein degradation”. I was a bit taken aback and told him that I never saw anything published by him on protein degradation. His reply was: “There is nothing worth publishing on protein degradation!” I liked his critical attitude and Ernie being such a character and therefore I asked him to spend my sabbatical year in his laboratory. It turned out that Ernie Rose was really interested in protein degradation. When he had been a young faculty in the fifties at the Department of Biochemistry of Yale University, he talked to Melvin Simpson, another young faculty there, and Simpson told him about his experiments on the energy-dependence of the liberation of amino acids from proteins in liver slices (see Lecture). This aroused Ernie’s interest, and from time to time he did experiments trying to understand the energy-dependence of protein degradation. He did not make any significant progress in these experiments, therefore he did not publish anything on protein degradation.  Ernie Rose is the third person, in addition to Mager and Tomkins, who had a great influence on my scientific life. He is very different from both Mager and from Tomkins. He likes problem solving, and his attitude to science is highly analytical. I am more intuitive, so we complemented each other very well. He is so brilliant that people do not always understand his ideas and are a little afraid of him. People are also often apprehensive of him because he can be very critical, and does not hesitate to voice his criticisms. We got along very well over a period of 20 years, which included several sabbaticals and many summer visits in his laboratory at Fox Chase Cancer Center in Philadelphia. Our only disputes were when he refused to be co-author of work to which he actually made significant contributions. In the case of the few papers on which he is co-author, I had to force him to agree. He was most unselfish in our joint work, a rare phenomenon in today’s science. I asked him once why he keeps inviting me back to his laboratory, and his answer was: “I like the excitement.” Ernie always downplayed his contributions to the ubiquitin field. He wrote an autobiographical article for *Protein Science* in 1995, and the word “ubiquitin” is not mentioned in this recollections paper. In our conversations he always described his role in the ubiquitin story as being merely supportive, but this is certainly not true. Although on occasions, when I worked in his laboratory and he was adsorbed with some problem in enzyme mechanisms, he would forget about my existence for a week or two, but then suddenly he would come up with a bright suggestion about my current work. I can state that Ernie’s input of ideas, inspiration and helpful criticism were essential for the discovery of the ubiquitin system and for the delineation of some of the main enzymatic reactions in this pathway.  The rest of my story is a lot about more work, but also a lot of more scientific excitement and fun. I continued to be obstinate, and continued to do what many considered to be old-fashioned biochemistry in the eighties, when the powerful technologies of molecular biology became available. This biochemical work resulted in the discovery of the three types of enzymes involved in ubiquitin-protein ligation (E1, E2 and E3), and of some further enzymes of this system. Subsequently, I became interested in the roles of ubiquitin-mediated protein degradation in the cell division cycle. This led me to the Marine Biological Laboratory (MBL) at Woods Hole, due to the availability of a clam oocycte cell-free system, which faithfully reproduces cell cycle related events in the test tube. This system was important for the discovery of the Cyclosome/Anaphase-Promoting Complex, as described in the Lecture. In the past decade, I spend my summers at the MBL for the same reason that I spent my summers previously at Fox Chase Cancer Center – to be able to devote almost all my time to do experiments in a tranquil environment. Benchwork is my great hobby; I also do benchwork in Haifa, but on a more part-time basis. I have always loved to do experiments with my own hands, both for peace of mind and for excitement. Also, my own experiments were important for almost every significant progress made in my laboratory. One cannot have a more beautiful place than the MBL for doing experiments: the great natural beauty of the surroundings, the tranquility and outstanding scientific environment – all combine to make the MBL a great place for doing summer research.  When I look back at my life until now, I am amazed how fortunate I have been in both my personal and my scientific life. After escaping the Holocaust, both my parents lived in Israel to a good old age. I am very happy with my wife, children and grandchildren. I was very fortunate to have outstanding mentors in science, and then to be able to use the knowledge gained for a significant contribution. If only there were some peace in the world, including between Israel and its neighbors – I would be completely satisfied. |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** | – Hello.  – Hello Avram. Congratulations to the prize. My name is Joanna Rose and I call from the Nobelprize.org, which is the official website of The Nobel Foundation.  – Yes.  – My congratulations to the prize.  – Thank you.  – How does it feel now?  – Oh, I am very happy. Very happy for my family, for my institution, my country, and for myself also. I think this is a very … as you know it is a very good recognition. I’m also very happy, I should add that … that Irwin Rose was included, because I got many prizes before, but he was never included. And he did make a very important contribution to the discovery. So I am glad that justice was made. I really think that justice was made at this time.  – Did you expect the message today?  – No. I was out on a picnic with four granddaughters. It is a holiday today in Israel. We call it a day of … a kids’ day. So I invited four grandchildren, and we went out for a picnic, and to a swimming pool in a kibbutz, and there I heard it from … somebody heard it on the radio.  – I understand.  – But it was good. It was very exciting.  – Yeah. What was your first reaction when you heard it from the radio?  – Well, I thought … I was very happy. My first reaction was I am very happy for Ernie Rose. And, also happy for myself, of course. And for Ciechanover.  – Can you tell me just how do you think that the Nobel Prize is going to affect your future work?  – I … you know I enjoy bench work very much. I try to do an experiment every day, even today. And, I would like to continue with that because it’s really exciting. So, I hope it won’t affect too much my life. But of course you never know. There will be distractions I am sure. And there will be some duties. I’m sure there will be some invitations I will have to say ”yes” to. But, more or less, I would like to continue to do my work. I think I can still contribute. Not in the same big way as twenty-five years ago, but still contributing and then still having a lot of fun at the bench.  – Did you realize, when you did your discovery for over twenty years ago, that it is worth a Nobel Prize?  – Yeah. I thought so. I wasn’t waiting for it you know, but I knew already that it … because the impact is really big, you know about … when I started to work on ubiquitin there were about ten papers a year on ubiquitin. And now there are thousands in a year. So, it really became a kind of a cascade, and many people heard about us all over the world … mind about us … very big about this … all over the world are working on different aspects of the ubiquitin system and different systems. So I knew it was important. But I wasn’t waiting for the prize. No, I wasn’t waiting for it. But of course, I am very grateful for it.  – I understand. Have you any good advice to young students that maybe dream about receiving the Nobel Prize in the future?  – Well, not about receiving the Nobel Prize, but about doing science. My advice is … well that’s what I did, you know, to try to find something novel, and open up new problems which is not yet reached a big level at this time, not yet interested, but you think is important. I think that’s what I did about thirty-five years ago. And then, continue with it. That’s my advice. Try to find a unique problem which is important, but which is not yet in the center of the attention of biology or of chemistry. I think that is true for discoveries, that’s how it should be done. So, that’s my advice for young people.  – Yeah. My last question is, have you ever visited the Nobel website?  – Pardon me?  – Have you ever visited the Nobel website on the internet?  – No.  – Um-hmm. So, now you will be there yourself.  – O.K.  – Yes, thank you very much and have a good day.  – Thank you. Same to you. Thanks for calling. Bye.  – Bye. |
| **Interview** |  |
| Q3 | **How come you left medicine?** |
|  | Avram Hershko: Well, I started out as a medical student, I wanted to be a doctor. And during my medical studies I studied biochemistry. That was one of the subjects that every medical student studies, so I liked it very much. I liked, you know, the whole concept of biochemistry, of looking for chemical processes in cells, so we had, we could take off one year from the studies to spend in research in the lab. I also found a very good teacher, Jacob Mager, and I wanted to spend it with him, so I did. That’s how I got involved in biochemistry. Afterwards, I finished my medical studies but already, I, after that one year, I knew that I will go to biochemistry and not to practical medicine. That’s how I started. So, it’s, it’s, like all things in life, it starts by some kind of accident or so, that was the accident, I met a subject during my studies that I liked. |
| Q2 | **Was it also a topic, an issue that you were interested in?** |
|  | Avram Hershko: No, no, not yet, not yet. Mager was interested in many subjects so that was … Actually, I continued with him after my army service as a doctor, and during the course of a couple of years I evolved in four completely different subjects, protein, synthesis, purine metabolism, and a certain disease called glucose-6-phosphate dehydrogenase deficiency, because he was interested in many things, so that gave me a very good background, a very, very, you know, very good basic background. |
| Q2 | **How did you meet together?** |
|  | Avram Hershko: Well, that’s another story. I got interested in protein degradation during my post-doc fellowship in San Francisco, and when I came back to Israel I continued with that, and at that time it was a very obscure field, you know. People, there were all kinds of, not too many people were interested in it. Those that were interested were not very good. So I looked for somebody, and so my first time I think I came up and I looked for somebody to spend a sabbatical with. I couldn’t find anybody that attracted me. So then I met Ernie at a meeting in 1976, one year before, before my sabbatical was due. And do you remember, we met in the breakfast, so I said can I, just began to talk …  Irwin Rose: It’s alright, I forgot.  Avram Hershko: … breakfast table, so I knew who he was, he was very well known for his work on enzyme mechanism. That I knew, but then I asked him what are you interested in, in other things? So it turned out that he was interested in protein degradation. And that was a secret, it was a secret because he never published anything on it, and I asked him how come you never published anything, and so he said there is nothing worth publishing on protein degradation. So that’s what he said.  Irwin Rose: Yeah, that was my opinion. Well, because I hadn’t done anything, you don’t say it right.  Avram Hershko: OK. Well, that’s how I remember it. And anyhow, I liked that attitude very much, and asked, I asked him can I spend my sabbatical with you? And he said yes, so that’s how it started, and then Aaron, the same year he started his PhD with me, and after my sabbatical the following, the summer after my sabbatical, Aaron joined us, and then he joined us for a couple of summers afterwards, so that’s how, that’s how the whole connection started. |
| Q3 | **But how come you pick up an obscure field in science, to work on?** |
|  | Irwin Rose: Well, I’ll tell you, because when I first worked at Yale, the guy who had a lab next to me had made the original observation that there was a protein, there was an energy dependent on protein breakdown. Now, nobody believed him, but he had made some pretty strong observations that if you …  Avram Hershko: Here, we could mention names.  Irwin Rose: Yes, Melvin Simpson. He made these important observations.  Aaron Ciechanover: He hardly believed himself, because when you go into discussion on the paper, you kind of come to a convoluted argument whether it’s a direct requirement or indirect. We can do the conclusion that it’s indirect. |
| Q2 | **You do nothing? Who is the worker?** |
|  | Avram Hershko: Well, that’s, first of all, that’s not true. I remember that you made some ubiquitin preparation …  Irwin Rose: I did.  Avram Hershko: Yes, and it fell on the floor, and then you collected it up from the floor … yeah, yeah. That first step is to boil the extra, because ubiquitin is heat stable, so you boiled it but then it fell on the floor, but you picked it up and it was good, yeah.  Irwin Rose: It was good, nothing could destroy it.  Irwin Rose: It was a licence only enzyme.  Aaron Ciechanover: The /- – -/ can take it, but not the floor.  Avram Hershko: But, yeah, but when I came to his lab we already had his first step, which was the fractionation, well, the reticulocyte cell-free system system was actually established in the laboratory of somebody else, Alfred Goldberg in Harvard, but they didn’t …  Aaron Ciechanover: /Inaudible./  Avram Hershko: No, no, but, yeah, but he made it first, he made it first.  Aaron Ciechanover: The first publication was from Harvard, no doubt.  Avram Hershko: But then he didn’t progress, but then he didn’t do what he should have done, which is fractionation. It’s hard to purify right away, but ATP dependent enzyme, he never found it. And what we did was fractionation and constitution, so we already had this first step of separating it into two, two fractions, fraction one and fraction two.  So during these two years between the beginning of ’77 when I write to your lab and December of ’79, when we made the breakthrough in your lab, we purified the component from fraction one, we found it a heat stable protein, and then you had a part in that, you also boiled ubiquitin, and then in Haifa we found that it gets … when we labelled it with iodine and we found it gets bound to proteins and ATP dependent reaction, but we didn’t really understand that it’s binding, its co-herent binding the substate until that summer in 1971 in the laboratory of Rose where you invited me, together with Aaron who was then my graduate student in /- – -/ who was there. 1979, 1979. So that is when, when the discovery that ubiquitin …  Irwin Rose: Shall I tell the story about the ubiquitin?  Avram Hershko: Yes. I think I have finished. So then, that’s how I remember it, and how …  Irwin Rose: OK, well, here they had a heat stable factor that was required, and they made the observation that the ubiquitin went on to proteins. And so one of my post docs went to a post doc of another student, of another faculty member at the Fox Chase Cancer Centre, and said, there was a conversation, and do you know of any examples of a protein covalently linked to a protein? And this post doctoral fellow said yes, there is in the nucleus, a protein called ubiquitin that’s covalently linked to histone. And so they rushed to look at the amino acid composition of that so-called ubiquitin, and they compared it to the amino acid composition which you had published, I guess …  Aaron Ciechanover: No, not yet.  Irwin Rose: Not yet published.  Aaron Ciechanover: But in the end it was published back to back with JBC.  Irwin Rose: No, no, no. But how did they know the conversation …  Aaron Ciechanover: No, because they knew, the end story is that the Wilkinson paper came back to back with ours on the /- – -/.  Avram Hershko: OK. Let’s not go into the detail.  Irwin Rose: Well, for some reason or other, they found confidence…  Avram Hershko: They knew that I published that.  Irwin Rose: Really, and I was not a leak.  Avram Hershko: No, no, you were not.  Aaron Ciechanover: No, he was in the lab, he was free and did this. We didn’t hide anything.  Irwin Rose: OK, you’re getting the inside story here. Now, wait a second. |
| Q4 | **So do you think you would get support today for such work, which was kind of apart?** |
|  | Avram Hershko: Well, I hope the fund /- – -/ look up your website and will hear these things. Because it’s … yeah, [Joe Goldstein](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1985/goldstein-facts.html), you know, a Nobel Laureate and a good one, wrote a nice article about this year’s Lasker Award, in which he compared science to a sculpture by this British sculptor who had his stone, it was a huge stone of two and a half ton, on which another stone, and another stone, and another stone, and at the end is a little stone, so he said that in science there are big stones and small stones. The important science is the opposite. When you have a little stone, and on top of it you put a bigger stone and then a bigger stone. If you throw out a big stone at the beginning so there’s a lot of publicity sometimes nothing comes out of it, and the scientist, to find his little stone, on which the other stones can be built. So I recommend to read his article. |
| Q7 | **Do you compete with each other?** |
|  | Avram Hershko: No, there is enough to do in the ubiquitin field, we don’t feel that we had to compete. There are different aspects of the ubiquitin field. I am working on cell cycle and he works on …  Aaron Ciechanover: /- – -/. Completely different. |
| Q10 | **How is it to live in a small country with big problems and to get funds for science?** |
|  | Avram Hershko: It is not easy, it is not easy. You have to know the daily tension which is of course distractive. The funds are small, some funds for science are small. Graduate students have to go to serve in the army and things like that, so it’s more difficult than elsewhere, but it’s possible, it’s possible. |

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| **Chemistry\_2024-2000** | |
| **ID** | 0353 |
| **Biographical** | We left my birthplace, Brooklyn, New York in 1939 when I was 13. I enjoyed the ethnic variety and the interesting students in my public school, P.S. 134. The kids in my neighborhood were only competitive in games although unfriendly gangs tended to define the limits of our neighborhood. The major extracurricular activities that I can remember were a Victory Garden on school grounds, our contribution to the war effort, and a favorite sport, handball, played between the walls of our apartment house.  Mother, Ella Greenwald, was an American born into a family that included one sister and four brothers, all born in Hungary. Father, Harry Royze, had two brothers and a sister from the Odessa region of Russia. The Greenwalds and the Roses were secular Jews and the children more so although my younger brother and I spent some time in Hebrew school to please Grandfather Rose.  Due to my brother having rheumatic fever the family was advised to go to a high and dry climate, Spokane, Washington, where my mother’s sister had a comfortable home that could accommodate us. This left my father behind tending his flooring business, an arrangement that I never understood and felt conflicted about. Father’s visits were few and far between. The war was going on. Mother did secretarial work in the Navy Supply Depot in Spokane while we kids were making our way through the Spokane school system.  I worked during the summers at a local hospital, chiefly helping out in the psychiatric ward. In time I came to see myself following some career that involved solving medical problems. No one in my family had followed a career in research. Uncle Arthur G. was an excellent violinist and artist, and taught cabinet making at a trade school in Brooklyn. Uncle Dave R. would have become a lawyer had the economic depression not led him into the U.S. Internal Revenue Service. There was no one in my circle from whom I could expect to get advice.  Initially, I thought problems on how the brain works to be the most interesting. But it was necessary to be practical, and concentrate on less obscure matters when I entered Washington State College. Besides, there were no courses given in neurobiology. However, I was strongly influenced by Prof. Herbert Eastlick, who urged his zoology students to set high standards for themselves, and then proceeded to the University of Chicago after a brief period in the Navy. My PhD thesis problem was to determine if the DNA content of rat tissues increased if there was B12 in the diet. This problem was suggested by my adviser based on the observation that thymine could replace vitamin B12 in a lactobacillus. I analyzed the DNA of tissues of rats fed with diets that varied in B12. This project was doomed to failure when the genetic nature of DNA was revealed, and I found that the DNA content per cell of liver was independent of diet[1](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not1).  *PhD Work.* I had to think of a new thesis project. Anxious to make up for lost time, I picked a problem out of my freshman biochemistry lecture notes. The Putnam/Evans group was interested in determining the origin of the nucleic acid components of bacteriophage synthesized in E. coli and Frank Putnam’s lectures described experiments of Hammarsten, Reichard, and Saluste[2](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not2) as background information. 15N-cytosine, the free base, had been found not to be incorporated into DNA although 15N-cytidine was incorporated into rat liver DNA. It was obvious for me to ask if there might be direct utilization of the whole of cytidine, ribose and all, in the biosynthesis of deoxycytidine. That would be a shock. I learned from Peter Reichard, during a 2004 meeting in Stockholm, that the export to Sweden of 14C-compounds was forbidden by the U.S. Atomic Energy Commission at that time, otherwise they certainly would have done the obvious follow-up experiment, using uniformly U-14C labeled cytidine themselves.  I made RNA from *Euglena gracilis* grown on 14CO2. I had to work out the determination of the independent specific activities of the sugars and bases which I did by treating the nucleosides with nucleoside phosphorylase and hypoxanthine to exchange for the base to be analyzed. Then by paper chromatography, using a medium containing borate to retard the migration of ribosides, I could also isolate deoxyinosine and cytosine. Although U-14C cytidine did not label the deoxyribose of *E. coli* DNA, I found the deoxycytidine of DNA of rat organs to be almost uniformly labeled. The 14C content was far in excess of the negligible radioactivity in the purine deoxynucleotides[3](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not3). Therefore by both criteria it appeared certain that the 14C reached the deoxyribose directly from the cytidine. Reichard repeated and extended this experiment with U-14C uridine in 1957 with much the same result for the deoxycytidine and thymidine[4](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not4).  It would have been reasonable for me to try to work out the enzymology of ribonucleotide reduction after graduating. Peter Reichard at Yale on a post-doc from Sweden, asked me about my intentions. But I was not anxious to take on a heroic problem at this early point in my career. I was interested in learning more about the principals of enzymology.  *Stereochemistry at Chicago*. Ogston’s 1948 paper proposing, in effect, that the ability of an enzyme-substrate complex to distinguish between identical groups on a tetrahedral carbon was a consequence of the asymmetry of the complex[5](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not5), was a matter of hot debate in chemistry/biochemistry circles at Chicago in 1950 where the enzyme was still a black box and the emphasis was on the chemistry of changes in the substrate. In particular the Ogston idea could justify the conclusion in the experiments of Myron Bender, done in Chemistry at University of Chicago, that the absence of back labeling of an ester in 18O-water during enzymatic hydrolysis could not rule out a tetrahedral intermediate. Bender had already shown that back labeling occurred during ester hydolysis in alkali[6](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not6). In the case of the enzymatic reaction based on Ogston one would expect to lose all the 18O on stereospecific return of such an intermediate to the ester. These thoughts morphed into the positional isotope exchange idea in 1976.  Thus I became challenged to establish the absolute stereochemistry of enzymatic reactions and determine its mechanistic significance, if any. This did not seem such a formidable task, although it was not until 1963 that Kenneth Hanson and I solved the historically important problem of the prochirality of citric acid[7](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not7), which was necessary for me to gain a proper perspective on the aconitate hydratase reaction.  *Yale.* In 1955, after post-doctorals at Western Reserve University with C. E. Carter and at New York University with [Severo Ochoa](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1959/index.html), I was fortunate to be invited by Joseph Fruton to become an Instructor in Biochemistry at Yale University Medical School. The first year at Yale was notable for the following three developments. Not willing to spend the time it would take to get the Department’s mass spectrometer working, I turned to the scintillation counter that was available in the medical school lab of Seymour Lipsky, an M.D. with a passion for exploring and exploiting new methods. One of the pioneer instruments to become available came from a small start-up company in New Haven that Lipsky had been encouraging, the Technical Instrument Company. Lipsky also had a sample of tritiated water which together with his counter got me started on experiments I wanted to do.  A second important event of my first year at Yale was to learn from Mel Simpson of his paper showing an apparent ATP requirement for protein breakdown in a liver slice system. This observation required further study which I attempted on the side for the next twenty years.  But the crowning event of 1954-1955 was my proposal of marriage to Zelda Budenstein, a graduate student in the Department. Fortunately, I caught up with her before she graduated. Her mother, widowed since Zelda was age five, came to live with us. She was much loved and a great help with the four children that were in our onrushing future. She enabled Zelda to have a research career, often paralleling mine, which she continued until 1987 when she retired to devote full time to her peace and social interests.  *Aldose-ketose isomerases.* Probably the most interesting experiment of my nine years at Yale, l954-1963, was interesting from the way it developed and the confidence it gave me that I might be able to do research after all. I had been looking for evidence of proton transfer in enzymes that catalyzed aldose-ketose interconversions. We had been mistakenly unsuccessful in not finding the small amount of transfer that was later detected in the triose P isomerase reaction. Y.J. Topper had reported that glucose 6-P isomerase in D2O formed glucose-6-P (G6P) containing about one deuterium using crystallization of the barium salt as a G6P trap[8](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not8) suggesting that there might be no proton transfer between reactants of this enzyme. The importance of showing some transfer would be that it would provide a clue to the catalytic process. Complete transfer would suggest a hydride transfer. Complete exchange would suggest a carbanion intermediate but would not implicate the enzyme as the base. However, the occurrence of both transfer and exchange would result if the abstracted proton were to exchange to some extent before a second proton transfer. Such a result would imply a single base mechanism. No such result had yet been reported. In unrelated experiments I observed a puzzling phenomenon with G6P isomerase. When G6P was used with isomerase in D2O the colorimetric analysis for fructose-6-P passed through a maximum before reaching a final value. This overshoot of equilibrium that occurred only in D2O, Figure 1, was very puzzling.  Professor Julian Sturtevant of the Chemistry Department sagely asked me if I was sure of my assumptions. I soon figured out that Topper’s experiment might have been misleading. Perhaps his barium trap of G6P was not good enough. If there were both transfer and exchange in D2O then as the product returns to the enzyme there would be another opportunity for exchange until the product becomes fully exchanged. The fructose-P would go from a partly H- form initially, to an all D-form in the exchanged position at C-1. Now the only thing necessary for my strange result to make sense was to find an isotope effect in the color reaction for ketoses in acid. This was shown by finding the equal amounts of fructose-6-P at 20 hrs when assayed by a different method[9](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not9).  We could show transfer using 1-T fructose-6-P with the isomerase using Ba to form the crystalline salt of G6P as it formed in the presence in a small amount of seed crystals, Figure 2. The 6Pgluconate made from the G6P was only labeled at C-2, the site to which transfer had occurred. We also showed that transfer was between carbons of the same molecule and that the extent of transfer was greatest at low temperature, indicating that the greatest effect of heat was on the dissociation of the intermediate E-T. The proposed intermediate, EH.enediol-P was found to partition about equally in the forward and back direction as shown by the equal incorporation of T-water into product and substrate at early times. A low specific activity of the product was consistent with the slow exchange of the intermediate which would also be expected to show some discrimination against T of the solvent. Since only one T entered the C-1 position of the fructose-6P at equilibrium in tritiated water the abstraction and exchange with solvent were stereospecific. The absolute stereochemistry of 1-2H-fructose-6P was rigorously established by neutron diffraction crystallography as suggested by Lindo Patterson of Fox Chase using the 6Li salt of monodeuteroglycolate[10](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not10). This was the first example of the use of neutron diffraction to establish the absolute configuration of a molecule made asymmetric by isotopic substitution.  *All isomerases use cis-enediols intermediates.* As shown in Table 1, isomerases that are specific for 2R-aldoses were found to activate the 1-R proton of the ketose produced. Isomerases specific for 2S-aldoses produce ketoses that exchange their 1S proton[11](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not11). For these proton transfers to have been intramolecular, they would both have come from the same face of the enediol intermediates. This implies a cis-enediol intermediate. cis-enediol intermediates have the advantage of requiring only a single electrophile to polarize the carbonyl of either substrate. The requirement for one base and one electrophile may be a major factor in preserving the cis-enediol mechanism in evolution.  *A relation between the cis-enediol mechanism and the anomeric specificity of isomerases.*The open chain forms of sugars are minor species in aqueous equilibria. Therefore a ring opening step will be the first step catalyzed by isomerases for any pentose or hexose substrate. Since ring closing is the reverse of ring opening, we wondered if enzymes with a cis-enediol intermediate would be defined in the ring closing step. Ring closing should occur from the face opposite that used by the proton donor. For example, if the proton approaches C-3 from above the plane, the C2-C3 bond will become oriented below the plane and the C5OH must approach the C-1 carbonyl that is being generated to form the cyclic product from below, see figure 3[11-13](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not11).  The anomeric specificities of 5 isomerases were determined in the course of our studies on the isomerases that continued until 1973. The results were as predicted, see Table 2. Thus a-xylose were the substrates for the 2R-aldose enzymes in their production of fructose 6P+NH3 and xylulose, respectively, and b-L-arabinose and B-D-mannose-6-P were the specific substrate for the 2S-aldose isomerase.  The specificity of glucose-6-P isomerase is unusual. Consistent with the above considerations a-G6P and a-F6P are the favored substrates. However, isomerization of b-G6P occurs at a significant rate. It has been proposed that the open chain aldose while on the enzyme undergoes torsional inversion at the C2-C3 bond before ring closing. This kind of motion, if it were to occur in the ene-diol of G6P could add the C-2 proton to the flip face and produce mannose-6-P. Seeholzer has reported the activation of the C-2 proton of mannose-6-P by G6P isomerase[14](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not14).  *A nomenclature for ring face designation*[15](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not15). In looking for a way to designate the ring face of a simple ring compound such as G6P or of the two rings of a nucleoside, or of fused ring compounds such as sterols, we realized that a universal method could be devised using the established rules for numbering the atoms of rings as contained in standard chemical handbooks[15](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not15). A face is considered a if the numbered ring atoms are seen to increase in a clockwise direction, otherwise this face is designated the b-face. The method is not subject to changes in ring substituents as is the D/L naming of sugars. One can readily communicate structural information without resorting to pictures by this method. For example, noting that in [Watson-Crick](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1962/index.html) base pairing the paired bases have the same face-orientation in forming the antiparallel double helix tells us much of what we need to know to build the correct structure.  *Fox Chase.* In l963, we moved to The Institute for Cancer Research of the Fox Chase Cancer Center in Philadelphia. The Institute was a unique place, in my experience. Since its founding it was governed by the notion that to understand cancer one needed a broader understanding of biological science. In its first expansion from center city in 1949, its faculty included crystallographers, embryologists, chemists, biochemists and medical biologists without departmental restrictions. I was attracted by the chance to learn from a wide range of researchers attending each other’s seminars as well as the freedom from teaching. Research support came from our own competitive grants but the Institute had a generous history of tiding you over. We were not required to go after our own salaries which came from an NIH core grant, the first of its kind, which also supported institutional facilities. Decisions were made by the Director, Timothy R. Talbot, M.D. with the advice of a group of the staff and eminent outsiders. Zelda had a lab and grant of her own. She quit science to be more active in the Nuclear Freeze and other peace efforts in 1987. In 1977 when Avram Hershko requested to share our lab space and facilities, he and his group were welcomed for the 22 years he was with us, either on sabbatical or during summers.  *Whole cell systems.* In the next few years I started a series of investigations using isotopes to examine problems of metabolism. It had been observed by Harland Wood’s group at Western Reserve that when 14C-lactate or 14C-glycerol are fed to a fasted animal the labeling of the glucose units of liver glycogen was such as to suggest that triose-P isomerase had failed to equilibrate its two triose phosphate substrates during synthesis, or that the condensation reaction of FDP aldolase did not give equal labeling of the two halves of FDP. We had earlier investigated this latter, using isotope exchange at equilibrium (possibly for the first time) showing that the C456 of FDP exchanged more rapidly than C123[16](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not16).  Asymmetric labeling due to incomplete equilibration at the triose-P isomerase step seemed unlikely given the enzyme’s high efficiency. This question was settled by showing, with Wood’s group, that the asymmetry obtained with 14C-labeled glycerol in which a deuterium was present in the position abstracted in the isomerase reaction was greater in the direction predicted by incomplete equilibration of that enzyme[17](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not17), an expression of the primary isotope effect of the isomerase reaction that we had shown previously.  Yale graduate student Bob Kemp determined the fates of reduced pyridine nucleotides, NAPDH and NADH in Leuconostoc mesenteroides fermentation and growth using 1-T glucose, 1-T 2 deoxy-glucose and 3-T glucose. Preferential use of 1-T for ethanol production and 3-T for lactate production indicated partial separation of dehydrogenase products[18](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not18). NADH derived from glucose 6P dehydrogenase which also oxidizes 2 deoxyglucose-6-P was the primary source of reducing equivalents for lipid brosynthesis.  *Control of glycolysis.* In the following years we reported studies on the regulation of glucose degradation in human red blood cells. Glucose transport is rapid so that the first irreversible step, hexokinase, must determine the rate of net flux. 14C-glucose utilization was shown to be inversely related to the G6P level over a 40 fold range using methylene blue and inosine to vary the steady state G6P, even as many other metabolites varied greatly without showing effects on this linearity[19](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not19). Thus any condition that affects the rate of glucose utilization of red cells must do so by either having an effect on G6P or on the activity of the hexokinase itself. A remarkable effect of Pi in stimulating red cell glycolysis was traced to its interference with the binding of G6P to the enzyme without itself having an effect on the hexokinase rate[20](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not20).  Using measurements of isotope exchange rates we were led to conclude that the accumulation of triose-P intermediates in human red cells that were incubated with high levels of orthophoshate was due to equilibrium and not a rate limiting step. The low levels of NAD and pyruvate caused by net synthesis of 2, 3-bisPglycerate shifted the equilibrium of the glycolytic intermediates toward high triose-Ps[21](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not21).  *Glucose-1, 6-P2 of the brain.* Lowry *et al.* reported the rapid depletion of the normally significant amount of G16P2 during mouse brain ischemia. We have been particularly interested in the role this compound might play in brain function. We purified an enzyme that used G1P with glycerate-1,3-P2, as the phosphate donor, not ATP or FDP[22, 23](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not22). Mg was a required confactor but Zn was equally active and much more tightly held. About 65% of the activity of a fresh brain extract resistant to EDTA is probably the enzyme in the Zn-form. The synthetase is strongly inhibited by concentrations of citrate and FDP that are found in the brain suggesting a regulatory role of G16P2, and that its synthetic rate may be different in different regions of the brain just as its distribution was shown to be localized[24](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not24).  Zelda discovered a brain-specific G16P2 phosphatase with an absolute requirement for inosine-5-P[25](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not25). Since IMP is the major product of ATP breakdown in the ischemic brain this strongly points to activation of the phosphatase as the cause of the rapid fall in G-1,6-P2 in ischemia.  *Mitochondrial hexokinase.* A problem that warrants further study derives from our observation in 1967 that instead of being in the cytosol most of the hexokinase of tumor and animal cells is associated with the outer membrane of the mitochondrial fraction[26](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not26). It has recently been reported that the release of mitochondrial hexokinase and some associated proteins may play a role in the onset of the apoptosis cascade[27](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not27).  *The mechanism of synthetases.* When I felt that we understood control of the red cell glycolytic system my attention returned to mechanism questions: ATP driven synthetases, reactions such as glutamine synthetase (gluamate + NH3+ ATP –> glutamine + ADP + Pi) may be written to go in three steps: ATP + E -> ADP + E~P, E~P + glutamate –> E. glutamyl~P, E. glutamyl~P + NH3 –> -glutamine + Pi[28](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not28). However, no ADP/ATP isotope exchange could be found unless all of the reaction components were present. On the other hand, Meister had performed a pulse/chase experiment that seemed to suggest the formation of an activated intermediate. The enzyme, pulsed with ATP and 14C-glutamate, was chased with unlabeled glutamate plus hydroxylamine. 14C-glutamyl-hydroxamate was found in the chase. However, one could argue that a non-covalent complex of E.ATP.glutamate may not have lost the labeled glutamate more rapidly than the chemical reaction would have occurred when the NH2OH entered the complex. A similar assumption was made by Jacob bar Tana, who I met at the Hadassah Medical School in Jerusalem on our sabbatical in 1972. He was having trouble with irreproducible results with phosphofructokinase testing for an E~P mechanism by preincubating the enzyme with ATP[32](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not32) and chasing it with a mixture of F-6-P and unlabeled ATP. I suggested that he might be capturing E.ATP rather than E~P.ADP. We agreed to examine the assumption that dissociation of a binary complex must be faster than chemistry on bar Tana’s next visit to the U.S. We used yeast hexokinase with 14C-glucose (the pulse) followed by ATP plus a large excess of unlabeled glucose (the chase). Labeled G6P was indeed found in Michaeli’s proportion to the ATP in the chase up to the full measure of enzyme occupied by glucose in the pulse[29](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not29). Dissociation of glucose was indeed slower than its phosphorylation contrary to the generalization that chemistry is slow. Thus was demonstrated the first pulse/chase experiment from which could be determined the functionality of binary complexes, their rate of dissociation and the extent of dissociation of glucose from the ternary complex.  *Pulse/chase variants.* Subsequently, our lab used the pulse/chase method to study hexokinase in the steady state by comparing the 14C-G6P formed in an acid quench with that formed in a high substrate chase with time of quenching, a procedure that gave the position of the central equilibrium, ~1, and the rate constants for all interconversions[30](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not30). We did pulse/chase experiments in which the labeled glucose came from hexokinase in the crystalline state either alone or together with ADP[31](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not31). Although the crystals dissolve slowly the results suggest that their form at that time reflects the form in the crystal. Crystals with glucose alone required the same amount of ATP for 50% trapping as did E.glucose in solution. On the other hand E.glucose.ADP grown crystals from which the ADP had been removed by washing required much less ATP. We also used standard pulse/chase to find that 4 atoms of tritium, with the specific activity of water in the pulse have positions on the enzyme aconitate hydratase, probably an arginine-threonine pair in the active site that could be trapped by the cis-aconitate in the conversion to citrate[32](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not32).  *Positional isotope exchange (PIX).* Although traditional ATP/ADP exchange as a test of E~PO3 or E-glutamyl~PO3 intermediates in the glutamine synthetase reaction would fail if the ADP did not leave the enzyme a different kind of isotope exchange might be observed, one in which the beta-gamma bridge oxygen and the beta-nonbridge oxygens of reisolated ATP had mixed with each other. This would only require the phosphoryl oxygens of the bound ADP intermediate be capable of undergoing positional isotope exchange, depending on a symmetrical torsional motion before returning to ATP. This new exchange process was observed in a cleverly designed experiment done by post doc, Fred Midelfort[33](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not33). The PIX rate in the presence of glutamate was consistent with the reverse rate of the enzyme. The exchange rate was decreased by NH4+ consistent with a decrease in the concentration of E.glut~P.ADP complex.  *Recycling.* More recently, we have become interested in how an enzyme recovers after product formation. Changes in the active site of an enzyme that occur when a substrate is converted to product must be reversed before the reaction can occur again. With rare exception, this recycling of the active site occurs before the product has left the enzyme and is therefore counted as part of the product-off step. Are recycling steps ordered or random? Does the sequence replicate the order of steps during the reaction itself? Fumarase has several properties that mark it as a rare example in which, when salt is present to accelerate the release of a product, a further sequence of steps remains that is rate limiting for the whole reaction cycle. Distinctive enzyme isoforms become identifiable as shown by the occurrence of noncompetitive inhibition by product analogues[34, 35](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not34). Added labeled reaction product rebounds to substrate when unlabeled substrate is added showing that the product form of the enzyme is slow to recycle, the Britton counterflow effect[36, 37](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not36). D2O and glycerol show uncompetitive inhibition patterns indicating that their effects occur after an irreversible step, product release. Noncompetitive inhibition is rarely seen in enzymes that catalyze reactions requiring only one substrate. When it is seen, it is an indication of slow recycling.  The chemical interconversion of fumarase reaction, a carbanion mechanism, is the most rapid part of the reaction cycle. Thus at equilibrium, 18O-water exchanges into malate more rapidly than does fumarate. Perhaps the details of the reaction chemistry can be determined from the details of the recycling. That this seems to be the case is indicated by the pattern of inhibition. The carbanion intermediate analog, 2-hydroxy, 3-nitropropionate is competitive with respect to both malate and fumarate and therefore represents the intermediate species in the recycling whereas all other inhibitors are competitive with only one or the other of the substrates and therefore represent product species.  The ability of salt to increase the rate of product release is lost when the basic amino acid residues that reside between the active site and the solvent are mutated to neutral forms[38](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not38). The mutated enzyme is now rate limited by the product-off step, not recycling. We speculated that the negatively charged products are released through a positively charged channel that is made more rapid by salt.  *Enol-pyruvate.* Heavy atom NMR spectroscopy of the hydrogens of P-enolpyruvate led to Mildred Cohn’s solution of the reaction stereochemistry of the reaction of enolase using (3R)-phosphoglyceric acid-3-d[39](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not39). This led us to the solution of many reaction stereochemistries with enzymes using specifically labeled 3D, T-PEP[40](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not40).  Our longstanding belief that enolpyruvate is the intermediate in the pyruvate kinase reaction was confirmed by direct chemical analysis of pyruvate kinase in the steady state[41](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not41). We could also show that enolpyruvate synthesized by treating PEP with a phosphatase was used by pyruvate kinase at an appropriate rate although its affinity was less than expected for an intermediate[42](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not42).  *Other problems.* In a surprise result, the Schiffs bases of dihydroxyacetone-P and of FDP were found to precipitate with the protein of muscle aldolase in cold acid[43](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not43). This property due to the stability of the Schiffs base intermediates in acid and the acid lability of the eneamin-Ps were used to determine their concentrations as intermediates in the aldolase reaction[44](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not44). Ring formation of the adducts was indicated. Thus 5-deoxyFDP formed a much less stable acid precipitate than did FDP.  The interconversion of citrate and isocitrate by aconitate hydratase was shown to occur with complete retention of the proton transferred between C2and C3 but with no retention of the OH- between C3 and C2. The bound cis-aconitate intermediate must flip over, probably around a CH2COO- pivoting on the ferrous iron of the active site so that the enzyme bound proton can approach from the opposite faces of the intermediate in generating either of the products[45](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not45).  Aconitate isomerase catalyzes the interconversion of cis- and trans-aconitate by a 1, 3 allylic rearrangement that uses the (pro-S) hydrogens of the two substrates. The stereochemistry and the transfer of tritium are consistent with a single base carbanion mechanism[46](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not46).  The physical separation of H- from D-labeled molecules made possible by their different rates of reaction was used to establish that the transfer of hydrogen in G6P isomerase was intramolecular[9](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not9) and that the site of attachment of CO2 to ribulose-1, 5-P2 to produce two molecules of phosphoglyceric acid had to be to C-2 rather than C-4 in the RUDP carboxylase reaction[47](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not47).  In this chapter I have mentioned most of the problems that have engaged me and my coworkers until the time of my retirement in 1997 with the exception of ubiquitin related studies that are summarized in the next chapter, “Ubiquitin at Fox Chase”. Following my retirement, Zelda and I moved to Laguna Woods in Southern California where I was able to continue lab work using space and facilities shared by Ralph Bradshaw at nearby U.C. Irvine.  During this period Dr. James Nowick of Chemistry and I examined the mechanism of methylglyoxal synthetase (dihydroxyacetone-P -> methylglyoxal) trying to understand our observation48 that the methyl group of the product was formed nonstereospecifically. We could show spectroscopically that the enol-aldehyde of methylglyoxal was really the enzyme’s product[49](https://www.nobelprize.org/prizes/chemistry/2004/rose/biographical/#not49). Ketonization occurs off the enzyme and therefore is nonstereospecific. Ketonization to methylglyoxal is very slow but is assisted by thiols which interrupt the double bond conjugation by formation of a thiolhemiacetal. It was perhaps for this reason that the next enzyme, of the sequence, glyoxalase I, has the adduct of methylglyoxal with glutathione as its substrate and D-lactyl – glutathione as its product.  We concluded our paper with the observation that organisms that had no glutathione would have to evolve another mechanism to dispose of methyglyoxal which is toxic to cells due to its action in cross linking macromolecules. Our most recent study shows that the mycobacteria that have mycothiol, (N-acetyl cysteine-glucosamine-inositol), as its major reducing compound have indeed evolved an enzyme that carries out the same kind of sequence with a “glyoxalase” that produces lactyl-mycothiol (unpublished). This is therefore a second example in which an enzyme uses the non-enzymatic product of a previous step as its substrate.  Looking back on my 50 year eclectic journey in research, I am grateful that it has gone as well as it has, although still not clever enough to open the black box of enzyme structure. The approach I have taken was successful, in the least, in attracting outstanding postdocs, some of whom were on hand in 1975-1980 when with Avram Hershko, we pursued the ubiquitin/protein breakdown work.  I am especially grateful to those who have helped me find solutions to the many problems that troubled us in the early days of biochemistry. Among them were Jacob bar Tana, Steve Benkovic, J. F. Biellmann, Mildred Cohn, Aaron Ciechanover, Don Creighton, Raj Gupta, Arthur Haas, Kenneth Hanson, Avram Hershko, Anthony Jaworowsky, G. Kaklij, Robert Kemp, Judith P. Klinman, David Kosow, Donald Kuo, Gustav Lienhard, Oliver Lowry, Alton Meister, C. Fred Midelfort, Gerd Mullhofer, Koko Murakami, James Nowick, Edward O’Connell, Frank Oski, Lindo Patterson, Cecile Pickart, Sidney Rieder, John Richard, James Robinson, Zelda Rose, Keith Schray, Steve Seeholzer, Frank Solomon, Michael Summers, Jessie Warms, Mary Wimmer, Keith Wilkinson, James Willard, Harland Wood and Alvin Zipursky. |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** |  |
| **Interview** |  |
| Q2 | **How did you meet together?** |
|  | Avram Hershko: Well, that’s another story. I got interested in protein degradation during my post-doc fellowship in San Francisco, and when I came back to Israel I continued with that, and at that time it was a very obscure field, you know. People, there were all kinds of, not too many people were interested in it. Those that were interested were not very good. So I looked for somebody, and so my first time I think I came up and I looked for somebody to spend a sabbatical with. I couldn’t find anybody that attracted me. So then I met Ernie at a meeting in 1976, one year before, before my sabbatical was due. And do you remember, we met in the breakfast, so I said can I, just began to talk …  Irwin Rose: It’s alright, I forgot.  Avram Hershko: … breakfast table, so I knew who he was, he was very well known for his work on enzyme mechanism. That I knew, but then I asked him what are you interested in, in other things? So it turned out that he was interested in protein degradation. And that was a secret, it was a secret because he never published anything on it, and I asked him how come you never published anything, and so he said there is nothing worth publishing on protein degradation. So that’s what he said.  Irwin Rose: Yeah, that was my opinion. Well, because I hadn’t done anything, you don’t say it right.  Avram Hershko: OK. Well, that’s how I remember it. And anyhow, I liked that attitude very much, and asked, I asked him can I spend my sabbatical with you? And he said yes, so that’s how it started, and then Aaron, the same year he started his PhD with me, and after my sabbatical the following, the summer after my sabbatical, Aaron joined us, and then he joined us for a couple of summers afterwards, so that’s how, that’s how the whole connection started. |
| Q3 | **But how come you pick up an obscure field in science, to work on?** |
|  | Irwin Rose: Well, I’ll tell you, because when I first worked at Yale, the guy who had a lab next to me had made the original observation that there was a protein, there was an energy dependent on protein breakdown. Now, nobody believed him, but he had made some pretty strong observations that if you …  Avram Hershko: Here, we could mention names.  Irwin Rose: Yes, Melvin Simpson. He made these important observations.  Aaron Ciechanover: He hardly believed himself, because when you go into discussion on the paper, you kind of come to a convoluted argument whether it’s a direct requirement or indirect. We can do the conclusion that it’s indirect. |
| Q2 | **You do nothing? Who is the worker?** |
|  | Avram Hershko: Well, that’s, first of all, that’s not true. I remember that you made some ubiquitin preparation …  Irwin Rose: I did.  Avram Hershko: Yes, and it fell on the floor, and then you collected it up from the floor … yeah, yeah. That first step is to boil the extra, because ubiquitin is heat stable, so you boiled it but then it fell on the floor, but you picked it up and it was good, yeah.  Irwin Rose: It was good, nothing could destroy it.  Irwin Rose: It was a licence only enzyme.  Aaron Ciechanover: The /- – -/ can take it, but not the floor.  Avram Hershko: But, yeah, but when I came to his lab we already had his first step, which was the fractionation, well, the reticulocyte cell-free system system was actually established in the laboratory of somebody else, Alfred Goldberg in Harvard, but they didn’t …  Aaron Ciechanover: /Inaudible./  Avram Hershko: No, no, but, yeah, but he made it first, he made it first.  Aaron Ciechanover: The first publication was from Harvard, no doubt.  Avram Hershko: But then he didn’t progress, but then he didn’t do what he should have done, which is fractionation. It’s hard to purify right away, but ATP dependent enzyme, he never found it. And what we did was fractionation and constitution, so we already had this first step of separating it into two, two fractions, fraction one and fraction two.  So during these two years between the beginning of ’77 when I write to your lab and December of ’79, when we made the breakthrough in your lab, we purified the component from fraction one, we found it a heat stable protein, and then you had a part in that, you also boiled ubiquitin, and then in Haifa we found that it gets … when we labelled it with iodine and we found it gets bound to proteins and ATP dependent reaction, but we didn’t really understand that it’s binding, its co-herent binding the substate until that summer in 1971 in the laboratory of Rose where you invited me, together with Aaron who was then my graduate student in /- – -/ who was there. 1979, 1979. So that is when, when the discovery that ubiquitin …  Irwin Rose: Shall I tell the story about the ubiquitin?  Avram Hershko: Yes. I think I have finished. So then, that’s how I remember it, and how …  Irwin Rose: OK, well, here they had a heat stable factor that was required, and they made the observation that the ubiquitin went on to proteins. And so one of my post docs went to a post doc of another student, of another faculty member at the Fox Chase Cancer Centre, and said, there was a conversation, and do you know of any examples of a protein covalently linked to a protein? And this post doctoral fellow said yes, there is in the nucleus, a protein called ubiquitin that’s covalently linked to histone. And so they rushed to look at the amino acid composition of that so-called ubiquitin, and they compared it to the amino acid composition which you had published, I guess …  Aaron Ciechanover: No, not yet.  Irwin Rose: Not yet published.  Aaron Ciechanover: But in the end it was published back to back with JBC.  Irwin Rose: No, no, no. But how did they know the conversation …  Aaron Ciechanover: No, because they knew, the end story is that the Wilkinson paper came back to back with ours on the /- – -/.  Avram Hershko: OK. Let’s not go into the detail.  Irwin Rose: Well, for some reason or other, they found confidence…  Avram Hershko: They knew that I published that.  Irwin Rose: Really, and I was not a leak.  Avram Hershko: No, no, you were not.  Aaron Ciechanover: No, he was in the lab, he was free and did this. We didn’t hide anything.  Irwin Rose: OK, you’re getting the inside story here. Now, wait a second. |
| Q2 | **How do you survive as a scientist when nobody believes you somehow?** |
|  | Irwin Rose: You’re making observations, and the observations get published, so the observations are true. Whether anybody will say that belongs to a big story like it turns out to be is not predictable, but so you don’t make claims like that. You say that this is very interesting and so on and so on and so on, and you keep following it up, and it doesn’t necessarily become the centre of attention yet, until you build a big enough story. I think that’s the way it works.  We all survive because funding for research was generous in those days, you know. It’s been less generous now, and we have a peer review system which is more critical and so I think you have to, you have to add successively to the picture you’re trying to portray. It’s not sufficient to just provide data. So I think that’s part of it. But I agree that it’s important to be left alone for a sufficient amount of time in order to be able to do it, and not feel that you’re in the middle of a big activity already, so you know, you need to do that sort of thing. |
| Q17 | **So are you the kind of scientists that work all day and all night long, kind of nerd scientists?** |
|  | Irwin Rose: I think we all work all day and all night long. I do. I don’t have any hobbies, you know, I’m very embarrassed when people ask me what are my hobbies, I don’t have any hobbies. I mean, it’s just enough to keep up with the things I’m trying to solve. You know, I used to work on little puzzles and so on and so forth. Each puzzle requires attention and, so you get an idea. You get your ideas at different times. Sometimes your wife makes a statement and you say: aha, maybe you’re right. And so you go off to your kitchen, and do a little experiment, so you try to, that’s the way you make progress, if you continue these things. So that’s my recommendation, do not retire. Do not retire fellas.  Avram Hershko: I won’t.  Aaron Ciechanover: I’m never going to. |

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| **Chemistry\_2024-2000** | |
| **ID** | 0354 |
| **Biographical** | A**ncestral origins** In 1862, Abraham Lincoln signed the Homestead Act, a bill opening one half million square miles of territory in the western United States for settlement. The Homestead Act offered new arrivals from other countries the opportunity to stake and develop farms of 160 acres by simply working the land for five years. Although they were only in their teens or early twenties, my great grandparents individually left their villages in Norway and Sweden between 1875 and 1885 and migrated to western Minnesota and South Dakota. Similar to the protagonists in the epics of Ole Rolvaag and Vilhelm Moberg, they worked the rich farmland, married, raised families, and achieved prosperity unattainable at that time in Scandinavia.  Things changed for my parents’ generation. My father, Courtland Agre, and his two sisters grew up in Wallace, a hamlet in eastern South Dakota where his parents ran the general store. Wallace was also the hometown of Hubert Humphrey, and while my aunt Pearl remembers baby-sitting young Hubert, my father, an ardent Republican, claimed that they never met. To accommodate their educational needs, my grandparents moved the family to a larger town and ultimately to Minneapolis where Dad earned his B.S. and Ph.D. in chemistry from the University of Minnesota. He contributed to the U.S. effort in World War II by working as an experimental polymer chemist for the 3M company. My mother, Ellen Swedberg, was the sixth of eight children. Her upbringing was more severe. She was only five years old when her mother died; later her father lost their farm in Twin Brooks, South Dakota during the Depression. At age 18, Mother moved to St. Paul in order to support herself. Despite eleven years difference in age, Dad and Mom met at a Lutheran church social, fell in love, and married. I was never certain how much their families approved, since even small differences in geographical origins are taken very seriously by Scandinavians. The Agres were Norwegian (Osterdalen and Trondelag), while the Swedbergs had mixed origins – Swedish (Skåne) and Norwegian (Telemark).  **Childhood** Following WWII, my parents moved to Northfield, a town 40 miles south of Minneapolis where Dad was recruited to the chemistry department at St. Olaf College. Dad was energetic and, with the help of his St. Olaf students during the summers, he built our house across the street from the college athletic fields and meadows. We could look up at the college from our living room. As was the tradition, Mom had babies and took care of the family. Preceded two years by my sister Annetta, I was born on January 30, 1949 and received the anglicized name of my grandfather, Peder. My closest sibling, James (Jim), was born one year later, followed by Paul, Ruth, and Mark. We had an idyllic childhood. Grandmother Agre lived nearby and coaxed us to speak rudimentary Norwegian in return for cookies and other bribes (“Jeg liker Bestemor’s mat!”). Northfield was in many ways a new-world enclave of pre-Ibsen Norway with 19th century religious and socially conservative values. My friends had family names like Lunder, Finholt, Berglund, and Fredriksen. We schoolchildren all sat on the hillside waving our Norwegian flags when King Haakon visited St. Olaf. He was chauffeured from the train station to the college in the only Cadillac in town – owned by the local plumber. We always had lutefisk for Christmas dinner, after which Dad read from the Norwegian Bible. During the summers, he welcomed us into his laboratory at St. Olaf where he rigged simple “experiments” for us such as changing the color of solutions containing indicator dye by adding acid or base. As a youngster, it was obvious to me that I would follow my father’s career path, since he was my greatest hero.  Life changed for our family while I was in the third grade. Grandmother Agre died, and Dad decided to take a sabbatical year at the University of California. Dad had high aspirations, and through the American Chemical Society he became acquainted with renowned scientists. Berkeley was an amazing change from Northfield, and Jim and I attempted, with limited success, to demonstrate our Norwegian athletic and scholastic superiority to the smart and culturally heterogeneous Berkeley youngsters. It was at this time that my brother Paul was recognized as mentally retarded, and my sister Ruth began to exhibit her lifelong personality disorder with lack of impulse control. While they never fretted openly, these problems must have caused my parents profound heartache.  Following the year in Berkeley, we returned to Minnesota. Always eager for a challenge, Dad accepted a professorship at Augsburg College, a small Norwegian Lutheran college in Minneapolis with a chemistry department in need of help. We lived in a beautiful, large brick house on the banks of Lake Nokomis and went to the public schools. My inconsistent academic performance was usually well tolerated, as I tried to amuse my school classes with my practical jokes and amateurish wit. As in Northfield, my teachers were the kindest and nicest people imaginable. It is impossible to overestimate the importance of a teacher in the life of a child, and my all-time favorite was my sixth grade teacher Richard Hughes whose kindly personality and gentle sense of humor inspired in us the idea that learning is wonderfully fun. This impression was shared by many. My classmate Julia Lofness remains a close personal friend and still cheers me by retelling events from our days in Mr. Hughes’ class.  My brother Jim and I spent many wonderful summers working on dairy farms in Wisconsin owned by Mom’s cousins, and as members of our local Boy Scout troop. Scouting was a particularly important activity for us, and through the generous instruction of our Scoutmasters, Harold Neuendorf and Francis McMahon, we learned the resourcefulness needed to camp out even in Minnesota winters. One of our happiest times was in 1964 when Jim and I received our Eagle Scout Awards together – Dad carried that snapshot in his wallet for the rest of his life. Dad’s presence was always palpable. Needing a medical doctor to perform physical examinations before summer camp, Dad always arranged for one of his former St. Olaf students to serve. One summer, Dr. Charles Mayo, grandson of the Mayo Clinic founder, examined the boys of Troop 185. Also as a Scout, I developed a deep interest in the culture of the Ojibway Indians of Northern Minnesota and explored the Canadian wilderness by canoe – an activity that I still undertake with family members each summer. In retrospect, another remarkable experience was the several-days visit to our home by Dad’s friend Linus Pauling who presented lectures on physical chemistry (subject of his [1954 Nobel Prize in Chemistry](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1954/index.html)) and the dangers of nuclear arms (subject of his [1962 Nobel Peace Prize](https://www.nobelprize.org/nobel_prizes/peace/laureates/1962/index.html)). In person, Pauling was jovial, confident, and more engaging than anyone we had ever met. Dad always raved that Pauling’s accomplishments were the greatest, and he instilled in us his view that the Nobel Prize is the closest thing to the Holy Grail.  **High school and college** My years at Theodore Roosevelt high school were notable for reasons other than academics. Like other adolescents, I developed a strong attraction to girls and discovered that my parents’ ideas were not the least bit interesting. I earned money as a concession salesman at the Minnesota Twins and Vikings games. At this time I developed a lifelong love of cross country skiing and long distance bicycling with my close friend and classmate Tom Page, an aspiring artist and fellow adventurer. Following my junior year in high school, I went on a camping trip through Russia in a group led by Horst Momber, a young language teacher from Roosevelt. This permanently sparked great enthusiasm for international travel in me. After my return, I gravitated in a Bohemian direction. Fancying myself as some sort of Bolshevik, my senior year in high school went badly in terms of conforming with my family’s expectations. Rebelling against the establishment, my friends and I self-published an underground newspaper, *The Substandard* – a parody of the *Roosevelt High School Standard*. Our foray into newspaper work caused much delight amongst everyone except the school administration. Facing dismissal, I withdrew from school in the winter of 1967 when my grade in chemistry had dropped to a “D.” Nevertheless, I finished my high school degree in night school, and I studied Russian language at the University of Minnesota during the day. I worked the evening shift and drove a truck for a factory making dummy land mines and parts for military equipment destined for the war in Vietnam.  This experience in the real world was far less appealing than I had anticipated, but Dad’s faculty position offered a logical solution. I swallowed my pride and enrolled at Augsburg where I majored in chemistry in preparation for a career in medicine. Living at home, my social life was restricted to bicycle rides along the Mississippi River and around the lakes. My closest friends Tom and Julia remained in Minnesota for college and were generous sources of support. My second year at Augsburg was enlivened when brother Jim and I organized and played for the varsity soccer team. I also worked part time delivering flowers for a local florist. Although I was not sympathetic to the Lutheran affiliation of the school, I developed my first real academic self-discipline at Augsburg. I greatly benefited from excellent faculty, especially John Holum, the organic chemistry professor, and from the warm and friendly personalities of the other chemistry majors. Unlike many campuses, Augsburg lacked an overly competitive pre-med atmosphere, and all eight of the premedical chemistry majors in the class of 1970 were accepted into medical school. My brothers Jim and Mark also attended Augsburg and went on to medical school. Annetta graduated from Augsburg before marrying and raising her family; her daughter Christina has also become a medical doctor.  **Early medical career and marriage** The long, cold Minnesota winters instilled in me a fascination for exotic far off places; I aspired toward a career in tropical diseases and world health problems. Johns Hopkins is highly regarded in these areas of research, and I was ecstatic when I was accepted into their medical school. Having enough credits to finish Augsburg early, I left Minnesota in the winter of 1970 to travel alone throughout Asia for several months. This was an eye-opening experience, and after hitchhiking throughout Japan and Taiwan, I journeyed to Laos where I traveled up the Mekong River and explored the hills of northern Thailand by motorcycle. Determined to visit Angkor Wat, I entered Cambodia and eventually arrived in Pnom Penh just as the U.S. Air Force launched its ‘Parrots Beak’ offensive against Vietcong east of the city. Advised by the U.S. Embassy to depart immediately, I boarded an evacuation flight to Vietnam where I viewed the U.S. forces in and around Saigon for several days before leaving for the calm and verdurous Malay highlands. Following a counterculture passage through Ceylon, India, Pakistan, Afghanistan, and Iran, I eventually arrived in Istanbul, weakened from multiple travelers’ ailments including viral hepatitis.  I began my medical studies at Johns Hopkins in September 1970. After being footloose in Asia, I found it difficult to concentrate on medical school, and my best efforts seemed barely enough to earn passing grades. I concluded that my presence at Hopkins fulfilled some sort of affirmative action quota for a Scandinavian student from Minnesota or the Dakotas. My medical school roommate, Vann Bennett, was from Hawaii, and he was thoroughly committed to surfing and laboratory science. Unlike most Hopkins medical students, Vann and I led severely ascetic lives, inhabiting a series of dilapidated rooms. We enjoyed touring the countryside by bicycle, and I made some long rides through Mexico and Canada. I maintained my counterculture image by always making my return trips to Minnesota by hitchhiking.  Johns Hopkins introduced me to two defining events in my life: commitment to biomedical research and meeting my future wife, Mary. It was known in 1970 that most traveler’s diarrhea was caused by a protein similar to the cholera toxin secreted by certain strains of *E. coli*. I began a summer project to purify the *E. coli* toxin in the lab of Brad Sack in the Infectious Disease group at Johns Hopkins. At Vann’s suggestion, I performed some of the biochemical studies in the laboratory of Pedro Cuatrecasas in the Pharmacology Department. The project fascinated me so much that I stayed in Pedro’s lab during my final year in medical school, 1974, and put in an additional year as a postdoctoral fellow. I eventually succeeded in purifying the toxin, but of larger importance was my discovery that I wanted to make biomedical research my life’s work. This was in part due to the fascinating scientists in the group. Looking back, it seems unlikely that such a passionate but disparate group of scientists could form a team and become close personal friends. Led by Pedro, a cosmopolitan intellectual with Spanish and South American roots, our group included a Palestinian from Lebanon, a conservative Jew from Brooklyn, a French psychiatrist, a Swiss-Indian chemist, a Canadian Rhodes Scholar, a Spanish anti-Franco activist, and a strikingly handsome Italian film actor who attracted the notice of every woman at Hopkins as he elucidated the molecular basis of femininity by performing the first purification of the estrogen receptor.  During these lab years, I met Mary Macgill, an attractive and intelligent young woman who was working in a Hopkins neurovirology lab. Mary and I immediately fell in love and became inseparable. Her calm and wise approach to life balanced my frenetic nature. From our first days together, Mary always encouraged me in my scientific career, and she often brought food to the lab late at night so we could keep working. Despite my ragamuffin appearance, Mary’s family received me warmly. Representing a fascinating mix of blueblood lineage and farm-raised practicality, both sides of her family were among the early settlers in Maryland. Her mother, who had died a year before I met Mary, was a direct descendant of Pocahontas, and her father was a distinguished trial judge in Howard County, Maryland. We were married on March 29, 1975.  **Postgraduate training** My goal was to develop into an independent research scientist studying clinical problems at the laboratory bench, but I felt that postgraduate residency training in internal medicine was necessary. Mary and I settled in Cleveland Heights, Ohio, from 1975 to 1978 while I completed clinical training at Case Western University Hospitals of Cleveland. The CWRU Hospitals were led by Charles C.J. Carpenter, Jr., a distinguished physician and former member of the cholera group at Hopkins. I found the clinical years to be emotionally and physically draining. Nevertheless, I enjoyed the patients and took pride when elderly African-American patients referred to me as their “jive doctor.”  During this time, Pedro’s group had moved to the Wellcome Laboratories in Research Triangle Park, North Carolina. I accepted a clinical fellowship in hematology and oncology at the nearby University of North Carolina (UNC), and Mary and I moved to Chapel Hill in late June 1978. I supplemented the meager fellowship stipend by working as a physician at the army hospital at Fort Bragg (home of the 82nd Airborne Division). Mary and I purchased a small cottage in the country and two Irish Setter puppies. Our daughter Sara was born in September; Claire was born a year and a half later. Our family life was Spartan but delightful. We made many bicycle trips to neighboring farms and camping trips in the Smokies with our adorable little daughters – Sara a towhead with beautiful blue eyes and an engaging smile, and Claire with a thick shock of red hair and many clever but often mischievous ideas.  My clinical duties taking care of cancer patients at UNC were frequently depressing, but I enjoyed attending the outpatient clinic with John Parker, a clear-sighted Professor of Medicine who always encouraged me to study red cell membranes. Vann had also joined the Wellcome Laboratories, and he developed techniques to study the principal structural proteins from red blood cell membranes – spectrin, which formed the girders of the membrane skeleton, and ankyrin, the attachment protein that he discovered. Campbell McMillan, a UNC pediatric hematologist, had identified two little girls in his clinic with an extreme form of hereditary spherocytosis, a disorder of red cell shape causing increased fragility. Spherocytosis is generally accompanied by only mild anemia, but the sisters were nearly lethally affected. Together with Vann, I evaluated the membranes and found them to be grossly deficient in spectrin, and we reported the study in the *New England Journal of Medicine*. This strongly reinforced my desire to pursue biomedical research.  **Return to Baltimore and Hopkins faculty** When Vann returned to Johns Hopkins in 1981 as a faculty member, I applied for an NIH career development grant to join him for more research training. This did not make sense financially, as it meant a 40% reduction in salary and loss of my staff position in the Wellcome Labs and adjunct faculty position at UNC. I consulted with my friend John Parker who generously reassured me that the opportunity at work with Vann at Hopkins would be important for me. Encouraged by Mary, we sold our lovely cottage, packed up our station wagon and a rental truck, and returned to Baltimore in August 1981. We scraped together funds and purchased a brick Dutch colonial house next to the Stoneleigh Elementary School and a large park and forest. The location was fortunate; I could commute the 6 miles to Hopkins every day by bicycle. To supplement our resources, I moonlighted as a ringside physician at professional boxing matches.  The Department of Cell Biology at Johns Hopkins was founded and directed by Tom Pollard, an engaging young scientist with remarkable energy and enthusiasm. I continued working with Vann and reported a series of studies of red cell membranes. I would have been happy to have remained in Vann’s lab, but he recognized my need for an independent faculty position. In early autumn 1983, I received a faculty offer from the Hematology Division at Brigham and Women’s Hospital at Harvard Medical School – a program regarded as the best in the country. I accepted the offer verbally, but Mary was pregnant with our third child, and while she remained supportive, she strongly desired to remain in Baltimore near her family. The Hematology Division at Johns Hopkins was in a transitional mode and exhibited minimal interest in me. However, Victor McKusick, then-Chairman of the Department of Medicine at Hopkins, interceded and I was offered an Assistant Professorship but with a much smaller start-up package.  This offer from Hopkins coincided with the blackest period in our family life. In the 9th month of her pregnancy, Mary experienced a premature separation of the placenta. After induction of labor, our daughter Lydia was born in severe distress. Although she survived, our baby never recovered. Like her sisters, Lydia was a gorgeous child, but her spontaneous movements were few. She moaned softly whenever she was repositioned in her crib, but she always relaxed when we held her. Devastated and expecting a need for permanent home nursing assistance, I accepted the offer at Hopkins, since it would provide the supplemental health care insurance needed for Lydia’s care. Although Mary always exhibited the utmost determination to provide the best possible life for Lydia, I wavered badly and only with great difficulty was I able to accept our situation. We were again crushed when Lydia died four days before Christmas 1983.  We had the advantage of broad support from family and friends but struggled to cope. Mary stayed home to care for Sara and Claire while I set up a tiny lab in the old Blalock Building in Johns Hopkins Hospital. I was able to hire a technician, Andy Asimos, a bright-eyed young man from a Greek family who applied to work for two years before going to medical school. Andy and I continued the spherocytosis studies, establishing that the level of spectrin deficiency correlated with the clinical severity of the disease in new reports published in *Nature* and the *New England Journal of Medicine*.  Although the importance of the blood group antigen Rh was universally recognized, I was surprised to learn from Wendell Rosse, our friend at Duke Medical Center, that the molecular identity of Rh was completely unknown. The existence of 32 kDa polypeptides in red cells from Rh(D) individuals was reported by two European groups. We initiated a new project on the Rh blood group antigen in the hope that isolation of the polypeptide would allow us to define the components of the Rh antigen. Andy and I injected a series of rabbits with the partially purified 32 kDa Rh polypeptide. When Andy left for medical school, Barbara Smith, a former blood bank technologist, replaced him and set about purifying the Rh polypeptide. We soon recognized that we actually had isolated two membrane proteins – the 32 kDa Rh and a second protein of 28 kDa. My research expanded and we focused our major attention on Rh but continued to dabble with the 28 kDa protein.  Our son Clarke was born in 1985 – an adorable little boy with a dimple in his left cheek. Mary and I took Clarke with us on a motor trip through Ireland the next year, and our family life gradually returned to normal. Mary organized camping trips for us to the national parks in the U.S and Canada each summer and Appalachian Trail hikes and visits to farms on the weekends. The tent shook as we played monkey pile, a game where I wrestled with the children and tickled them until they giggled themselves speechless. The children loved camping, and I made up crazy bedtime stories about a pirate named Cinco Grumpy and his brother Buffalo Grumpy who rode a horse named Snapping Pony. Sara and Claire attended Stoneleigh Elementary, played on recreation league soccer teams, and greatly enjoyed the synchronized swim program at the community pool. Mary always played the major role of parent. She organized an aluminum-recycling program for the elementary school and volunteered to teach science to the children at Stoneleigh. She made friends with the McKnights, a neighboring family with three children close in age to our own. I met the father, Steve, at a neighborhood function when Claire pointed him out as “Gracie’s Dad.” Steve had done pioneering work on DNA transcription factors and had already established himself as a major figure in molecular biology. I was inspired to join his lab at the Carnegie Institution as a sabbatical worker for the 1988-1989 academic year. This proved to be enormously productive – I learned DNA technology and made a worthwhile contribution to the understanding of transcription factor-DNA interactions. By coincidence, another child was born to each family in 1989 – Johnny McKnight and Anne Carlyle Agre (Carly).  **Discovery of the aquaporins and growth of our children** Upon returning to our lab, I felt that we should explore the 28 kDa protein further. Barb and postdoctoral Fellow Brad Denker worked to develop a simple method for purifying the 28 kDa protein from the membranes of human red blood cells based upon its relative insolubility in N-lauroylsarcosine, a detergent that extracted the other membrane proteins. The 28 kDa protein was found to be amazingly abundant in red cell membranes (approximately 200,000 copies per cell) and behaved physically like a membrane-spanning homotetramer. Other scientists had failed to observe the protein because it did not react with the usual protein stains. The 28 kDa protein was astonishingly abundant in renal proximal tubules and in thin descending limbs of the loop of Henle. Determination of the N-terminal sequence of the purified protein showed it to be related to a series of proteins from diverse sources – lens of cow eye, fruit fly brain, bacteria, and plants.  These clues intrigued me. I wondered if the 28 kDa protein might be some sort of channel. I discussed the protein with numerous scientists who were as puzzled as I and who could not provide any insight. In April 1991, we stopped in Chapel Hill while returning from a camping trip to Florida – a compromise vacation during which we took the children to their choice of park (Disney World) and our choice (the Everglades). I visited Vann, who had joined Duke as a Howard Hughes Investigator. I then dropped by UNC to visit John Parker. Although it was late in the afternoon, and he was visibly tired from a long day in the clinic, John sat quietly as I described the mysterious 28 kDa protein. After listening thoughtfully, John leaned forward in his chair and suggested that the protein might be a channel for water – something he stated that physiologists regarded as controversial since no one had ever been able to define the molecular identity of such a protein.  John’s idea yielded the breakthrough that opened a new field. Greg Preston, a Postdoctoral Fellow with strong molecular biological experience, cloned the cDNA for the 28 kDa protein. We were also extremely fortunate to have Bill Guggino, Hopkins Department of Physiology, as a collaborator. Greg expressed the protein in frog eggs isolated from *Xenopus laevis* – a useful expression system known to have low water permeability. Greg tested our hypothesis on October 9, 1991. Although the oocytes expressing the 28 kDa protein and the control oocytes looked the same, when he transferred them from isotonic solution to distilled water, an amazing difference was immediately obvious – all six control oocytes were unaffected whereas all six 28 kDa oocytes immediately exploded like popcorn. Greg ran into my office almost speechless, and we both celebrated with joy. We knew from the first experiment that the 28 kDa protein conferred water permeability and must be the long-sought water channel.  **Professional fulfillment and home front amusements** Our lab had always refrained from keeping our studies secret. We openly shared the information of our studies with Joseph Handler and his group in the Hopkins Nephrology Division. Joe considered this a major breakthrough and congratulated us; however, he warned me to publish the information as soon as possible. He was aware of other scientists with large groups who were attempting to isolate or clone the putative water channel. Word got out quickly, and within a month investigators from high-powered laboratories in the U.S., Japan, and Europe requested our plasmid and information about our studies. Intensely nervous, Greg and I worked through the Christmas holidays in marathon sessions to perform every conceivable control.  We submitted the paper on February 4, 1992, but I lay awake at night worrying that my openness would cause us to be scooped. My departmental chairmen Jack Stobo, Department of Medicine, and Tom Pollard, Department of Cell Biology/Anatomy, reassured me that we had taken the ethical high road and would not be denied credit for the discovery. I subsequently learned that other groups had immediately focused all their attention on the 28 kDa protein after hearing about our unpublished observations. We succeeded in attaining priority when our paper was accepted for publication in the April 17 issue of *Science*. Greg was selected to present the study as a plenary lecture at the American Society of Clinical Investigation. Several colleagues joined us for lunch before Greg’s talk, and the name “aquaporin” emerged. We all agreed that it was perfect, and our 28 kDa protein became officially designated as AQP1.  We initiated a series of collaborations with laboratories outside of Hopkins, and these scientists soon became close friends of my lab and family. The collaborations yielded a rich set of studies that catapulted us into prominence within the membrane transport field. Mark Knepper, at the NIH Laboratory for Kidney and Electrolyte Metabolism, introduced us to his junior colleague, Søren Nielsen, at the University of Aarhus, and his former mentor, Arvid Maunsbach. With Søren in the lead, we defined the sites of expression of AQP1 in kidney, brain, capillaries, and other tissues by high resolution light microscopy and immunogold electron microscopy. Using AQP1 protein that Barb Smith purified to homogeneity, our collaborators Mark Zeidel at Harvard and Suresh Amubudkar at Hopkins defined the biophysical functions of AQP1 reconstituted into synthetic liposomes. Ueli Aebi, a former Hopkins colleague, introduced us to Andreas Engel at the M.E. Müller- Institute at the Biozentrum of the University of Basel in Switzerland. Andreas and his grad student Tom Walz prepared membrane crystals containing our highly purified AQP1 protein and determined the structure by negative staining electron microscopy, atomic force microscopy, and electron crystallography.  The next two years (1992-94) proved critical to my academic development and our laboratory’s research. My lab had temporarily resided within the Cell Biology Department, but when space constraints emerged, we were faced with the need to relocate. This was not initially popular with our team, and signs emblazoned “Hell No – We won’t go!” appeared in the lab. Fortunately, Dan Lane, Chairman of the Department of Biological Chemistry, offered me the lab once occupied by the renowned biochemist, Albert Lehninger. This was a godsend, and I have held a faculty position in the Department of Biological Chemistry ever since. Promotion to full professor came in 1993. Also at this time, I assisted Tom Pollard in the launching of a new Ph.D. graduate program. With funding from the Markey Charitable Trust, the Johns Hopkins Graduate Program in Cellular and Molecular Medicine (CMM) was initiated to permit talented students in the laboratories of clinical and basic science departments to attain fundamental research skills and in-depth understanding of clinical diseases. Our first students matriculated in September 1994.  These years brought the realities of adult life. Mary was always very close to her father, but his health had declined and he died at age 81 while we were on a camping trip in California. Rather than returning for his funeral, we joined with the children in a special Jamie-remembrance at our campsite at Yosemite. John Parker was tragically stricken with a malignancy and died soon after at age 58. My father had been diagnosed with prostate cancer and succumbed at age 82. Mary and I both became the senior generation of our families. Fortunately, Mary’s sister Sally moved nearby and added immensely to our lives and the lives of our four children. Sara and Claire became artists and scholars in high school. Clarke became a Cub Scout. Carly enjoyed special status as the “baby of the family” and kept us all amused with her wacky sense of humor. Sometimes her siblings teased Carly too much. The children all enjoyed our family dogs – especially when they misbehaved, but Carly experienced an emotional meltdown when Sara once misinformed her that the rabbit that our dog had killed was the Easter Bunny!  **Getting the word out – a scientific itinerant** The decade of 1994-2003 proved exhilarating but exhausting. We continued at a fast pace in our own laboratory and in key collaborations with outstanding laboratories in Europe; together we generated more than 100 publications. Of these, a few stand out in my mind as particularly notable achievements.  The structural studies begun with analysis of recombinants in our lab by Greg Preston and Jin Sup Jung led to proposition of the hourglass model – a unique structure with four subunits each containing an individual aqueous pore formed from two hemi-channels oriented at 180° to each other that overlap within the bilayer. The electron crystallographic studies with Andreas Engel were expanded to include Yoshinori Fujiyoshi and his group in Kyoto. These studies of biologically active membrane crystals revealed electron densities at 3.8 Å, and merging with the recombinant studies yielded the first high resolution structure of a human membrane channel. X-ray crystallography and molecular dynamics simulations by other scientists soon advanced the structure further.  The identification of humans lacking AQP1 protein resulted from co-localization of the structural gene with the Co blood group antigens on human chromosome 7 by Chulso Moon and demonstration of the Co polymorphism by Barb Smith and Greg Preston. Co-null individuals are extremely rare, and knockout mutations were identified in the gene encoding AQP1 (hence, AQP1-null). Although AQP1-null individuals are extremely rare, they feel perfectly well. Nevertheless, definitive studies by Landon King elucidated a major defect in renal concentration after thirsting and a marked delay in vascular water permeability.  Cloning the AQP4 homolog in brain by Jin Sup Jung led to a major new chapter in the recognition of water transporters at the blood brain barrier by Søren Nielsen and Ole Petter Ottersen. The structural basis of AQP4 localization resulted from a pivotal observation by John Neely and led to the recognition by Mahmood Amiry-Moghaddam that AQP4 contributes detrimentally to the onset of brain edema.  AQP5, the aquaporin from secretory glands, was cloned by Surabhi Raina and was shown by Landon and Søren to have unique distribution in glands and alveolar pneumocytes. While multiple clinical roles are anticipated, functional demonstration of AQP5 in sweating may have profound relevance to body temperature regulation. AQP6 was shown by Masato Yasui to be unique amongst aquaporins in that it freely transports anions within acid secretory cells of renal collecting ducts. Experiments by Jen Carbrey and Dan Gorelick predict that AQP9 is essential for conversion of glycerol to glucose in liver during starvation. Barry Rosen and his group at Wayne State identified arsenite transport through AQP9, thereby explaining the hepatotoxicity of the compound. Multiple studies by Giuseppe Calamita, Melanie Bonhivers, Jen Carbrey, David Kozono, Mario Borgnia, and Eric Beitz have documented fascinating roles for aquaporins in micro-organisms.  The astonishing interest in our work demonstrated by groups throughout the U.S. and abroad provided a direct means of showcasing the efforts of our young scientists and collaborators. During the decade, I undertook an extensive series of lecture trips, making over 250 presentations at universities, institutes, and scientific meetings on five continents. While the opportunity to speak directly to scientists around the world was important to establish visibility for the aquaporin field, the chance to meet and encourage hundreds of students and postdoctoral fellows was a most wonderful experience, since these young people represent the future of science.  Our family life accommodated my extended absences. We undertook special family wilderness camping trips and each child accompanied me on some of the international travels. However, missing birthday celebrations, anniversaries, and graduations is something I am not proud of. Nevertheless, all members of the family have done very well. Sara graduated from Colgate University and is an administrator at the University of Virginia in Charlottesville. Engaged to Jason Watson, we look forward to her wedding this coming summer. Claire graduated from Duke University and taught science to 8-yearold children in Italy. She is now studying landscape architecture at Harvard Graduate School of Design in Cambridge. Clarke earned his Eagle Scout Award and received numerous honors for art and photography. He is a student at Hampshire College in Amherst MA. Carly sometimes expresses dismay for being the only child left at home, but her interests in wilderness adventures and studio arts follow the interests of her siblings. Mary took graduate school courses in education and became a pre-school teacher. When we share observations, it is clear that her 3-year-old pupils bite each other more often than my 25-year-old graduate students do, but the difference is quantitative and not absolute.  **“It’s unbelievable”** Prior to the acclaim resulting from the aquaporin studies, my greatest academic recognition was the 1991 Young Investigator Award from the Eastern Section of the American Federation of Clinical Research. The presentation at a small meeting in New York City was delightful. My children, however, concluded that I, at age 42, must be “the world’s oldest young investigator.” Although I never considered myself a physiologist or a nephrologist, scientists in those fields generously embraced our studies on aquaporins and showered our lab with accolades including the 1999 Homer Smith Award. The international recognition of our work was made shockingly real when I received an invitation to present the aquaporin story as part of the Jubilee Symposium in Stockholm preceding the 100th anniversary of the Nobel Prizes in December 2001.  The possibility that I might someday actually win a Nobel was raised by my father during his terminal illness. Not being superstitious, I chose to disregard the notion, but pleasant Nobel daydreams must occasionally enter the minds of many scientists. It became a vivid reality when the phone rang at 5:30 a.m. on October 8, 2003. The Royal Swedish Academy of Sciences and the Nobel Chemistry Committee awakened me with extraordinary news. A deluge of journalists descended upon our house, and only with difficulty was Mary able to contact my mother to share the news. Consistent with her modest Scandinavian farming origins, she responded calmly, “That’s very nice, but tell Peter not to let it go to his head.” When I arrived at the laboratory, celebrations had already begun. The telephone message system had filled up, but the excited voice of my Norwegian colleague was special. “Peter, Peter, we just heard the news. It’s unbelievable!” Then, after a short pause, the voice returned. “I mean it’s very believable, but it’s wonderful!” Within the next few days, I was contacted by hundreds of scientific colleagues, relatives from the U.S. and Scandinavia, friends from childhood, classmates from grade school through medical school – many whom I had not seen in years. For me, the chance to renew these bonds is perhaps the best part of winning a Nobel Prize. |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** |  |
| **Interview** |  |
| Q2 | **What would you say about this styles of doing science?** |
|  | Peter Agre: Well there are different styles and there are different types of discoveries. There is an incremental advance in an area. It’s been said that hypothesis has driven research is greatly overrated. I think [Al Gilman](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1994/gilman-facts.html) said that. But you have to have a hypothesis in order to go to work. We don’t just randomly do things. Rod said a random walk with a purpose. But that’s where science stops engineering, because the engineer has a goal. He has to build the bridge at this location. He’s not out there to look for landscaping or for archaeological sites. He has a goal. And that must be achieved. But in science we purposely pursue goals. We have meaningful objectives we want to achieve. But the discoveries sometimes discover us.  The unforeseen like Rod says talk to your experiments or let your experiments talk to you because you can force things out and that’s usually predictable science. But the big breaks in sciences have always been the unpredictable events. And [Alexander Fleming](https://www.nobelprize.org/prizes/medicine/1945/fleming/facts/) had a Petri dish that was uncovered and a mould happened to land on it and killed the bacteria. That was an unpredicted event. That was a big discovery. |
| Q4 | **What about aquaporins, your discovery?** |
|  | Peter Agre: In our case I consider the aquaporins was what I consider a real discovery because we were doing I thought very knowledgeable and a logical approach to studying the human RH blood group antigen and red cells. I’m a blood specialist in my earlier career. And we found something that didn’t fit and it turned out to be unrelated and had some curious properties. And we were given enough free time – the demands at being an administrator at that point in my career was smaller – and we let the experiments talk to us. It was extremely abundant red cells. No one had ever seen it before. Wasn’t supposed to be there. And I like to tell people it’s like driving in a remote area of Northern Sweden and you come across a city of 200 thousand people that’s not on the map. It gets your attention. And so this was the discovery. Then we figured it out. But it was not part of my life plan. It’s probably much better than it would have been if I had a life plan. |
| Q18 | **What would you say about the relation between science and society?** |
|  | Peter Agre: I think science owes a lot to society but society owes a lot to science. To be a scientist we’re doing research activities in laboratories that are very expensive. To have staff, time in the synchrotron, laboratory space in New York City you know we’re talking about enormous amounts of money but society chooses to do that. The poor countries in the world have no choice. They cannot pursue discovery level science in poor countries. And the people from those poor countries who are creative and inquisitive end up leaving and coming to place like Sweden, Western Europe, the United States. We happen to be lucky in that we were born in the US where all these things were made available by society. The taxpayers’ dollars. But in return we need to be thinking of things that are not only fun for us to do. That’s where Huckleberry Finn ends. Things that are actually good for people. You don’t always know immediately what will be good or how good it will be.  Two of my professors when I was a medical student, [Dan Nathans](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1978/nathans-facts.html) at Hammersmith won the Nobel Prize 25 years ago this week for the discovery of the restriction enzymes. The enzymes that cut DNA which permitted this whole revolution in biology to occur. But when they first discovered it was a bacterial protein that cut up some viral DNA samples. It seemed very basic. They used it practically and in a limited manner. And they knew they would be important. But they weren’t running off saying this will lead to breakthroughs in cancer, and gene therapy which of course they have. So I think we need to provide things to society that are worth wile. But I don’t think we should worry minute by minute how will the structure of the potassium channel lead to an improved society or will the water channel proteins be immediately useful. There are many discoveries that are very important for which we still haven’t been able to use it too well. I think an example that I share with the medical students is the discovery of sickle cell haemoglobin by [Linus Pauling](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1954/pauling-facts.html) in 1949. Fundamental advance. We could understand what causes this horrible disease but we still can’t treat it well. |
| Q18 | **Do you think that scientists should be kept responsible for the applications of their results?** |
|  | Peter Agre: Responsible in the sense that they have a mission that they need to convey. And I suspect one of the reasons that Rod and I are here in Stockholm this week is not to pat ourselves on the back for being good scientists and making important things but to share the love of science and to encourage young scientists. Frankly in terms of my work in the water channel proteins, the aquaporins, I think what we’ve done is the easy work. We’ve discovered something that most people didn’t believe. We know they’re important, but how can we use that? How can we apply that to improve the lives of people? To improve the agricultural output for countries where people are living in hunger. I can’t take full responsibility for that. I do take responsibility for sharing the level of this and exciting the young people and challenging them to step up. They’re the ones who are going to do the next level of research. They’re the future of science.  Roderick MacKinnon: I agree and I would say that scientists have to act responsibly in the way they do science. In other words not be doing experiments that are of immediate obvious danger to themselves or people around them. But at the same time I wouldn’t say that scientists before doing experiments should try to think ahead of all the possible applications to decide whether or not they should do that experiment. I think the reason for that is that none of us are smart enough to think that far ahead. We can all think of examples of things, discoveries that have been used for very good purposes and for very bad purposes. I think scientists shouldn’t be making this decision before they do experiments. We should be curious and trying to discover the world around us and responsible in the way that it would be very special if we can point some of our work in some way to application. Wouldn’t that be wonderful? After all it would be fantastic to be able to help people.  Peter Agre: I think often times others will see the usefulness of the discoveries we’ve made and designing inhibitors of ion channels. It’s probably not something that will come from your lab.  Roderick MacKinnon: Probably not.  Peter Agre: But they’re going to be following the information that you’ve discovered and the coordinates that you’ve established and in that way I guess we do contribute to the next step. We have to report accurately what’s there. I think at this point a lot of what we should be doing is exciting others that this is important.  Roderick MacKinnon: I couldn’t agree more. |
| Q15 | **If you could dream about the application of aquaporins for example, what would this be?** |
|  | Peter Agre: There are a lot of things I would dream for. If I had to pick one I would hope that the aquaporins present in the malaria organisation would be useful drug targets because this is a horrible disease, malaria. Three million children die every year in Africa of malaria. And the current drugs are no longer so useful. Not that they’re expensive but the organism is becoming resistant. We need new ideas. That’s one thing that I could dream of I would dream for that. |
| Q9 | **I know that you’re engaged in social and political activities outside science. Can you tell us what you’re going to do with part of your Nobel Prize money?** |
|  | Peter Agre: They asked me that the morning of the announcements and I have been involved in some human rights activities. This is not a major issue in terms that I’ve quit my day job, but I have been very concerned. There is a community in the National Academy of Sciences of Human Rights which I’ve participated in. [Torsten Wiesel](https://www.nobelprize.org/prizes/medicine/1981/wiesel/facts/), originally here from Sweden is the Chair of that. In particular I have been very active in the case of Thomas C. Butler, an American scientist who’s facing life in prison from having lost some samples from his laboratory and consequences of that which I feel our government has unfairly presented and manipulated. Butler by the way has strong Swedish roots. His wife Elizabeth is a Stockholm university graduate. He himself was a sabbatical worker at Karolinska and I knew him as a student. He’s a very fine person. It’s impossible not to become active in that. We’re supporting his legal defence fund as much as we can and we hope others will as well. |
| Q10 | **It sounds wonderful. How do you keep such a heterogenic group together?** |
|  | Peter Agre: Well that’s the interesting thing it just happens. The best people you’re not trying to track them down and drag them to the labs, they actually want to come and work in the laboratories. They apply. They ask is it possible I can work in your laboratory. I can’t imagine more flattery than that.  Roderick MacKinnon: It’s true. I have somewhat of a system where when somebody applies if things look right and they seem enthusiastic in their application I then invite them to the lab for a day. I talk to them. Just talk about science. And then they give a little talk to the lab. Then they go around and talk to everybody in the lab who tells them all about their projects so they can learn about the lab and then we go out to dinner as a big group and we all have a big dinner at some restaurant in New York. Then they stay over. Then we say goodbye and they leave the next day. We get together and say what do you think? |
| Q10 | **What about the competition within this group?** |
|  | Roderick MacKinnon: You have to make sure people are not working on the same thing. At least if things are related they know what their boundaries and what is theirs because people will do the best work if they feel they’re doing this as part of them. They want to make it beautiful. So you have to make that clear that people know what is coming from their mind and from their efforts.  Peter Agre: I think competition within the group is a big problem in some labs. Avoiding that is essential. I think when the young people enjoy each other they help each other a lot. Just like brothers and sisters will help each other. The parents are there. They set out the guidelines. But I learned a lot of things from my brother growing up but my father and my mother really weren’t concerned about. Couldn’t advise me. The teams are like that. If there is a sibling rivalry that can be disruptive. I don’t think you see that in the better labs.  Roderick MacKinnon: But if you keep objectives, even if they’re related, if you keep the main objectives separate in what people want to pursue. If two people come in and say they want to work on the exact same thing you say no. If somebody came to me and said I want to work on this but somebody is working on it I would say that’s a very good idea but you know somebody in my lab is working on that. And you can talk to them about it. And anybody who wouldn’t understand that you wouldn’t want to be working with anyway. And so what happens in terms of when somebody’s project really starts to work. It’s taking off. For example they finally get to diffract the crystals and getting a structure everyone else in the lab gets so excited. It revs them up. They’re excited for that person and they’re also more energised about their own project. It just happens. |

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| **Chemistry\_2024-2000** | |
| **ID** | 0355 |
| **Biographical** | I was born on February 19, 1956 in the middle of a snowstorm. It remains one of those humorous family stories that my mother likes to tell. My father the planner had rehearsed the way to the hospital but apparently things looked a lot different at night in a blizzard. Eventually they made it and so did I, the fourth of seven children. My father was a postal worker when I was very young but studied computers and became a programmer on the big IBM main frames. My mother worked as a part time schoolteacher, but mostly took care of the children at home. Thinking back on it now I know we did not have much money but I never knew that growing up. My parents provided a happy environment and made their expectations clear to us. Television is bad for you, reading is good for you, and you better get an A for effort in school. What you end up doing in life is up to you. Just make sure you enjoy what you do because then you will do it well. We all pursued completely different walks of life. I became the scientist.  I suppose there were some early indications of my tendency to a life of curiosity. Apparently from a very young age I had a habit of asking lots of questions: ‘what would happen if?’ was a favorite. And I liked having facts straight and knowing how things work and did not hesitate to give explanations to those around me, apparently to an annoying degree sometimes. I remember one day my father, at the end of his patience, commenting that I was a ‘compendium of useless information’. I certainly can understand his plight with one of the seven having way too many questions and answers all the time. On the positive side, I learned a new word that day when I looked up compendium in the dictionary.  There were probably even indications that my curiosity might be scientific. Burlington Massachusetts was rural when I was young and I loved to roam and explore. I had rock collections and read children’s books on geology and the history of the earth. I made little volcanoes out of plaster of paris and added baking soda and vinegar to the craters to simulate volcanic eruptions. I had an accident one day that made my mother laugh to my utter frustration: at that young age I failed to appreciate the humor in a little boy telling his mother he had dropped a volcano on his toe! In the summer I collected butterflies, turtles, snakes and other living things. One summer my mother enrolled me in a science enrichment class for elementary school students and I was allowed to take home a microscope. I used it to look at everything I could find: microorganisms from the nearby pond, leaves and blades of grass. I spent hour after hour alone, mesmerized by the tiny little things that I could see.  My scientific curiosity took a back seat to athletics through junior high and high school. Gymnastics was a good match to my small build and to my solitary nature. I was a member of a team but gymnastics is an individual sport. You learn a technique, then a ‘move’, and then a ‘routine’. And then you perfect it through practice, working mostly alone. I had a very good no nonsense teacher, coach Hayes, who really instilled in me the idea of perfection through practice. I was actually not all that bad, particularly at floor exercise and high bar. I even considered pursuing gymnastics in college, but during my final year of high school I began to wonder what I should pursue for a career.  I attended the University of Massachusetts in Boston for one year and then transferred to Brandeis University. Brandeis was an eye opening experience for me. For the first time in my life I was in a seriously intellectual environment. The classes tended to be small, intense, and stimulating. I discovered that I had a passion for science, and that I was very good at it. I chose Biochemistry as a major and a newly arrived assistant professor named Chris Miller for my honors thesis advisor. He had a little laboratory with big windows and lots of light shining in. I studied calcium transport and learned about the cell membrane as an electrode. I could see that Chris Miller was a man having lots of fun in his daily life and it was inspiring to me, and the memory of this stayed with me. But the biggest influence Brandeis had on my life happened in Physics class. There I met my future wife Alice Lee, whose sparkling eyes and sharp mind caught my attention.  Against Chris Miller’s advice I went to medical school after Brandeis. I studied at Tufts University School of Medicine and then at Beth Israel Hospital Boston for house officer training in Internal Medicine. I learned a lot but in the end I should have taken Chris’ advice to pursue science. Medicine required a lot of memorization and little analytical problem solving. To keep a certain part of my brain active I began to study mathematics, and continue this even today, learning new methods and solving problems with the same disciplined approach I had learned in gymnastics. I started back to science near the end of house officer training working with Jim Morgan studying calcium in cardiac muscle contractility, which was very enjoyable and kept me connected to medicine. But I had a yearning to work on a very basic science problem, which meant I would have to break my medical ties. This was a difficult decision because I had invested so many years in medical education; to abandon it was to admit to myself that I had misspent a big piece of my life. And there were practical considerations as well. It was time finally to get a permanent job; after all, my wife Alice had supported me through years of training. Not to mention I was nearly 30 years old with no real basic science training beyond my Brandeis undergraduate education: would I even be able to make it as a scientist?  Two factors had the greatest influence on my decision. Back in my first year of medical school I lost my sister Elley, an artist only two years my senior. Diagnosed with leukemia during my hematology clerkship as I learned about the dreaded disease, she lasted only two months. This horrifying event impressed upon me how fragile and precious life is, and how important it is to seize the moment and enjoy what you do while you can. I remember thinking when I look back upon my life at the age of seventy, thirty will seem young: just go for it. And the second factor was Alice. She had complete faith in my ability to succeed. Never mind that postdoctoral studies meant a reduction of my already piddling house officer salary. She simply said you have no choice; we will manage somehow.  Memories of Chris Miller’s laboratory beckoned so I returned for postdoctoral studies. Of course I will never out live his reminding me that I should have listened to him in the first place. Feeling far behind in my knowledge I approached my postdoctoral studies with intensity, learning techniques and theory. I felt I should be an expert in electrochemistry, stochastic processes, linear systems theory, and many more subjects. I read books, solved the problem sets, mastered the subjects, and carried out experiments. I had the very good fortune of a coworker Jacques Neyton, a postdoctoral scientist from France. Jacques is a very critical thinker who would brood on a problem. We exchanged ideas often. When I would tell him one of my ideas he had a tendency just to listen quietly. Then, after a while, if his response started with ‘Hey Roddy, there’s something I don’t understand’ I knew I was in trouble – my idea was probably no good!  After I completed a series of biophysical studies on K+ channels it came time to apply for an academic position. During the late 1980s physiology departments were more interested in hiring channel gene cloners than bio-physicists. But Peter Hess convinced his colleagues at Harvard that my work showed promise and I was offered an assistant professorship there. My laboratory made good progress on K+ channels. It was exciting for a while but in just a few years I began to feel that the return on what we could learn from studying the functional effects of mutations was diminishing. We had identified the K+ channel signature sequence, but without knowing its structure we never would understand the chemical principles of ion selectivity in K+ channels. I decided at that point to learn X-ray crystallography to someday see a K+ channel.  I began to learn methods of protein purification and X-ray crystallography while still at Harvard, initially working with channel toxins and a small soluble protein called a PDZ domain. However, I thought it best to move away from my familiar environment at Harvard to pursue channel structure. There were really two reasons motivating me to move. First was the practical issue of obtaining funding to work in an area in which I had no background: start-up funds associated with moving to a new university would be useful for this purpose. The second and far more important reason was that moving would enable me to immerse myself completely in the new endeavor. A change of environment would remove the distractions of everyday life, isolate me from the temptation to fall back on channel physiology studies that I was already good at, and allow me to focus with singular purpose on the structural studies. I needed this to become an expert in membrane protein biochemistry and X-ray crystallography, and to develop a ‘feel’ for protein structure. When the president of Rockefeller University [Torsten Wiesel](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1981/index.html) heard about my scientific plans he suggested that I move to Rockefeller University and I did. Rockefeller provided a wonderful environment for concentrating on a difficult problem.  It has been said that giving up my already successful lab at Harvard in order to pursue the structure of a K+ channel was a risky thing to do. At the time I was told that my aspirations were altogether unrealistic. From my perspective I had little choice because I wanted to understand K+ selectivity and I knew that the atomic structure provided the only path to understanding. I would rather fail trying than never try at all. It helped that I was accustomed to making transitions and had become good at teaching myself new subjects. I have to admit that few people working with me at the time wanted much to do with the new endeavor – only one new postdoctoral scientist Declan Doyle was enthusiastic. My wife Alice, an organic chemist, saw that I was going to be pretty lonely and decided to join me in the lab. And to my good fortune she has worked with me since. I have learned that most people do not like change but I do. For me change is challenging, good for creativity, and it definitely keeps life interesting.  I think of the past eight years of my life in New York at Rockefeller University as a personal odyssey. The new laboratory started out very small, with only Declan, Alice and me. But it grew in the first year with the addition of other enthusiastic postdoctoral scientists, including João Morais Cabral and John Imredy. Working with membrane proteins was very difficult as expected. We had our periods of despair, but every time we felt left without options something good happened and despair gave way to excitement. Persistence and dedication eventually paid off. The atomic structure of the K+ selectivity filter was more informative and more beautiful than I ever could have imagined. My laboratory now is an incredible place, overflowing with excitement and ideas sustained by the continual infusion of bright young scientists who come from around the world to work with me. It gives me great satisfaction to know that these young scientists who are sophisticated in their knowledge of protein chemistry and structure will lead the field of ion channel research into the future. This has been a wonderful adventure. I owe thanks for the life I have: to Alice, to all my loving family of MacKinnons and Lees, to my scientific family of students, postdocs and colleagues, to senior colleagues who have helped me along my way to pursue my passion, and to the Rockefeller University, the Howard Hughes Medical Institute, and the National Institutes of Health for their support. I am very thankful for my life as a scientist, for the opportunity to understand in some small way the world around me. I hope my best experiment and scientific ideas are yet to come. This hope keeps me going. |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** |  |
| **Interview** |  |
| Q17 | **Welcome to the Nobel E-Museum and also to this interview, Professor Peter Agre and Roderick MacKinnon. I would like to congratulate you to the Nobel Prize. It’s a prize of the scientific community to the most prominent scientists in the community, I would say. And I would like you to tell us: What is it like to be a scientist? Professor MacKinnon?** |
|  | Roderick MacKinnon: I always say to my students that being a scientist is like being an explorer and I really mean that, because in a sense I think in science we explore the world, the universe around us. Some people look at big things and other people look at very small things, but in a sense we’re all trying to understand the world around us. In a sense we’re looking in little corners and places that nobody has ever looked before. And that’s a lot of fun. We go to work and we have problems that we’re interested in.  And when I say we, from my kind of work, I run a laboratory and that means there are people who have come to the laboratory to work with me because they’re interested in the same problems. It’s like a family, if you will, interested in problems. And we get excited about things and we figure out how to do experiments to test them. |
| Q2 | **How do you make a discovery actually?** |
|  | Roderick MacKinnon: I think different discoveries happen in different ways. A lot of them happen because, you know, most of them … It’s a good question because a lot of times, at the end of something when we’ve finally shown something, like there is a beautiful structure here that does a certain thing and people look at it and say Oh that’s very beautiful. Have you thought of this, and it led to this … but often times actually what happens is you have this idea and you start to pursue it. It’s in an area. And then you think you know how something works, so you do tests. And actually you find out what you thought was wrong. |
| Q18 | **Do you think that scientists should be kept responsible for the applications of their results?** |
|  | Peter Agre: Responsible in the sense that they have a mission that they need to convey. And I suspect one of the reasons that Rod and I are here in Stockholm this week is not to pat ourselves on the back for being good scientists and making important things but to share the love of science and to encourage young scientists. Frankly in terms of my work in the water channel proteins, the aquaporins, I think what we’ve done is the easy work. We’ve discovered something that most people didn’t believe. We know they’re important, but how can we use that? How can we apply that to improve the lives of people? To improve the agricultural output for countries where people are living in hunger. I can’t take full responsibility for that. I do take responsibility for sharing the level of this and exciting the young people and challenging them to step up. They’re the ones who are going to do the next level of research. They’re the future of science.  Roderick MacKinnon: I agree and I would say that scientists have to act responsibly in the way they do science. In other words not be doing experiments that are of immediate obvious danger to themselves or people around them. But at the same time I wouldn’t say that scientists before doing experiments should try to think ahead of all the possible applications to decide whether or not they should do that experiment. I think the reason for that is that none of us are smart enough to think that far ahead. We can all think of examples of things, discoveries that have been used for very good purposes and for very bad purposes. I think scientists shouldn’t be making this decision before they do experiments. We should be curious and trying to discover the world around us and responsible in the way that it would be very special if we can point some of our work in some way to application. Wouldn’t that be wonderful? After all it would be fantastic to be able to help people.  Peter Agre: I think often times others will see the usefulness of the discoveries we’ve made and designing inhibitors of ion channels. It’s probably not something that will come from your lab.  Roderick MacKinnon: Probably not.  Peter Agre: But they’re going to be following the information that you’ve discovered and the coordinates that you’ve established and in that way I guess we do contribute to the next step. We have to report accurately what’s there. I think at this point a lot of what we should be doing is exciting others that this is important.  Roderick MacKinnon: I couldn’t agree more. |
| Q15 | **Do you have any such dreams?** |
|  | Roderick MacKinnon: Again it would be a case of others applying the work. That we reach a level where we can alter the function of channels and I’m sure structure should help in being able to modify compounds to do that in ways that will help conditions that afflict people. |
| Q10 | **How do you keep such a heterogenic group together?** |
|  | Peter Agre: Well that’s the interesting thing it just happens. The best people you’re not trying to track them down and drag them to the labs, they actually want to come and work in the laboratories. They apply. They ask is it possible I can work in your laboratory. I can’t imagine more flattery than that.  Roderick MacKinnon: It’s true. I have somewhat of a system where when somebody applies if things look right and they seem enthusiastic in their application I then invite them to the lab for a day. I talk to them. Just talk about science. And then they give a little talk to the lab. Then they go around and talk to everybody in the lab who tells them all about their projects so they can learn about the lab and then we go out to dinner as a big group and we all have a big dinner at some restaurant in New York. Then they stay over. Then we say goodbye and they leave the next day. We get together and say what do you think? |
| Q6 | **What about the competition within this group?** |
|  | Roderick MacKinnon: You have to make sure people are not working on the same thing. At least if things are related they know what their boundaries and what is theirs because people will do the best work if they feel they’re doing this as part of them. They want to make it beautiful. So you have to make that clear that people know what is coming from their mind and from their efforts.  Peter Agre: I think competition within the group is a big problem in some labs. Avoiding that is essential. I think when the young people enjoy each other they help each other a lot. Just like brothers and sisters will help each other. The parents are there. They set out the guidelines. But I learned a lot of things from my brother growing up but my father and my mother really weren’t concerned about. Couldn’t advise me. The teams are like that. If there is a sibling rivalry that can be disruptive. I don’t think you see that in the better labs.  Roderick MacKinnon: But if you keep objectives, even if they’re related, if you keep the main objectives separate in what people want to pursue. If two people come in and say they want to work on the exact same thing you say no. If somebody came to me and said I want to work on this but somebody is working on it I would say that’s a very good idea but you know somebody in my lab is working on that. And you can talk to them about it. And anybody who wouldn’t understand that you wouldn’t want to be working with anyway. And so what happens in terms of when somebody’s project really starts to work. It’s taking off. For example they finally get to diffract the crystals and getting a structure everyone else in the lab gets so excited. It revs them up. They’re excited for that person and they’re also more energised about their own project. It just happens. |

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| **Biographical** | My father, Herbert Bennett Fenn, the eldest of three children was born and raised on a farm in northern Delaware which his father operated but did not own. I never saw that farm but I vividly remember my Grandmother’s frequent reference to a single chestnut tree in the front yard, so large and prolific that the nuts from that one tree paid the taxes on the farm every year! My mother was the sixth of ten children in the family of John Clarence Dingman, a country doctor in Spring Valley, N.Y. whose three surviving sons also became physicians. Dad worked his way through college, graduating in Electrical Engineering from Rutgers in 1910, the same year that mother received a degree in Home Economics and Nutrition from Columbia. They were both hired by the Presbyterian Mission Board to teach at the Sheldon Jackson Mission School in Sitka, originally settled by the Russians and sometime capital (until replaced by Juneau in 1900). The Chairman of that Board told each one about the other and warned them both not to fall in love, but if they did and got married he would provide them with a house for as long as they stayed in Sitka! They did and he did, so after mother’s death in 1990 (Dad had died in 1944) we found in her papers a clipping from the Sitka paper with a photograph of the “Honeymoon Cottage”.  During a cruise in 1996 I spent a day in Sitka. The Mission School is now Sheldon-Jackson University. I visited the library, discovered a complete file of student newspapers, and found several articles about my parents! Moreover, the present Librarian was then living in the “Honeymoon Cottage” and gave me a tour so I was actually able to look out through its front windows and see the magnificent view of Sitka Bay that my parents used to rave about.  The newlyweds were very happy in Alaska and no doubt would have remained there indefinitely had it not emerged that mother would be unable to bear children except by Caesarian Section, a procedure not then available in Sitka. Determined to have a family she persuaded Dad to move back to the States where he became manager of the Metacloth Company, a small enterprise in Lodi, N.J. whose main product was cotton duck treated by immersion in a concentrated ammoniacal solution of copper hydroxide followed by a wash in acid. The deep blue “cuprammonium” solution dissolved some of the cellulose which reprecipitated during passage through the succeeding acid bath, filling the pores of the cloth enough to make it “water resistant” but not “water-proof”. Residual copper provided a characteristic blue-green color along with a high resistance to attack by micro-organisms and white ants. For these reasons, “Metacloth” was in fairly steady demand for tents and tarpaulins in tropical latitudes. My abrupt introduction to “chemistry” occurred on one of the treasured Saturdays when Dad took me to the plant. Nosing around outside I lifted a small flap on the cover of a large tank half full of cuprammonium solution. I still recoil at the memory of that ammoniacal, and demoniacal, assault on my eyes and nose. It was a startling revelation on how and why a whiff of smelling salts can often revive people from a dead faint!  Our home was in Hackensack, N.J., next door to Lodi and County Seat of Bergen County. I was born in New York City in 1917 and three plus years later my brother Norman arrived in Paterson, N.J. where two of mother’s brothers were surgeons. The Metacloth company was sold in 1926 and Dad was unceremoniously dumped by the new owners. He was not a vindictive man but he got no little satisfaction out of the several occasions in the next two years when his help was needed in overcoming mistakes made by the new management. Meanwhile, approaching fifty and finding equivalent jobs scarce, he was paying the bills by working as a draftsman at the Fokker Aircraft Company in Teterboro, N.J. The value of having a trade as back-up for a profession was an enduring object lesson for a youngster on the eve of the Great Depression but there was for him a far more exciting consequence of the Fokker connection. When Lindbergh’s “Spirit of St. Louis” was shipped back from Paris after its famous flight across the Atlantic, it was parked for a time in a hangar at the Teterboro airport. The thrill of a lifetime for a ten year old boy was when his Dad took him into that hangar where he was allowed to sit in the cockpit and move the controls, pretending to be pilot of that famous plane!  Meanwhile the family fortunes were going down hill, much further than my brother and I were aware. Just before Dad lost his job, he and mother had invested their life savings in a new (for us) house that everyone insisted was worth “every nickel” of the $15,000 that it cost! Unfortunately, after we had to move and before the house could be sold the great depression had begun. No prospective buyers had enough nickels so those savings disappeared in the meltdown of foreclosure. Meanwhile, a door of opportunity had opened in Berea, Kentucky, a small community of 3500 or so inhabitants at the edge of bluegrass country some 40 miles south of Lexington and roughly halfway between Cincinnati, Ohio and Knoxville, Tennessee. The town of Berea was home for a remarkable institution known by the same name but officially entitled “Berea College and Allied Schools”. Both the community and the school had their roots in a non-sectarian Union Church founded in 1848 by John G. Fee, on a ridge of land donated by Cassius Clay, a brother of Henry Clay, the famous orator and statesman from Lexington, Ky.  Fee was a Congregational Minister from Massachusetts and a fervent abolitionist determined to provide educational opportunities for needy students, regardless of their race or creed. After decades of effort by himself and his followers his dream grew into what in 1928 comprised a coeducational student body of about 1700 divided among four schools: (1) The *Foundation-Junior-High School* with an ungraded program into which students with as little as two years of formal schooling could enroll and progress at their own rate up through the equivalent of 8th grade into a standard and accredited 9th grade curriculum; (2) The *Academy*, with an accredited curriculum for grades 10 through 12, (3) the *Normal School* with a two year program leading to a Teaching Certificate, and (4) the *College* which offered accredited curricula leading to BA degrees in the liberal arts and sciences as well as BS degrees in Home Economics and Agriculture. Mother’s sister was teaching in the College and knew that the Industrial Arts Department of the Foundation School and the Academy needed someone to teach Auto Mechanics and Practical Electricity. Dad was eminently qualified and got the job. We moved to Kentucky in time for me to enter the eighth grade in the “Training School” of Berea’s Normal School in the fall of 1928. The next fall I entered ninth grade in the Foundation School and continued on through the Academy and College.  A lot of misgivings, pain and confusion attended our passage through the newly opened door, including an automobile accident on the way to Kentucky, but life on the other side turned out to be rich and rewarding beyond what any of us had dreamed. In later years Dad and Mother both said, time and again, that losing his “good” job in New Jersey turned out to be the greatest blessing that we could have received! To this day my brother and I share those sentiments and count ourselves especially privileged to have been reared in what was a truly remarkable community. Its soul was its President, William J. Hutchins, father of Robert Maynard Hutchins, the “boy wonder” of the American education scene who became Secretary of Yale at the age of 24, Dean of its Law School at 26 and President of the University of Chicago at 30! “William J”, as the father was fondly known at his own institution, was truly one of nature’s noblemen. A striking man of vision and patrician to the core, his Berea was a singular stage on which the play was always provocative and the message meaningful. Name an outstanding man or woman of letters, the arts, science, or religion, of those days and the odds are high that he or she came to Berea to talk at one of the thrice weekly “United Chapels” for students from all schools. Attendance was required of all, and resented by most, but at my 50th class reunion there was a remarkable consensus among my surviving classmates that the community experiences of those United Chapel services were by far the most memorable and valuable components of their educational. Alas, that tradition has long since disappeared, one more victim of “students’ rights” and television. Moreover, as the public education system improved in surrounding “Appalachia”, the need for Berea’s Foundation School, Academy and Normal School faded over the years, so that the only survivor is a now a substantially larger Berea College.  A unique feature of Berea was and is a student labor program that provided much of the manpower required to run the institution. Under the supervision of permanent staff, the dining halls, dormitories, offices, and yard work were all maintained and operated by student labor. In addition were several “Industries” including a bakery, broom factory, dairy, large truck garden, sheep farm, piggery, a “woodwork department” that made fine furniture, and a weaving establishment. The normal work load was two hours a day by which a student could earn as much as half or two thirds of his or her out of pocket expenses that in the 1930’s averaged only $250 to $300 per year because tuition was free! The system was very democratic because every student was required to work at least two hours a day. A fair fraction of the student body comprised so-called half-day students who worked four hours a day, earning enough to pay all expenses. I knew students who arrived at Berea with nothing but the clothes on their backs, having dropped out of school after the second grade, and worked their way through college! It is not surprising that competition to enter Berea, especially the college, was extremely keen. In order to avoid having to reject such a large fraction of applicants, the Trustees had established a policy requiring that 85 per cent of the student body come from a region of Appalachia comprising some 500 or so counties in Virginia, West Virginia, Kentucky, Tennessee, and North Carolina. The remaining 15 percent of the students came from the rest of the world. Today’s Berea is quite a different place because the growth of alternative educational opportunities in Berea’s “Territory”, has decreased demand to the point that in 1987, at my 50th reunion, I learned there were only two applicants for every opening in the College compared to 20 or 30 in my day. Part of that decrease in demand is due to a higher level of average income in that “territory” so that fewer students can show that they cannot afford to go elsewhere, a requisite for admission.  When I graduated from the Academy in 1932 I was only 15, too young, my parents thought, to go to college, so I stayed in the Academy an extra year taking courses in mechanical drawing and shorthand. I also continued the piano lessons that I had started the year before and spent enough time practicing so that I actually gave a recital during my last year in college! Alas, whatever piano skills I had have faded until now I do well to play chopsticks with my grandchildren! When I entered College with the class of ’38 I had not decided on a major but I leaned toward a science, probably because of my long affair with the Book of Knowledge, an encyclopedia for young people which my parents bought when I was around eight or nine. During the hours that I pored over them, its 20 volumes became a well worn magic carpet to new and fascinating worlds. I’ve often quipped that “I got through college on the Book of Knowledge”, a bit of rhyming hyperbole that contains an appreciable kernel of truth.  The College required at least one course in science for all students no matter what their major. Having enjoyed my chemistry course in the Academy I enrolled in Introductory Chemistry during my freshman year. It was taught by Professor Julian Capps, the senior of the two member chemistry faculty. He was a wonderful teacher who made his subject live. I was so seduced that Chemistry became my major even though Gravimetric Analysis gave me fits in my sophomore year. I repeated the lengthy phosphorous determination on three samples each of ten unknowns before I got one set of three results with acceptable agreement! It seems ironic that mass spectrometry, the center of my scientific life for the last 20 years, is really just an exercise in gravimetric analysis!  During that sophomore year an experiment in another kind of chemistry turned out to have a big effect on my chemical education. I fell in love with a girl in the junior class. Determined to catch up with her and graduate when she did, I went to summer school in 1936 at the University of Iowa because it had a 10 week session that allowed me to earn 12 semester hours of credit in Organic Chemistry under “Uncle Charlie” Raiford, and Inorganic Chemistry under Professors Jacob Cornog and Perry Bond. All in all it was a very hot and grueling summer. The romance that had blossomed in the spring and sent me off to summer school, withered the following fall. However, because I would be within two courses of finishing my degree requirements by end of that year, my third in college, I managed to get classified as a Senior and became a provisional member of Class of ’37 at the June commencement, the objective inspired by a young man’s fancy of the previous spring. My courses in chemistry thus far had required only some facility in simple algebra. Straight A’s in all Prof. Peck’s courses in the Academy (plane geometry, advanced algebra, solid geometry and trigonometry) had excused me from freshman math in college, all that was then required for a major in chemistry.  Fortunately for my future our next door neighbor, George Bent, was visited by his brother Henry, then an assistant professor of chemistry at Harvard. When Henry discovered that I was contemplating graduate work in chemistry, having had no college math, he was aghast and spent a couple of hours impressing me with the importance of mathematics in chemistry. As a result I spent much of my third and last year of college immersed in that subject. Fortune had tossed me another favor in the form of Berea’s new curriculum based on four 9 week quarters instead of two 18 week semesters. So-called “intensive” courses met 6 hours a week for nine weeks while “running” courses met 3 hours a week for eighteen. Thus, a standard full load of l5 class hours per week comprised two intensive courses and one running course, an arrangement which I heartily endorse. One major advantage is that a student takes only three courses at any one time instead of five. It is much less distracting to be studying three subjects at a time rather than five. The particular advantage for me was that the calendar time for a three credit-hour course was cut in half so that both Course B, and its prerequisie Course A, could be completed in two nine week quarters instead of two eighteen week semesters. Thus, in my senior year I was able to take Analytic Geometry, Differential Calculus, Integral Calculus, and Complex variable, all in that same year! It was pretty heavy going, but it enabled me to survive in graduate school where I took one more undergraduate course in Advanced Calculus. The record seems to say that I have also survived after graduate school but a lack of mathematical skills has been a great handicap throughout my life.  Though I had taken part in the June Commencement exercises at Berea in 1937, I still had course requirements to complete before I could get my degree. I fulfilled those requirements at Purdue University that summer by taking Physical Chemistry with lectures by Roy Newton and laboratory under Hershel Hunt, along with a course in Chemical Microscopy under Ed F. Degering.  During that hectic last year in college I had applied to several universities for graduate study in chemistry. Yale and Northwestern responded with offers of teaching assistantships that would meet most of my expenses. I first leaned toward Northwestern but, for reasons I won’t take space to enlarge on, I finally decided on Yale. That decision delayed by half a century my meeting Malcolm Dole who in 1937 was a young assistant professor of chemistry at Northwestern. It was the experiments he reported much later (in 1968) that changed the course of my scientific life.  At Yale I found myself in a new and different world. I had done time in two much larger universities and one much smaller college but I was completely unprepared for, and awed by, the splendor of Yale’s campus. Its architectural theme has been disdainfully dubbed “Fifth Avenue Gothic” by the self-styled experts who sneer at such expensive imitation of the old world. But a wide eyed small town youth from Kentucky found it all fascinating and loved to wander around and through the gardens, gargoyles and gates that were scattered throughout the campus. To me it was rewarding recreation to discover and explore the little nooks and courtyards where one could sit in the shade of a tree completely oblivious to the cacaphony of a busy city, only a few yards away but completely shut out by the thickest walls and heaviest masonry I had ever seen. Sterling Library, then said to be the largest in the world with open stacks, became a favorite haunt where I spent many winter weekend afternoons with a good book and an apple or a candy bar. My room in the Hall of Graduate Studies looked out on a forest of chimneys, slate roofs, and Gothic towers that resembled a Hollywood version of medieval London. I ate in an elegant dining hall, complete with menus and waiters – twenty one meals per week for a now incredible eight dollars! Even so, to save money I took advantage of an option in the board contract and “signed out” every week for dinner on Friday night along with breakfast and lunch on Saturday. This “fasting” saved me $1.15 every week and probably was good for my figure! My assistantship paid a total of $850 for nine months, of which $350 went for tuition and fees. By such frugalities as the weekly “fast” I could make the remaining $500 cover most of my other expenses. My parents were horrified when they later learned of my miserly existence at Yale but I was determined to get along without their support.  On the appointed day in September the six new graduate students in physical chemistry met in Sterling Chemistry Laboratory with Professor Herbert Harned, the ranking faculty member in that subject whose colleagues included [Lars Onsager](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1968/index.html), Benton B. Owen, Rodney Smith, George Murphy, John Vance, and Gosta “Gus” Akerlof. With little or no ceremony, no introductions and no opportunity to ask questions or indicate preferences, we were assigned to advisors. I recall “Herbie” as he was known but not addressed, saying to me: “Fenn, you might as well go with Gus.” Thus, began what blossomed into a close friendship that lasted until the day Gus died, many years later, in Princeton.  The Yale curriculum for chemistry graduate students in those days was pretty cut and dried. During the first year we took four courses, spent 12 to 14 hours per week as assistants in undergraduate labs and the rest of the time getting our feet wet in the laboratory on what would become our dissertation research. At the end of that first year the faculty, on the basis of course grades and day to day observations, decided whether or not each student was Ph.D. material. Those for whom thumbs were down were given a Master’s degree and dismissed. The others continued, almost always receiving a Ph.D. after two more years. The second year was much like the first except that we took only a couple of courses and spent much more time on our research projects. At the beginning of the third year we had to take a two day written comprehensive exam. While I was a student, all who took that exam passed it so I don’t know what the consequences of failing would have been. One very big difference in the third year was that we could no longer be teaching assistants but were expected to spend full time on research. Thus, unless we were lucky enough to win one of the two fellowships available to third year students, we were on our own financially. My solution to this problem was to get married, not to my sophomore flame but to Margaret Wilson, who became supervisor of my student labor at Berea while I was working in the Registrar’s Office. She was a beautiful woman by whom I (then in the tenth grade!) was smitten the first day she started work as Assistant Registrar. Always ten years older than I she seemed to be so far beyond my reach that I never dreamed she could ever be more than the close friend and confidante that she became. I had escorted her to several events while I was in college and when I was home after I graduated. Romance bloomed while I was at Yale and she finally agreed to become my bride at end of my second year. She also became my “fellowship” during that third year at Yale, supporting us both on the 50 cents per hour she earned at various odd jobs. To this day I marvel that the daughter of a very conservative minister had the courage to ignore the disapproval of her parents and the inevitable elevation of eyebrows by everybody, everywhere, at our flagrant departure from the social norm. One of my closest friends told us decades later that he had been sure our marriage would not last more than a year or so. In fact it was not until 1992 that I lost my bride of 53 years in a New Zealand car crash. She was then 85 but looked and acted ten years younger than the husband she had “snatched from the cradle.”  The plain truth is that in matters of matrimony this society’s norms are genetically out of joint. Women on average live about ten years longer than men and yet become the wives of husbands who are several years older. That is why widows greatly outnumber widowers. Some say that this imbalance in life expectancy will be redressed as women increasingly become exposed to the stresses of employment in the workplace. I am much more inclined to believe the geneticist who told me that the female of the species lived longer than the male because she is fundamentally tougher and more resistant to the ravages of age. In choosing a mate men should follow the advice of Ben Franklin in his letter of advice to a young man on choosing a mistress. His message? “be sure she is older than you are!”  Only in choosing a graduate school did I exert any influence on the research I would do for my thesis. That influence was unwitting because I knew nothing of the faculty research interests at either Yale or Northwestern. Indeed I had only the vaguest idea of what graduate study and research were all about. Thus, I felt neither joy nor apprehension when I was summarily assigned to Gus Akerlof’s group. Most of the research by Harned and his colleagues was on the properties of electrolyte solutions, the more dilute the better. So narrow was this focus that when I left Yale I halfway believed the old cliche that “Physical Chemistry was the study of slightly contaminated water.” Gus was a bit of a maverick because he had an interest in concentrated solutions. In essence what I had to do was measure the potential difference between electrodes of silver-silver chloride and platinum-hydrogen in solutions of HCl with molalities from 0.01 to 10.0 in solvents comprising methanol in water at concentration intervals of 10 per cent from zero to ninety, at temperatures every ten degrees from zero to 50 Celsius. As I remember the total number of acceptable emf measurements was around 3000, taking into account that each measurement was made in duplicate. Thus, my routine every afternoon for most of two years was to prepare three pairs of cells with both cells of each pair containing the same solution. The cells were suspended in a large water bath or “thermostat” and allowed to equilibrate over night (i.e. with hydrogen bubbling over the Pt electrodes.) If by the next morning the emfs in each pair of cells agreed to within some forgotten small fraction of a millivolt, then I would haul some 80 pounds or so of ice from the basement to lower the bath temperature to near 273 K. The rest of the day would be spent recording emf values for all six cells at every ten K as the thermostat was heated to 313 or 323 K depending on the vapor pressure (i.e. the methanol content) of the cell solvent. All the results were fitted by least squares to a quadratic curve for the dependence of emf on concentration. The least square calculations were all carried out on a hand-cranked Monroe Calculator, except when I was lucky enough to grab the one electrically driven machine in the calculating room. Clearly, I was less than inspired by this introduction to “original research”. The experiments were a boring chore with few redeeming features. The results contained no surprises and nothing of much interest to anyone, least of all me. It was some years later before any of them found their way into the literature and then only as part of a table in a review article that Gus had been asked to write. My dissertation attested to the sterility of that project, consisting as it did of 45 pages of tables with only three pages of text! Although this first experience in “original research” shattered some illusions, my three years at Yale were a rewarding experience. I made many long lasting friendships with both fellow students and faculty. The Physical Chemists were a very congenial group and Herbie Harned was really a very interesting man, except in the class room. He came by almost every lab almost every day to chat with us students about almost everything. Sometimes his visits were inconveniently long and would interfere with experiments. One of the older graduate students had told me that Herbie would run for cover if he were asked to help, for example by holding a light or a tool during some adjustment. That ploy worked like a charm and saved me many hours. Actually, the Harneds were very kind and warm hearted people. They held an open house every Friday night which both students and faculty felt obliged to attend more or less regularly. More often than not we ended up around the piano in a group sing-along with Roger Bates, then a Sterling Fellow and accomplished musician, at the keyboard.  I also learned a lot about life and lore outside of chemistry, e.g. to play bridge, to drink beer and to smoke a pipe during the mostly dull seminars every Tuesday night. I had many interactions with many interesting people. The weekly university calendar was filled with provocative events ranging from seminars to sermons and concerts to contests. My perspectives were stretched by memorable if abstruse encounters with great minds, including lectures on resonance by [Linus Pauling](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1954/index.html), and two required courses in statistical mechanics under Lars Onsager (known to the students as Norwegian I and II!). Gus and his wife Rosalie, who was the sister of Joe Hirschfelder, looked after his students with great care and affection, making their house our home away from home. Rosalie took my new bride under her wing, showering us newlyweds with almost too much attention. I was extremely fond of Gus and most grateful for his always calm demeanor and seeming imperturbability. He strongly disapproved of marriage for graduate students but when I told him I wanted to take a wife he protested not at all and simply said “OK, we take it from here.” He and “Magee” as my wife was later known, became extremely fond of each other and he later told me many times that marrying her was the smartest thing I ever did, an opinion shared by everyone who has known us both. All in all, my time at Yale was happy and rewarding but I left with a much diminished interest in “scholarly research”, and no desire to return. I often think about how surprised and pleased Gus would have been to know that six decades later his son [George Akerlof](https://www.nobelprize.org/nobel_prizes/economics/laureates/2001/index.html) would share the 2001 Nobel Prize in economics and his student John Fenn would share the 2002 Prize in Chemistry!  My immediate and exciting prospect after graduation from Yale was a job in the research department of the Phosphate Division of Monsanto Chemical Company in Anniston, Alabama. The starting salary was $2700 per year, then the going rate for new PhD’s in industry and a mind-boggling jump from the $1000 or so a year Magee and I had been living on. I couldn’t understand why my mother laughed when I once remarked that I didn’t know how we could spend so much money!  Anniston, the county seat of Calhoun county and “Cast Iron Pipe Capital of the World”, was located halfway between Atlanta and Birmingham. Living there was my introduction to the deep south where cotton still grew and the Confederate Flag still flew. It was the home of Fort McClellan, a long time army base that was already gearing up for America’s forthcoming participation in World War II. Two of my mother’s brothers had been medical officers at McClellan during World War I and two of our closest friends from New Haven passed through there after being drafted in the wake of Pearl Harbor. We had the chance to compensate them a wee bit with an occasional home-cooked meal. I was more fortunate because the army was not yet drafting husbands.  Monsanto had recently acquired the Anniston Plant when it bought Swann Chemical Company started by a legendary character named Theodore Swann. He had pioneered the production of phosphoric acid from elemental phosphorous shipped in by tank car from a plant in Columbia, Tennessee where it was produced by smelting “phos rock” in an electric furnace. At Anniston the phosphorous was burned in air to produce its pentoxide which could be hydrated to form acid of any desired concentration. Major customers for the acid per se included the soft drink industry, especially the Coca Cola Company in nearby Atlanta. According to local folk lore, the first tank car of food grade acid to be delivered was filtered through laboratory Buechner funnels because the filtration plant was not ready in time to meet the deadline on the sales contract! Much of the phosphoric acid left the plant in the form of sodium and potassium phosphates that among other applications were widely used as soap builders, water conditioners and in food products such as baking powders.  The other main product line, which some said was the main reason Monsanto bought Swann, comprised biphenyl and its chlorinated derivatives known as Arochlors, the now notorious PCBs. Biphenyl was produced by bubbling benzene vapor through large baths of molten lead at a temperature of around 800°C, as I remember. Liquid metal as a heating agent provided a rapid rise and close control of the temperature, thus minimizing formation of byproducts which mostly comprised ortho, meta and para diphenyl benzenes. The various Arochlors were characterized by their chlorine content which ranged from 10 per cent to 60 per cent by weight. One of their main uses was as transformer oils because they had very good heat transfer characteristics, would not burn and were very inert. Indeed, they were so inert and sticky that the chemists insisted that if Arochlors ever got into a laboratory some of it would remain forever! Because it was so inert we practically bathed in the stuff, never dreaming that it might be toxic. General Electric dumped PCB wastes into the Hudson River for many years and is now resisting Federal orders to dredge it all up. Recently, the press has reported growing anger in Anniston and threats of legal action as new surveys have shown the extent to which PCBs from the plant where I worked have contaminated the soil and waters around the town. My own substantial exposure seems to have had no ill effects, but I daresay that even today, sixty years later, the PCB content of my fatty tissue would horrify the EPA! There is no doubt that PCBs in the environment accumulate in the fatty tissues of mammals and fish. The evidence of resulting toxicity is less convincing. I remember a paper by an Australian chemist claiming that the only documented evidence of significant toxicity stemmed from two cases in which PCB’s, used as the heat transfer medium in the heating coils of deep fat fryers, leaked into the fat. The resulting reaction produced highly toxic benzo-compounds whose identity I have forgotten. I do know that sixty years ago I practically bathed in the stuff while operating a pilot plant in which PCB was produced in the vapor phase by reaction of biphenyl with HCl and air over a copper catalyst in a variation of the old Deacon process for producing chlorine by the oxidation of HCl. Occasionally I would get a slight skin rash, as did the other operators, but I have detected no lasting effects.  After I had been at Anniston for a year, James W. Mullen II., a young Ph.D. organic chemist from Princeton came aboard. He and I became good friends, sharing a growing dissatisfaction with the way things were being run at work. Jim insisted that someday he was going to start a research company and that when he did he wanted me to join him. Talking about what we might do was fun but it all seemed like pipe dreaming to me. Having become increasingly disenchanted with the work situation we both resigned and left Anniston on the same day in 1943. Jim went to Bell Labs in New Jersey. I took my family, which now included an 18 month old daughter, Marianne, to Wyandotte, Michigan where I had obtained a job in the research department of Sharples Chemicals, a relatively small producer of alcohols, amines, esters and other derivatives of amyl chloride produced by the chlorination of pentane. One day in June of 1945 a letter came from Jim saying that he had finally started his company and wanted me to join him. I took a train down to Richmond to find out more. At Bell Labs he had become involved in Project Bumblebee, a large scale effort by the Navy to develop a ramjet-powered anti-aircraft missile for the fleet. The ramjet depends upon ram pressure from high speed flight to compress air enough so that its expansion after heating by combustion could provide useful thrust. It was clear that supersonic flight velocities would be required to achieve substantial thrust but because there was little or no information on drag at such velocities, nobody knew whether that thrust could equal or exceed the drag. The Project name, Bumblebee, derived from a bit of aeronautical badinage to the effect that by all the laws of modern aerodynamics it is impossible for a bumblebee to fly, but the bumblebee doesn’t know any aerodynamics so it goes ahead and flies anyway!  **From flames to flying elephants** Experiment, Inc., the name Jim Mullen gave his company, prospered over the next seven years. To watch and participate in its growth, from a total of three employees when I arrived to perhaps 45 or so when I left in 1952, was an exciting experience. Most of its business was based on R&D contracts with government agencies for which the central theme was combustion and propulsion but we did pursue some commercial ventures. There were some important personal dividends from my investment of time at Experiment. One was that I learned a little bit about the dynamics and thermodynamics of compressible flow, a newly popular area of research spawned by the advent of jet propulsion and sometimes referred to as “Aerothermodynamics”, or “Aerothermochemistry” if changes in chemical composition were involved. Another personal dividend was the opportunity to do some research in combustion, both applied and fundamental. Jim was a strong believer in publishing our results. Thus the first research publication of my life was a paper on ignition in high speed flow, co-authored by Jim and a junior colleague, M.R. Irby. That paper appeared in 1949, almost a decade after I left graduate school[1](https://www.nobelprize.org/prizes/chemistry/2002/fenn/biographical/#not1). Consequent to several more papers, visits to other labs, and attendance at various meetings, I began to get some recognition in the Combustion Community. Moreover, in an about-face from my feelings at Yale, I found I enjoyed doing research and communicating with others about my findings and theirs.  My life in Berea had made me think that I would someday like to become a college professor. But I had also thought that I should get some of the realworld industrial experience that had seemed to help make Julian Capps, my chemistry professor at Berea, such an effective teacher. That desire to join a college faculty had faded somewhat at Yale but was revived a bit during my experience at Experiment, Inc. We obtained a number of provocative results on some properties of flames, in particular on stabilizing them in high velocity flows. Both Jim and the sponsors of our studies were happy to have us attend technical meetings and to publish results of our studies, (so long as they didn’t involve classified information.) Consequently, I got to know, and become known by, a number of people in the combustion community. One result of this new and limited “notoriety” was an offer from Princeton University to serve as Director of Project SQUID, a program of pure and applied research in “those fields of science relating to jet propulsion” including combustion, fluid flow and heat transfer. Financed by the Office of Naval Research (ONR) and administered by Princeton, Project SQUID was named after the jet-propelled decapod of the sea. (That name had additional but unpremeditated relevance in that both the animal and its namesake secreted ink, the former in clouds that confused predators, the latter in print in reports that confused readers!) SQUID’s organizational structure comprised a prime contract between ONR and Princeton, with subcontracts at any one time between Princeton and from 12 to 20 or so university and industrial laboratories. The overall purpose was to cultivate interest and activity by students, faculty and other investigators in combustion, fluid flow and heat transfer.  One reason for my interest in Princeton was that by then I had learned that research could be a lot more fun than it had been when I was a student at Yale. Another reason was that my Yale mentor, Gus Akerlof, had set up a laboratory in its newly established James Forrestal Center to develop, with Navy (but not SQUID) support, an electrical discharge process for the production of hydrazine, an attractive rocket propellant. Gus had once visited me in Richmond and in fact had put my name in the pot at Princeton when he learned that the previous director of SQUID was leaving. One of the “other reasons” for my interest was that Jim Mullen and many of his friends, were Princeton graduates. After seven years among those fiercely loyal alumni I had been brainwashed to the point of believing that maybe Old Nassau really was the “best old place of all.” Moreover, as I have already noted, my life in Berea had long made me think that I would enjoy becoming a teacher and living in a college community.  At Princeton I would report directly to Sir Hugh Taylor, long-time Chairman of Princeton’s Chemistry Department, then Dean of the Graduate School and Chairman of the University Research Board. The position was “with rank of Professor” and the Dean assured me that I would be welcomed as an active member of the academic community. And so, after much soul searching, Magee and I decided to leave the “Cradle of the Confederacy” for what was and is often called “the northernmost southern town in the country”. That epithet stemmed from the substantial numbers of Princeton students that over the years have come from below the Mason Dixon line. Before the Civil War it had become customary for students from the south to celebrate graduation by freeing their personal servants. An interesting result is that Princeton has a much larger black population than do other towns of comparable size in that part of the country.  My new job turned out to be very interesting and highly educational. I had to travel a lot but was able to visit many laboratories and meet well known scientists in many fields all over the country. I got to know the people in ONR pretty well and my circle of acquaintances included people in ARO (Army Research Office) and AFOSR (Air Force Office of Scientific Research) both of which were providing some support for Project SQUID and were represented on its Steering Committee. ONR had a branch in London (ONRL) that maintained a rotating corps of 12 to 15 Scientific Liaison Officers whose job was to promote interaction between scientists and engineers in Europe and America by visiting laboratories and attending scientific meetings. They would get to know the investigators, learn about what they were doing, help them establish contacts with their counterparts in America, arrange visits, find items of equipment, assist with travel arrangements, and the like. Research laboratories in Europe were beginning to recover from the trauma of World War II and they welcomed the communication links and the help with their needs that ONRL could provide. The SQUID office had occasionally been involved in making travel and visiting arrangements for some of the European scientists who came to America under ONRL’s auspices. After I had been at Princeton for about three years I was invited to serve a year as an ONRL Liaison Officer in the areas of combustion and propulsion. My bosses in ONR Washington approved and I persuaded John Scott, who had just finished his Ph.D. in Aeronautical Engineering at Princeton, to mind the store at SQUID while I was gone. Thus, Magee and I and the children, then 9, 11 and 13, went to London for the calendar year of 1955. And what a wonderful year it was! The children still insist that living London was the high point in the Fenn family fortunes which have been going down hill ever since! I share some of those sentiments because that year was also a marvelous experience for the parents. The kids were in school so Magee was free to roam London during the day. I visited many laboratories in many countries, made many friends, and learned “more things than had been dreamt of in my philosophy.”  Among these “things” was my stumbling on to something that was to set the stage for the rest of my scientific life. Up to that time flames and their behaviour were the focal point of almost all efforts to elucidate the kinetics and mechanisms of the important reactions in high temperature combustion. The general approach was mostly based on attempts to measure and interpret flame characteristics such as propagation velocity, flammability limits, ignition temperatures and the like. I had become convinced that flames, with their extremely high gradients of temperature and composition, were much too complex to be useful as stages for the study of those reactions. I often recalled a comment by Philip Rudnick, professor of Physics at Vanderbilt, who was active in the propulsion Panel of Project Bumblebee. He said that the more he learned about flames the more he was convinced that they were organisms whose study properly belonged in the province of biology! I’m sure that view strikes a responsive note in many investigators who have been exasperated by the vagaries of flame behaviour that seem to give them a life of their own. Indeed, the analogy can be extended. Flames, like organisms, are born, need fuel and oxidant for nourishment, grow and multiply to the extent that those necessities are accessible, and are poisoned unto death when immersed in their own waste products! Not only is their structure and behavior complex but the conversion of reactants to products involves sequences of so many reactions over such short distances that to determine how the composition and temperature changed with distance (i.e. time) in real flames, i.e. the relation between their “fine structure” and their behaviour, was not experimentally feasible with the tools and techniques then available.  Thus, for some time I had been somewhat naively musing about whether and how it might be possible to study chemical reactions by the same approach that physicists so successfully use in the study of nuclear reactions. They build accelerators to produce beams of atomic nuclei with energies of megavolts to gigavolts with which they bombard stationary targets comprising collision partners of interest. They then characterize the products from reactive collisions by analyzing the post-collision trajectories of the product particles as measured by appropriate detectors, e.g. bubble or cloud chambers. I had been introduced to the possible uses of molecular beam scattering experiments in chemistry by Professor I. (Izzy) Amdur, a colleague of the Professor Frederick Keyes at MIT whose elegant measurements on the transport properties of gases were being supported by Project SQUID. Amdur was using beam scattering experiments to characterize the intermolecular potentials of molecules. His approach was based on electrostatic acceleration of ions to relatively high energies and then neutralizing them by charge-exchange collisions with neutral molecules for which the cross-sections are much larger than those for momentum exchange. In this way he could produce beams of neutral molecules with translational energies equal to those of the incident ions. Space-charge effects give rise to the Childs-[Langmuir](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1932/index.html) law by which the maximum intensity (current density) of an ion beam is proportional to the square root of its energy. Consequently, neutral beams with intensities high enough to provide good signal/noise in a scattering experiment, must perforce have energies substantially higher than the intermolecular potentials that Amdur was trying to probe. His solution to this problem was to locate his detector so that it would “see” only the post-collision beam molecules whose trajectories differed by only a very small amount from their pre-collision values. This “small-angle scattering” approach allowed him to exploit the high intensities obtainable with beams of high energy molecules (in laboratory coordinates) in the study of molecule-molecule interactions at low energies in center-of-mass coordinates of the colliding partners. Unfortunately, that approach did not seem to lend itself to the study of reactive collisions.  When I went to ONR London in late 1954, nobody had successfully carried out reactive scattering experiments with molecular beams on any chemical reaction, even one with a negligibly small activation energy. Moreover, activation energies for many combustion reactions were known to be as high as 30 kcal per moltwo or more. The energies of beam molecules from conventional effusive sources are always limited by the temperature at which the source can be operated. The average translational energy of an oxygen molecule from a source at 3000 K would be only about 10 kcal/mol or 1.2 eV, (but that temperature is well above the melting point of most materials from which the source might be made!). Any polyatomic molecules of interest in combustion would completely decompose even at much lower temperatures. In sum, the collision energies that can be reached simply by raising beam source temperatures are severely limited. Even so, the possibility of bringing about reactive collisions by colliding a beam of reactant molecules with other gaseous molecules had been contemplated since the late 1920’s. In spite of numerous attempts, no really convincing results had been obtained when we left for London at the end of 1954. However, shortly after we returned to Princeton in early 1956, the age of reactive scattering experiments with molecular beams dawned when Datz and Taylor reported that intersecting beams of K atoms and HBr molecules produced detectable amounts of KBr.[2](https://www.nobelprize.org/prizes/chemistry/2002/fenn/biographical/#not2) These results gave some substance to my musings but there was a fundamental problem with the idea of applying the same method to combustion reactions. Activation energies for K+HBr are negligibly small. For many of the most interesting reactions in combustion the activation energies were thought to range from 0.5 to 2.0 or more eV, much much higher than for the reaction studied by Datz and Taylor. Amdur’s charge exchange technique could easily produce beams with much higher energies but because of space charge effects could not provide useful intensities at energies as low as a few eV. Nor did Amdur’s ploy of looking only at small angle scattering seem applicable in the study reactive scattering. To produce beam molecules from classical effusive sources with energies of even 0.5 eV would require source temperatures of 3000 K. Neither materials of construction for the source, nor reactant molecules other than atoms, could endure such temperatures. The situation thus seemed hopeless.  One day in London I was calculating rocket exhaust velocities achievable with various propellants and suddenly realized that many reactant molecules at the velocities attainable with some such propellants would have translational energies as high as two or more eV. I began to fantasize about using micro- rockets in vacuum as molecular beam sources, anticipating by 30 years an experiment we actually carried out for another purpose! I then remembered that rocket visionaries had often touted hydrogen as an ideal propellant fluid for nuclear powered rockets because its of its low molecular weight. The limiting maximum convective velocity that can be reached by a gas expanding into vacuum is equal to (Cp/MT0)1/2 where Cp is its constant pressure heat capacity, M its molecular weight and T0 its source temperature. Thus the maximum velocity reachable by helium is about 3.33 times that for argon. If the helium is “seeded” with one or two per cent argon, and if those argon atoms are swept along like dust particles in a wind storm, the translational kinetic energy of the argon atoms after free jet expansion of the mixture would be almost 10 times that of the helium atoms, if the two reached the same terminal flow velocity.  A few days later I was browsing in ONRL’s library and ran across the now famous paper by E.W. Becker and K. Bier reporting the production of intense beams of hydrogen molecules by expansion of the gas from high pressure through a small converging-diverging nozzle into vacuum[3](https://www.nobelprize.org/prizes/chemistry/2002/fenn/biographical/#not3). That paper referenced the also now famous paper by Kantrowitz and Grey in the Review of Scientific Instruments which proposed the use of a converging-diverging nozzle to produce a jet of high velocity molecules in a region of low pressure.[4](https://www.nobelprize.org/prizes/chemistry/2002/fenn/biographical/#not4) A small core portion of that jet would be admitted through a conical “skimmer” into a high vacuum region to form a jet of molecules. The “static” temperature of the molecules (as measured by a thermometer traveling with the gas and at the same velocity) would be very low so that the divergence of the molecular trajectories downstream of the skimmer would be very small and the velocity distribution in the direction of flow would also be very narrow. In sum, the jet would comprise a very intense beam of molecules, all traveling at nearly the same velocity! Another paper in the same issue of that journal reported a not very successful attempt by Kistiakowsky and Schlichter to reduce the Kantrowitz-Grey idea to practice.[5](https://www.nobelprize.org/prizes/chemistry/2002/fenn/biographical/#not5) Both of those papers also happened to be in the ONRL library and when I read them I began to take my musings seriously. (It is said that Kistiakowsky and Schlicter were so frustrated by troubles in their experiment that when Schlicter had suffered enough to deserve a degree, they vented their frustration by demolishing the apparatus with an axe!)  I later learned that twentyfive years earlier, T.H. Johnson, a Sterling Fellow at Yale, had produced intense beams of mercury atoms by expanding the vapor from a “boiler” at several hundred torr into vacuum[6](https://www.nobelprize.org/prizes/chemistry/2002/fenn/biographical/#not6). Unfortunately this truly remarkable result had been ignored because it was at odds with the dogma from Stern’s lab in Hamburg that raising the source gas pressure (density) would produce a sort of stagnant cloud of molecules at the exit of the source orifice. That mythical cloud would scatter a large fraction of the emerging molecules that might otherwise have contributed to beam intensity. Later in his career at the Franklin Institute Johnson he also found diffraction effects in the scattering of hydrogen from an LiF crystal, confirming the wave nature of particles much heavier than the electrons with which Davisson and Germer had earlier found diffraction effects. Unfortunately, some eight weeks earlier Estermann, Frisch and Stern had found the same result in Göttingen[7](https://www.nobelprize.org/prizes/chemistry/2002/fenn/biographical/#not7) so Johnson’s work again went unnoticed while [Stern](https://www.nobelprize.org/nobel_prizes/physics/laureates/1943/index.html) got the Nobel Prize! An able investigator who was 25 years too early with one landmark experiment and 8 weeks too late with another, Johnson had every right to feel frustrated by the fickleness of fate.  The results predicted by Kantrowitz and Grey in 1951, having been already achieved by Johnson in 1929, were confirmed in the above-mentioned paper by Becker and Bier in 1954. They showed that convective flow of gas through a small orifice from high pressure into vacuum could indeed produce molecular beams with much higher intensities than could the effusive sources introduced and exploited to great advantage by Otto Stern and his colleagues. Moreover, these “convective” beams had much narrower velocity distributions than did their effusive cousins. Consequently, the achievable intensity within a narrow velocity interval, a highly desirable feature, could be very much higher with convective beams. What had not yet been shown, nor apparently considered, was that heavy molecules could be accelerated to suprathermal translational energies by expansion of a light carrier gas such as hydrogen or helium in which those heavy molecules were present a low levels.  When I returned to Princeton after my year in London, I found that John Scott, who had run the SQUID Office during my absence, was going to the University of Virginia as an assistant professor of Aeronautical Engineering. He was wondering what research he ought to work on and I told him about my musings on molecular beams from high pressure sources. I also told him that if he would submit proposal on such work to Project SQUID I would try my best to get support for it. When he arrived at Virginia he found a group that was already using beam scattering experiments to characterize the exchange of energy and momentum between molecules and surfaces. Their goal was to understand and predict surface heat transfer and drag for aerodynamic bodies at very high altitudes where flow was molecular rather than continuum. The high intensities achievable with beams from supersonic free jets (or “nozzle beams”, as they came to be known) would be most useful in such surface scattering experiments. Moreover, the high translational energies that seemed achievable with the seeded beams I was dreaming about, would make possible the study of drag and heat transfer in molecular flow under conditions much closer to those expected in ultra high altitude flight than those obtainable with the effusive beams they had been using. As a result of their enthusiasm and mine, the first nozzle beam system in America was built in Charlottesville, VA.[8](https://www.nobelprize.org/prizes/chemistry/2002/fenn/biographical/#not8) I should really say, the first in America since the one T.H. Johnson built at Yale in 1929 that produced high intensity beams of mercury atoms but had been ignored. It now seems clear that the reason for Johnson’s success was that the walls of his system were all water cooled enough to condense most of the incident mercury atoms. The net result was an effective pumping speed orders of magnitude higher than the nominal speed of his vacuum pumps or those of any of the other molecular beam systems then in existence. (Fraser in his 1932 book on “Molecular Rays” refers to a system then being built with the “exorbitant” pumping speed of 100 liters per second[9](https://www.nobelprize.org/prizes/chemistry/2002/fenn/biographical/#not9). The nominal speed of each of two 32 inch pumps that we bought “off the shelf” 45 years later was 30,000 liters per second!) The real reason for the generally observed decrease in beam intensity with increasing source gas density was scattering due not to the molecules in a “cloud” at the source orifice exit but to those in the relatively high density of background gas throughout the system due to inadequate pumping speed.  Meanwhile, I was getting more and more intrigued with the problems and possibilities of beams from free jet sources and eager to become more directly involved. I had by this time learned that in spite of Dean Taylor’s rosy assurances I could not become an active participant in academic research unless I had some direct association with a department. SQUID had been supporting research on two-phase flow by Shao Lee (Charlie) Soo, a young assistant professor of Mechanical Engineering. During a visit to Soo’s lab one day I met Robert Drake, the new chairman hired to refurbish that department’s image by expanding its research activities. I described my wild ideas on free jet beams and said: “If I write a proposal and get some support will your department provide a home for the project?” Bob had done his doctoral research in rarefied gas dynamics at UC Berkeley. Familiar with the molecular perspective on gas dynamics he immediately said yes. I prepared a proposal on which I was listed as a “Consultant” because I was not on the faculty and under university rules could not be a Principal Investigator. That role was assumed jointly by Bob Drake and Michele Boudart, my next door neighbor and close friend who was interested in chemical kinetics and catalysis and was on the faculty of Chemical Engineering. I had been discussing my beam ideas with him and he too found them intriguing. The proposal was submitted to NSF who sent it for review to Immanuel Estermann, a co-author with Stern and Frisch of the landmark paper on diffractive scattering of hydrogen from LiF, one of the two papers cited when Stern won the Nobel prize in 1943. Estermann had become Director of ONR’s Material Sciences Division (whose Power Branch was responsible for Project SQUID) and was thus my ultimate boss. He took his reviewing seriously and spent a day in Princeton discussing the proposal with me. (The fact that his daughter was then living in Princeton was no doubt something of an inducement for him to make the trip from Washington.) He had visited Becker’s laboratory in Marburg, Germany and was aware of the difficulties Becker had encountered in fabricating the tiny converging-diverging nozzles prescribed by Kantrowitz and Grey. As he took his leave he said: “John, I’m afraid this research may be too difficult to pursue with graduate students but I think it is important so I’m going to recommend support.” He apparently was as good as his word because NSF gave us the money we had sought and we began work in the fall of 1960. As it turned out, Estermann’s fears about the difficulties of making very small Laval (converging- diverging) nozzles were groundless. The Marburg group discovered empirically, that beam intensities became higher when the diverging section of the nozzle was cut off![10](https://www.nobelprize.org/prizes/chemistry/2002/fenn/biographical/#not10) The lower intensities obtained with a diverging nozzle are due to viscosity effects which Kantrowitz and Grey had ignored in their analysis. Dave Miller’s group in San Diego, later showed experimentally that for most practical purposes the jets from a simple orificea (hole in a flat plate), a simple converging nozzle, or a long tube, had almost identical properties as long as the flow was “choked”, i.e. reached sonic velocity, at the exit plane of the nozzle, tube or orifice.[11](https://www.nobelprize.org/prizes/chemistry/2002/fenn/biographical/#not11) |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** |  |
| **Interview** |  |
| Q2 | **What was it, maybe back in your childhood, that made you interested in science in specific?** |
|  | John B. Fenn: Well my father was an electrical engineer and he was a very ingenious and handy fellow, he did lots of things. I had a brother who was three years younger and when I was about eight or something like that my parents bought *The Book Of Knowledge* which is a children’s encyclopaedia, 20 volumes or so. And I just was reading that all the time. I think I was educated by my experience of reading *The Book Of Knowledge*. And I know years later, when I dug it out to give to the next door neighbour’s children to look at, those books were pretty well worn and I must have spent an awful lot of time on it. So I have always been interested in science and things technical. And my dad subscribed to the *Popular Science Monthly* and *Popular Mechanics* and so I was exposed to technology and science all along and I just liked it. |
| Q9 | **So did you life change a lot after that?** |
|  | John B. Fenn: Oh God yes. The telephone did not stop ringing for the next month it seemed like. And we are a publicity conscious society, you know, you get your name in the papers and then everybody wants you to do this that and other things. And so you get invitations to everywhere. I think I told you I was away from home 100 nights in the first year after I got it. |
| Q1 | **When you now get to talk to students what kind of message would you like to relay to them?** |
|  | John B. Fenn: Forget about your text books, science is fun! The text books are terrible. |
| Q14 | **In which fields do you believe that there will be major breakthroughs in the future? What are the most important issues?** |
|  | ohn B. Fenn: Of course there are all kinds of technological problems that are important. I mean, what are we going to do about the warming of the atmosphere? We understand what causes it but we are too bloody stupid to do what is necessary to stop it. The idea that everybody has to have a car and that there is no speed limit and they make these SUV’s. It takes 20 times as much fuel to haul a tonne of freight a mile in a truck as it does in a train.  And yet we subsidise the trucking industry by building these roads which they don’t pay for and even they don’t pay for the damage they do to them because the damage to the road by traffic goes up with the cube of the mass of the traffic. So a truck does a tremendous amount more damage to a highway than a car does. And we should put a tax on the fuel so that the trucks will be on a par with the trains. Because the railroads have to maintain the road. Our politics are all crazy. Too many special interests are controlling what is done and it is not in the best interest of the people. |

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| **Chemistry\_2024-2000** | |
| **ID** | 0357 |
| **Biographical** | I was born in Japan on August 3, 1959. My natural mother died one month after I was born, apparently due to giving birth at an advanced age. Because my father was also physically frail, I was brought up by my uncle and aunt. When I use the words “father” and “mother” now, I am referring to the father and mother who raised me. Perhaps it was because of my easygoing character that I remained ignorant of my early circumstances until I was 18 years old, when my parents informed me of these circumstances. More likely, however, my blissful ignorance was due to the completely fair-minded upbringing I received by my parents, older sister and brothers, relatives and neighbours.  My parents operated a business selling and repairing carpentry tools in Toyama Prefecture. I grew up with images of my father sharpening saw-blade teeth and planes, images in which he was seemingly always busy working quietly with his hands. My mother was not only busy performing housework, but also making end-of-month collections and keeping the books of the family business until late at night. I have no memory of my parents encouraging me with words like ‘study’ or ‘succeed.’ There is no doubt, however, that the values they instilled in me were much more important than those suggested by these words. From my father, I learned the importance of working sincerely at things to which I had committed myself, and to persevere untiringly even in the face of little progress. My mother also stressed the importance of working quietly towards achieving my missions in life, without neglecting attention to details. My father passed away three years ago (1999).  Apart from my parents, I was also influenced by my grandmother. She often admonished me, using the expression “What a waste!” (“Mottai-nai!” in Japanese). While these words are approaching extinction these days, they used to be an integral part of the cultural values in Japan. My grandmother valued even the smallest of things. Once, when she noticed me crumpling up a sheet of paper to throw it away, she angrily reproached me, saying “What a waste. You could straighten that paper out and use it to blow your nose.” It is no wonder the concept “What a waste!” is so ingrained in my psyche.  The prefecture name “Toyama” means “rich in mountains.” Toyama is surrounded by the Tateyama Mountains to the east, other mountains to the south and west, and the Sea of Japan to the north. Just the sight of the Tateyama Mountains brings me a sense of calm. This area is blessed with bountiful nature, eliciting in me a feeling of awe towards all living things and a compelling interest in the mysteries of nature, so difficult to find in urban settings.  I was enrolled in the Hachininmachi Elementary School in Toyama City in 1966. I cannot say that I was a particularly diligent student, especially during the lower grades. One event, however, did make a lasting impression on me, and that was Expo ’70, Japan’s first world fair, held in Osaka in 1970. The Exposition site displayed the future of technology, which would actually be realized 20 to 30 years later. I truly felt the power of science and technology. Our teacher for the last three years of elementary school was Mr. Kyosei Sawagaki. He taught us not by having us memorize textbooks, but through the joy of performing scientific experimentation and discovering phenomena with our own eyes. One day our teacher showed us an experiment in which boric acid was first dissolved in water, and then re-crystallized. As I watched and experienced this incredible phenomenon, I blurted out, “It’s starting to snow!” While this would have been considered incorrect as an answer in a test, my teacher cherished that response. That was when I discovered that learning could be enjoyable, and not just a painful experience.  I enrolled in Toyama Municipal Shibazono Middle School in 1972. This was not an especially elite middle school, but I did apply myself singlemindedly to my studies. My efforts enabled me to attain a ranking in the top ten percent of the class.  In 1975, I enrolled in Toyama Chubu High School in Toyama Prefecture. This high school is known for its competitive first or second ranking in Toyama Prefecture as a school for sending graduates on to “first-class” universities. Together with just about every other student in the school, I devoted a great deal of effort to studying for the university entrance examination. The tenacious character I’ve possessed since I was a small child propelled me to successfully meet this challenge, and I was able to safely gain acceptance to the university of my choice.  Upon receiving my notification of acceptance to the university, my parents noticed that they were obliged to submit to the university, among other things, a copy of my official family register. After much mental anguish, they decided to inform me of the secret of my birth. The truth came as a considerable shock to me, and the trauma surged over me in waves for a long time afterwards. At the same time, however, it was a chance for me to assert my independence. The thought grew strong in me that since I had gone to the trouble of being born, I might as well be useful in helping people live long and healthy lives. And this thought has always resided in the back of my mind.  In 1978, I entered Tohoku University, into the Department of Electrical Engineering, Faculty of Technology. I suppose the reason I chose electrical engineering was because I had always been interested in electricity, involving myself in such projects as building radios from the time I was a child. Moreover, I thought that electrical-related skills would be useful upon graduation, and that it would be easy to find a job among the electronics-related businesses so active in Japan at that time. Perhaps as a reaction to the tremendous efforts I had made to pass the university entrance examination, I let up somewhat in my first- and second-year studies at the university. As a result, my grades suffered in German class, and I was forced to repeat the year. Aware that I had placed a burden on my parents, from that point on, I diligently applied myself to my studies. In my senior year at the university, we were obliged to complete a graduation research project, and mine was entitled “Absorption of a Plane Wave by an Impedance-Loaded Dipole Array Buried in a Lossy Medium.” The objective of the research was to reduce the ghost effect of television broadcast waves by placing an array of line-shaped conductors in front of a building to prevent the reflection of electric waves from the building. I was guided in my research by Professor Saburo Adachi. Needless to say, my present research endeavors have practically no relevance to that subject.  The Faculty of Technology of Tohoku University is renowned for its tradition of practical studies. For instance, historical individuals associated with the university include Professor Kotaro Honda for his contributions in metallurgical engineering, Professor Hidetsugu Yagi, the inventor of the wellknown Yagi antenna (patented in 1940), and Professor Jun-ichi Nishizawa for his opto-electronics and semiconductor research. In such an environment, I was able to study things that could be of immediate usefulness to the world. That learning experience undoubtedly served me well when I eventually entered the work force.  When it came time to find employment, I set my sights on becoming an engineer at a home electronics manufacturer, a field that was closely related to my major at university. I took an entrance examination for employment at one such company, but failed the examination. Despite my desire to be an electrical engineer, I am sure my answers to the electricity-related questions were somewhat less than acceptable. Even though I failed, however, I still hold that company in high regard.  At that point, I decided that there was no need to focus solely on electrical engineering, especially because I had only two years of electrical-related knowledge. I turned to my mentor, Professor Adachi, and he was kind enough to introduce me to Shimadzu Corporation. I learned from Shimadzu’s employment literature that the company was manufacturing Xray devices and other types of medical equipment. This struck a chord with me, rekindling the possibility that I might yet satisfy my desire to help suffering people, albeit indirectly. I decided to take the employment examination, and that time, I passed without problem. However, instead of being assigned to the area of medical equipment, I learned I was to be involved in research and development of analytical instrumentation. Fortunately, that field also held interest for me, and it became the central area of my work.  Kyoto city is home to Shimadzu’s main factories and research divisions, and has fostered six out of Japan’s nine Nobel Prize laureates in scientific fields, including Prof. [Hideki Yukawa](https://www.nobelprize.org/nobel_prizes/physics/laureates/1949/index.html) (selected in 1949), Professor [Shin-ichiro Tomonaga](https://www.nobelprize.org/nobel_prizes/physics/laureates/1965/index.html) (1965), Prof. [Ken-ichi Fukui](https://www.nobelprize.org/nobel_prizes/physics/laureates/1981/index.html) (1981), Prof. [Susumu Tonegawa](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1987/index.html) (1987), Prof. [Ryoji Noyori](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/2001/index.html) (2001), and myself. Probably no one can explain exactly why so many laureates hail from Kyoto, but the knowledge of this fact did have somewhat of an effect on me. I might even have mused that I could reach to such a level if I were to put my heart and soul into the effort.  I joined Shimadzu Corporation in 1983, and was immediately assigned to the Central Research Laboratory, a new department which had been established in 1980. At that time, there were three laboratories, for mechanical-, chemical- and electrical-related research, respectively. I was assigned to the laboratory for electrical systems-related research, and joined a team charged with developing component technology for analytical instruments. This team comprised Dr. Tamio Yoshida, Mr. Yoshikazu Yoshida, Mr. Satoshi Akita, Mr. Yutaka Ido, the one member who joined the company with me, and myself. We were a very young team, with an average age in the 20’s, with me being the youngest of all.  Even before I joined the company, Shimadzu had been engaged in research involving the mapping the elements on the surface of a semiconductors and metals after ionizing the surfaces using an Nd-YAG laser beam concentrated to a diameter of about one micrometer. An instrument that was to be competitive with a German product was developed, but since its performance did not significantly exceed that of the other product, it was not placed on the market. However, rather than give up at that point, our team consulted with a product manager in the Scientific Equipment Division to find a more constructive alternative. We decided to utilize the instrumentation we had been using in our research together with the accumulated laser-related technology we had developed, and we shifted the focus of our work to the field of mass analysis of biological-related substances. That research and development began in 1984. Since Mr. Akita was already a talented designer of electrical circuits and systems, I assumed the responsibility of acquiring data from the chemical experiments. This would be a first-time ever experience for me to irradiate substances with a laser, and the first time to perform chemical experiments away from the educational context of school. However, I undertook this project thinking that it would be very interesting, drawing on the inquisitiveness that had guided me since my elementary school days.  My specific task was to search for a matrix that would enable non-destructive ionization of macromolecules by efficiently absorbing the laser energy. The laboratory stocked hundreds of substances that were candidates for the matrix. Without having studied the theory of ionization coupled with my paucity of knowledge in chemistry, I single-mindedly, day-after-day, repeated trial and error experiments with the candidate substances. Continuing this regimen tirelessly, I felt like I had become one with these substances and the instrument. However, a solution was not easily found.  One day in February of 1985, instead of using Cobalt Ultra Fine Metal Powder (UFMP) as a matrix, I mistakenly used a glycerin-UFMP mixed matrix. I noticed this mistake immediately, but I thought, “Mottai-nai!” at the idea of throwing the mixture away. If I allowed the glycerin to evaporate, I thought that I could still make use of the UFMP, so I placed the mixture in the vacuum chamber to dry it out. Thinking that I could even speed up the drying process by irradiating the mixture with the laser, I switched on the laser beam. On top of that, anxious to confirm the elimination of the glycerin as soon as possible, I kept the spectrometer running and monitored the results. And then, I noticed a signal peak I had never before seen mixed in with the noise peaks. I think because up to that point I had always felt annoyance at the sight of that noise wave data in the experiments, I noticed a slight difference. The signal peak that I had never seen before now appeared at the same position no matter how many times I ran the experiment.  Thinking about it now, this “monumental blunder” was the start of it all. From then on, noticeable progress was evident every time I ran an experiment. This contrasted entirely with the situation that continued day-after-day until a few days prior, when I would say to myself each time I failed, “Well now I know that method won’t work.” During that productive period of time I was truly happy as an engineer. Most of the work performed by a development engineer results in failure. However, the occasional visit of success provides just the excitement an engineer needs to face work the following day.  To say that I discovered the method of ionization does not take into account the complete story. It is necessary to point out that because the signal was so minute, the discovery could not have been made if it were not for the sensitivity and high performance of the instrument. Technologies for the mass separation mechanism, the detector and the signal processor were developed by Dr. Tamio Yoshida, Mr. Yoshikazu Yoshida, Mr. Yutaka Ido and Mr. Satoshi Akita of the research team. Many advancements that exceeded the technological levels at that time were incorporated into these components. Rather than to mention only my excellence, I believe it is more appropriate to say that the overall support of the research team was excellent. We were also probably influenced by the climate within Shimadzu Corporation, which provided a large degree of freedom for this type of research to a team composed of such young members.  The product was developed based on our research results. These were announced for the first time outside the company at the Annual Conference of the Mass Spectrometry Society of Japan held in Kyoto in May 1987. At that time, the mass number that we had been able to measure had already exceeded 48,000. However, this announcement did not cause much of a stir in the world of mass spectrometry. We, on the other hand, were just satisfied that we had achieved our goal and were able to announce it publicly. We were not at all troubled by the lack of reverberating excitement in the world of mass spectrometry. In September 1987, the Second Japan-China Joint Symposium on Mass Spectrometry was held in Takarazuka, Japan, and it was there that we announced our results in English for the first time (at that time we could measure mass numbers in the range of 72,000). There is a double significance here, in that not only were the research results written in English, I actually presented the results in English for the first time. Although my English was far from good, my meaning was well enough understood by Professor Cotter for him to make the results known around the world.  Our first product, the “LAMS-50K,” was put on the market in 1988. I visited many research laboratories at universities and companies to introduce and explain the product. I also performed analysis on many samples provided by potential customers. However, because the performance fell short of the expectations of customers performing analysis of biological samples, and because the instrument was so expensive, we were not able to sell any of these instruments in Japan. Ultimately, we were able to sell only one instrument, and that was to the City of Hope’s Beckman Research Institute in the US, where the instrument’s performance received a satisfactory evaluation (1990). After that, manufacture of this instrument was discontinued, and I was obliged to join the development team for Gas Chromatograph Mass Spectrometer (GCMS) instruments, another kind of mass spectrometer.  In May of 1989, Mr. Yoshikazu Yoshida and I won a Research Award from the Mass Spectrometry Society of Japan for “Research on Macromolecular Ion Detection using a Laser Ionization Time of Flight Mass Spectrometric Method.” That was the only acknowledgement I had ever received publicly before being selected for the Nobel Prize in Chemistry 2002. I was so pleased to receive that first award for the research in which I had participated.  In January of 1992, I was transferred temporarily to KRATOS Analytical Ltd. (a subsidiary company of Shimadzu Corporation) in Manchester, England for a period of one year. This was my first experience to reside overseas, and it was a bewildering experience from various viewpoints, the most prominent being language and culture. To begin with, I was to act as a liaison between the two companies. However, I also joined the development team charged with developing compact MALDI mass spectrometers (KOMPACT MALDI series). Although I returned to Japan midway through the development project, I subsequently continued my cooperation through involvement in domestic sales of the product, as well as performing MALDI technology-related research. There are many engineers who dislike being involved in sales efforts through education of potential customers. But as long as I am an engineer, I think it is important to assure that customers obtain satisfaction with a product that I have had a hand in developing. Moreover, because such contact with customers widens one’s own knowledge, this knowledge cannot but help in focusing on desirable features in development of the next product.  In May of 1995, at the age of 35, I married Yuko Ikegami who also grew up in my native Toyama Prefecture. Thirty-five years of age is generally considered to be a bit late for a first marriage in Japan. Because I have always had a tendency to tense up whenever speaking to a woman, I never had good karma when it came to women. What’s more, being so involved with work all the time, I had little time to think of marriage. I suppose the correct interpretation is that by the time I noticed, I was 35 years old. However, even for someone like me, my joy was undeniable when my wife said to me “There is nothing about you I don’t like.” In front of her, I lost my awkwardness and I am now able to behave naturally. Furthermore, after getting married, I became much more stable. I am normally too embarrassed to express my thanks verbally, but I want to take this opportunity to tell my wife “Thank you.”  From April of 1997 to May of 2002, I was posted once again to the UK for the purpose of developing a new type MALDI-MS called a “Matrix Assisted Laser Desorption Ionization Quadrupole Ion Trap Time of Flight Mass Spectrometer (MALDI-QIT-TOFMS)” (Model Name: AXIMA-QIT). The theory and results were presented to the public for the first time at the Annual Conference of the American Society for Mass Spectrometry in 1999.  One fond remembrance I have occurred in May of 2002. Just before leaving the KRATOS premises, I was summoned to the boardroom. When I entered the room, there was a surprise farewell party all prepared for me. I received as a present a bright red uniform with the number 7 printed on it, along with my name. Of course, number 7 is the number of the renowned football player David Beckham, a member of the world famous Manchester United football team, whose stadium is located very near the KRATOS home office.  In May of 2002, I returned to Japan to begin preparing for sales of the new AXIMA-QIT product. I performed marketing to widen the sales opportunities of the instrument, and also continued feasibility studies on analytical methods for biological macromolecules beyond those for proteins. However, my destiny changed suddenly and dramatically with one telephone call from Sweden received on October 9, 2002.  Until writing these passages, I have never looked back on my life as I am doing so now. I have always thought that I was doing what I desired to do, doing what was interesting to me. However, upon reflecting on my life in this way, it seems that my life is a product of my relationship with such factors as my birth, my family, teachers, friends, companions at work, and even the business world, geographical regions, the natural environment as well as my cultural environment. I am sure that receiving this Nobel Prize will also have an effect on my life. However, just as when there is an unexpected result in an experiment which brings a pleasant surprise, I hope that I will be able to continue enjoying my life in a natural manner after receiving this prize. It is my desire to keep walking through life as an engineer, and to continue producing results that are useful to society.  Finally, I’d like to express my thanks to everyone who gave me the opportunity to walk freely through this life. “ARIGATO GOZAIMASU!” |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** |  |
| **Interview** |  |
| Q9 | **Can you already tell us how the prize has changed your life? What are the advantages of the prize?** |
|  | Koichi Tanaka: Yes. My life is completely changed and so, as you may know, I am unfortunately too popular in Japan, so I’m actually chased by many press people, even in Sweden – so, completely changed. I actually want to go back to my normal life, it means previous life, before I received the prize, but maybe it is very good for me, because I’m in a kind of research job, so if I want to do some latest research job, I have to contact as many people as possible. Now, my name is very popular in Japan, even in foreign countries so, if I want to know something I didn’t know, I can contact such people and I can communicate each other. That will be very good in near future, but at this moment too busy so I have no time to do such job. |
| Q14 | **What is your main interest now or in the nearest future, at work?** |
|  | Koichi Tanaka: My present job is trying to understand the structure of protein but in a near future, that kind of research will be ended so all the information will be reviewed. Protein information will be reviewed maybe within several years or five years later. After that, the next target will be probably sugar, we call it polymer saccharide, because we’re constructed by protein, sugar, fat and of course water and if after we know the protein information, the next target will be other compounds like sugar and lipid, fat. My next target is to try to review what kind of compound we are made of, so sugar and lipid. That’s my next target. |
| Q14 | **So you are heading for the next invention and next Nobel Prize maybe?** |
|  | Koichi Tanaka: Because I’m trying to develop some kind of instrument that will be very useful for such research, but at this moment we developed an instrument but that is just a tool, so we have to develop some other technique which will make the best use of such a tool so I am actually trying to contact … even before receiving this prize, I aspired to contact such people, so now it’s probably very easy for me to contact such people. |
| Q4 | **What is your experience of working with such revolutionary invention, I would say?** |
|  | Koichi Tanaka: In 1980s, you’re talking about 1980s, our group consisting of five people, including me, are trying to develop all the system, so that is called mass spectrometer, so try to know the size or weight more accurate, and I was trying to develop the … how to say, ionisation, so try to make such compound which charge, so after that such kind of compound will be separated by something and detected and measured, so I try to make such compound ionisation, so at that time, for example protein, was thought it was impossible to ionise such big size more accurate but fortunately I was not a specialist. |
| Q10 | **What do you think is the difference to work for a company?** |
|  | Koichi Tanaka: So yes, so normally the researcher in company has some limitation because such people are forced to develop something that will be useful just for next year, so just very short-term development. In such case, we have to do something easy to do within a short time. On the other hand, researchers, for example in government institute or university can concentrate, and do such research maybe three years or five years, but in my case, at that time, in 1980s, I can do such similar job like university and the money was not a problem, not limitless, but we can spend some big money at that time. |
| Q10 | **Time was not problem either?** |
|  | Koichi Tanaka: No, no problem, so that is the one biggest merit for me to discover such a new thing and one merit for the company. If the company thought that is not useful for developing new machine which will be sought in near future, such kind of activity will be halted and sometime it will be completely forgotten, but fortunately, my boss thought this is a very new technique and will be useful in the near future. His opinion was like that, so we are lucky to continue that development, but most of the projects in the companies will be controlled by such decisions so there are so many lucky and me, so at first money was not a problem and we can do some long term development and we can launch such a machine. So many things help me to show such results or discovery to, at first Japan and finally, such kind of information was transferred to Europe and America by several people, so I have to say thank you to so many people here. |
| Q17 | **How did you get accustomed to being interviewed in public over time?** |
|  | Koichi Tanaka: Probably up to university student, I was a completely shy guy and if I, for example, even in Japan, I had to give some talk in front of, for example 100 people, I would be completely upset and I couldn’t say anything, just ahh. But fortunately, my colleague at that time tried to teach me how to cope with such stress, so at first just try to say something in front of the colleagues and I did and so next step is to say something in front of my employees in my company, so next step is try to give a talk to the people in the conference. So, step by step I learn how to do in front of bigger and bigger number of people, so now I’m here. |

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| **Chemistry\_2024-2000** | |
| **ID** | 0358 |
| **Biographical** | I was born in Aarberg, Switzerland, on October 4, 1938, and during my childhood I lived in the small town of Lyss in the Berner Seeland. At the time this was a rural area of farmland, forests and rivers. The roots of the Wüthrich family are in an even more rural, mountainous area, the farming village of Trub in the Emmental near Bern. My mother’s family owned the Restaurant “Bären” and a bakery in Lyss. My grandfather, Otto Kuchen, enjoyed fishing and hunting, and his jugged hare dish was a widely known fall season delicacy at the “Bären”. My interests during childhood were largely influenced by our living in an old farmhouse, where my second grandfather, Jakob Wüthrich, had been a farmer. Although my father, Herrmann Wüthrich, took up an occupation as an accountant, he remained very much attached to his upbringings and our family produced a wide range of farming goods. My mother, Gertrud Wüthrich-Kuchen was the true center of our family life. In addition to raising me and my two younger sisters, Elisabeth and Ruth, she did marvelous things in the kitchen, tended our big garden, raised fowl, and was involved in various activities in the community.  My intense contacts with the rural environment of plants and animals awakened my interest in natural science at an early age. In particular, I acquired a thorough knowledge of the behavior of all sorts of water animals, mostly through observations made while enjoying all aspects of work and fun with a private trout river. On rare occasions I still enjoy fishing trips, and I am a member of the Mercury Bay Game Fishing Club in Whitianga, New Zealand, which lists [Ernest Hemingway](https://www.nobelprize.org/nobel_prizes/literature/laureates/1954/index.html) and Zane Grey among its all-time membership. With regard to my professional life, I had set my mind on becoming a forest engineer. Although I subsequently changed my mind in this regard, I still enjoy tending the family forest, which now contains trees that were planted by three generations of our family starting with my grandfather.  My formal training toward an academic profession started in 1952, when I transferred from the village schools in Lyss to the Gymnasium in the nearby “bilingue” city of Biel/Bienne. During the Gymnasium years my interests widened beyond forestry and fishing. We had the good fortune that our science and language teachers were either former University professors, who had left their academic positions elsewhere in Europe during the Second World War and found a haven in Biel, or followed the then common practice of using a teaching assignment at Gymnasium level as a stepping-stone for an academic career. At age 14 to 18 we were a group of seven students specializing in “natural sciences” who were thus trained in mathematics and physics at university level, and I happily accepted the challenge. According to my mother, it was during those years that I got used to working through the nights. Another focus was the French language, French literature, and French theatre and movies, which was largely motivated by the fact that the composition of our class as well as our teachers represented the bilingual character of Biel/Bienne. The Gymnasium Biel was informally attached to the Swiss Federal School of Sports and Gymnastics in nearby Magglingen, and thus my interest in competitive sports was awakened. These three areas all play an important role in my life up to the present days. Physics and mathematics are key activities in my professional life, professional visits in Paris and “les provinces” are combined with the sampling of French food, wine and culture, and I not only obtained the “Eidgenössisches Turn- und Sportlehrerdiplom” as one of my University degrees, but also played in a competitive soccer league well beyond the age of 50.  By now I can look back on 40 years of intense involvement with techniques referred to as “magnetic resonance spectroscopy”. At the outset in 1962 and throughout my graduate studies there was electron paramagnetic resonance (EPR spectroscopy). EPR was complemented during my postdoctoral training from 1965-1967 by nuclear magnetic resonance (NMR) spectroscopy applied to chemical physics projects, and since the fall of 1967 I have used NMR for studies of biological macromolecules. From there it was a sinuous avenue that led by 1984 to the NMR method for protein structure determination in solution. Our results were occasionally met with doubts and disbelief, so that considerable moral strength and perseverance was at times called for.  During my student years from 1957-1962, NMR spectroscopy was just being introduced as an analytical tool in chemistry, molecular biology was not yet established as an independent discipline, and the initial three-dimensional protein crystal structures were just emerging. My education at the University of Bern could thus not possibly cover the areas of our current research. The faculty and the student classes in Bern were small in numbers, with three physics students and seven chemistry students starting in 1957. From my curriculum in chemistry, physics and mathematics, I best remember intense work in linear algebra, classical mechanics, chemical thermodynamics, physical chemistry of synthetic polymers, and preparative biochemistry of proteins and nucleic acids. This combination turned out to be an excellent foundation for my later scientific activities. The last two years of formal education, from 1962 to 1964, were spent at the University of Basel, majoring in sports and getting a Ph.D. in chemistry. Studying sports included about 25 weekly hours of intense physical exercise as well as premedical courses in human anatomy and physiology. Combined with experience gained from observations made on myself in the pursuit of competitive sports, this provided an additional dimension to my education. The subject of my Ph.D. thesis in inorganic chemistry with Professor Silvio Fallab was the catalytic activity of copper compounds in autoxidation reactions, and for this project the availability of a state-of-the-art EPR spectrometer in the Physics Institute was a great opportunity.  Studying natural sciences has always been a lot of fun for me, but nonetheless my mind was quite solidly set on a career as a high school teacher with a heavy involvement in sports. In parallel to my studies in natural sciences, I extensively yielded to what I thought to be my vocation. Thus, during the years 1957-1962, I spent part of each winter as a ski instructor in Swiss mountain resorts. From 1959 to 1965, I had part-time jobs in high schools, first teaching physics at the Kantonsschule Solothurn, then chemistry at the Gymnasium Biel, and finally gymnastics at the Mädchengymnasium in Basel. These teaching assignments also had an important impact on my personal life. In 1961, while on my job as a ski instructor in the resort town of Saanenmöser in the Berner Oberland, I met my wife, Marianne Briner, who at the time was an elementary school teacher. We were married in 1963, and Marianne then joined me in studying sports at the University of Basel, graduating with the “Eidgenössisches Turn- und Sportlehrerdiplom” and specializing in modern dance. After the graduate student and postdoctoral years we started a family, with our son Bernhard Andrew being born in 1968 in Berkeley Heights, NJ, USA, and our daughter Karin Lynn joining us in 1970 in Greifensee near Zürich, Switzerland.  After finishing my graduate studies I spent another year in Basel concentrating on EPR studies of metal complexes in solution. In the spring of 1965 we moved to the USA, where I joined Professor Robert E. Connick at the University of California, Berkeley, for postdoctoral training. We used NMR spin relaxation measurements of 17O, 2H and 1H in addition to EPR for studies of the hydration of metal ions and metal complexes. The Berkeley period was devoted to intensive work on the theory of nuclear spin relaxation, group theory and quantum mechanics, which was motivated by Bob Connick’s weekly group seminar, a graduate course on “Group Theory and Quantum Mechanics” by Professor Michael Tinkham, and an intense collaboration with another Swiss postdoc, Alex von Zelewsky, who soon thereafter accepted the chair of inorganic chemistry at the University of Fribourg in Switzerland. Over the years, Marianne and I returned at regular intervals to Berkeley, to renew the friendships of the 1960s and revive fond memories.  In October 1967 I joined the Biophysics Department of Dr. Robert G. Shulman at Bell Telephone Laboratories in Murray Hill, New Jersey. I was given responsibility for the maintenance of what was one of the first superconducting high resolution NMR spectrometers, which operated at a proton resonance frequency of 220 MHz, and I was otherwise free to use this instrument for “research on protein structure and function”. Due to my background, my interest was focused on metal centers rather than on polypeptide chains, and all my initial projects in high resolution NMR had to do with hemoproteins. Using blood sampled from my arm in the first aid station, a Japanese colleague at Bell Labs, Dr. Tetsuo Yamane, prepared “hemoglobin (KW)”, and within a few months we found entirely new avenues of deriving information on structure-function correlations from the NMR spectra of hemoglobin and other hemoproteins. These projects were a lucky choice: with the limited sensitivity and spectral resolution of the instrumentation available in 1968, the special spectral properties of hemoproteins were a great asset for successful NMR applications. Many years later, the unique NMR spectral features that enabled the early work with these metalloproteins had an important role in various aspects of the development of the NMR method for threedimensional protein structure determination.  In October 1969 I returned to Switzerland to join the ETH Zürich. From the start I was equally well equipped with NMR and EPR instrumentation as previously at Bell Telephone Laboratories, and during the following 32 years the ETH provided us in regular intervals with the most advanced NMR equipment. Until 1975 I was working with a small group of students, a chemical engineer, Rudolf Baumann, who has stayed with me throughout all these years, and a postdoctoral associate with a physics Ph.D. in solid state EPR, Dr. Regula Keller, who largely took responsibility for the research with hemoproteins from 1970 to 1982. In 1973, Gerhard Wagner decided to do his graduate work with me. Gerhard then stayed with the group until 1987, pursuing a classical European academic career with Habilitation before settling as a Professor at Harvard Medical School. Being able to keep outstanding junior scientists as research associates over extended periods of time was a special privilege enjoyed by senior faculty in the traditional “European system”, and the continued presence of Rudolf, Regula and Gerhard during most of my initial 15 years in Zürich was a key factor for success with our research program.  In Zürich, we continued research on hemoproteins with the use of NMR and EPR spectroscopy, where the biochemical work was mostly done by groups outside of the ETH who joined us for collaborative projects, and the spectroscopic work was done by Regula Keller, myself and a succession of graduate students. In addition, we started a program of systematic studies on the application of NMR techniques with polypeptides and small proteins. Spirits were kept high by successful studies of cyclic peptides in collaboration with the Head of the Institute of Molecular Biology and Biophysics, Professor Robert Schwyzer, the observation of unexpectedly well-resolved and longlived NMR lines of amide protons in the small protein basic pancreatic trypsin inhibitor (BPTI), and the discovery of “ring flips” in BPTI. On the main line of research, which should lead to a method for protein structure determination in solution, there was only little progress. In 1975, in an attempt to survey the state of the field of NMR spectroscopy with biological macromolecules, I wrote the monograph *NMR in Biological Research: Peptides and Proteins*. There were two principal conclusions from this venture that should greatly affect the continuation of our work plan. First, I fully realized that we really had been extremely fortunate in choosing hemoproteins as a focus for our early NMR efforts. Second, it became clear that attempts of the early 1970s to derive *de novo* three-dimensional protein structures from conformation-dependent proton chemical shifts was not a promising approach, independent of whether these shifts were caused by intrinsic or extrinsic diamagnetic or paramagnetic probes. We thus had to look for novel avenues for NMR structure determination, where hemoproteins with their unique NMRspectral properties could be an ideal testing ground for new ideas.  Shortly after I had learned my lessons from writing the 1976 monograph, the conditions under which I could pursue my work evolved in quite important ways. After working for more than 5 years with a small group of students and research associates from the environs of Zürich, and being able to spend long hours of my own time at the bench and on the NMR spectrometers, I found myself suddenly surrounded by more than 20 postdoctoral fellows and students from all over the world. At around the same time, I also started to travel quite extensively in all parts of the world, with a first visit to India at the end of 1974, and a first “round-the-world” trip including stops in the USA and in Japan in the fall of 1975. The visits to India and Japan resulted in new, lasting friendships with local colleagues, and also in attracting a number of most talented postdoctoral fellows to Zürich. Ever since, professional travel has become an important part of my activities. Over the years this also included visiting faculty appointments at the University of California, Berkeley, Cornell University in Ithaca, NY, Johns Hopkins University in Baltimore, MD, the California Institute of Technology in Pasadena, CA, the Scripps Research Institute in La Jolla, CA, RIKEN in Tokyo, Japan, and the University of Edinburgh, UK. Spending part of my time in these places of highest standards added greatly to my quality of life as well as to the progress of our research in Zürich. The international aspect of my activities got a special boost in 1975, when – out of the blue – I was elected to membership in the Council of the International Union of Pure and Applied Biophysics (IUPAB). There was little work involved in this assignment, but in 1978 my IUPAB affiliation changed to being its Secretary General, and with this I also became a member of the “General Committee” of the International Council of Scientific Unions (ICSU) and of the ICSU Standing Committee on the Free Circulation of Scientists. During the six-year term as Secretary General the demands on my time were thus quite heavy. Fortunately, Marianne agreed to run the IUPAB office. This made things easier, since she would travel with me and we dealt with the IUPAB business in makeshift offices temporarily installed in hotels all around the world. The sunny side was that I got to know many prominent scientists, whose names I had previously mostly known from the textbooks. For example, structural biology was represented in the IUPAB Council from 1978-81 by Britton Chance, Henryk Eisenberg, David Phillips, Frederic Richards and Akiyoshi Wada, a true center of excellence! In the business meetings as well as in the social gatherings, we spent much of our time discussing the latest research advances long before they appeared in print. There was a particularly close collaboration with the IUPAB Presidents during my tenure as Secretary General, Professor Setsuro Ebashi and Professor Richard Keynes. Richard Keynes is a great-grandson of Charles Darwin. During IUPAB-related joint travel in Europe and the Far East in 1982/83, I listened to a more and more enjoyable but seemingly endless series of presentations of his “Darwin Lecture” commemorating the 100th anniversary of Darwin’s death; in return, Richard lived through a heavy dose of biomolecular NMR spectroscopy.  Through my association with ICSU and IUPAB, I also got involved in entirely novel business. Most notable in hindsight were negotiations during the period 1980-1983 about joint adherence of China and Taiwan in international science organizations. We eventually defined terms and conditions for adherence to IUPAB of both “The Biophysical Society of China located in Beijing, China” and “The Chinese Biophysical Society located in Taipei, China”. This involved extensive, highly formal correspondence, as well as visits and personal negotiations with Government and Academy officials in both countries. I also participated in IUPAB and ICSU programs of support for scientists in developing countries, and I organized summer schools and symposia in Africa, the Far East and Latin America. This all greatly influenced my outlook to the world. Although each year the IUPAB-related activities and my research-related travel kept me out of my laboratory for several months, the effect on our research was overall highly beneficial. As a bonus, I gained experience in directing a research group at a distance, and my junior associates could test their own initiatives during my absences.  With all the new talent assembled in my group by 1976, we started to develop new NMR experiments and novel algorithms for the structural interpretation of NMR data, which eventually resulted in the NMR method for protein structure determination. This included the identification of the nuclear Overhauser effect (NOE) as a NMR parameter that can be related in an unambiguous way to three-dimensional macromolecular structures. We made used of the outstanding resolution of parts of the hemoprotein 1H-NMR spectra for calibrating NOE distance measurements with the then-available onedimensional (1D) NMR techniques. In addition to Regula Keller, Sidney Gordon, a sabbatical visitor, made a key contribution with the introduction of the 1D “transient NOE” experiment. Subsequently, the NOE had a key role in the approach used for obtaining sequence-specific assignments of the many hundred to several thousand NMR lines in a protein. The “sequential assignment strategy” was initially implemented by Gerhard Wagner and a diploma student, Andreas Dubs, using 1D NOE and spin decoupling experiments. In parallel with the 1D NMR investigations on NOEs and NMR assignment, the development of two-dimensional (2D) NMR techniques for macromolecular studies had been started in 1976 as a joint project with Professor Richard R. Ernst, (Nobel prize in Chemistry, 1991). In 1977 the first 2D NMR spectrum of a protein was recorded, and by 1980 we had assembled four 2D NMR experiments that were then used for the initial protein structure determinations: COSY (2D correlated spectroscopy), SECSY (2D spin-echo correlated spectroscopy), FOCSY (2D foldover-corrected correlated spectroscopy) and NOESY (2D nuclear Overhauser enhancement spectroscopy). It was a lot of fun at the time to decide on these acronyms! Soon my group started to use 2D NMR experiments in daily practice, and the experience from more than a decade of one-dimensional NMR spectroscopy with proteins was happily and profitably married with the new potentialities of 2D NMR.  By 1982, complete sequence-specific assignments had been obtained for a small protein, BPTI, and for the polypeptide hormone glucagon bound to lipid micelles. This was published in a series of four 1982 papers. Although the first one of these papers already outlines the presently used protocol for protein structure determination by NMR, it took two more years of intense work on metric matrix distance geometry algorithms and their implementation in efficient software packages before the first NMR structure determination of a globular protein, bull seminal protease inhibitor (BUSI), could be completed. A large number of brilliant junior scientists working in my group from 1976 to 1985 contributed directly or indirectly to this result: Gerhard Wagner was involved in each step of the project; Kuniaki Nagayama and Peter Bachmann devised the first generation of 2D NMR experiments for studies of biological macromolecules and wrote the software needed to handle such data with the then-available limited computational facilities; Anil Kumar recorded the first 2D NOESY experiment with a protein; Gerhard Wider made key contributions to 2D NMR spectroscopy and to the sequential assignment method; Werner Braun, Martin Billeter and Timothy Havel started a tradition in my laboratory of theoretical work on the structural interpretation of NMR data; Peter Strop prepared BUSI and worked on its resonance assignments; finally, Michael Williamson and Timothy Havel actually solved the structure of BUSI. They all, and many additional students and postdoctoral associates from the “heroic period” 1976-85 have in the meantime started highly successful independent academic careers.  The completion of the first NMR structure of a protein brought new, unexpected challenges. When I presented the structure of BUSI in some lectures in the spring of 1984, the reaction was one of disbelief and suggestions that our structure must have been modeled after the crystal structure of a homologous protein. Apparently the structural biology community had thoroughly adjusted to the role of NMR as a method that could provide some exotic supplementary data, but which would not be suitable for *de novo* structure determination at atomic resolution. The criticism raised had two major consequences. The first one resulted from a discussion with Professor [Robert Huber](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1988/index.html) (Nobel laureate in Chemistry, 1988) after a seminar in Munich on May 14, 1984. Robert proposed to settle the matter by independently solving a new protein structure in his laboratory by X-ray crystallography and in my laboratory by NMR. For this purpose, each one of us received an ample supply of the \_-amylase inhibitor Tendamistat from Hoechst AG. Virtually identical three-dimensional structures of Tendamistat were obtained by NMR in solution and by X-ray diffraction in single crystals, which settled matters once and for all. This was particularly comforting in the context of the fact that the subsequently solved NMR structure of metallothionein was completely different from an independently solved metallothionein crystal structure (it took six years before the crystal structure was redetermined and found to coincide with the NMR structure!). The second consequence was that I asked for a sabbatical leave and ended up in Wengen, a beautiful mountain resort in the Berner Oberland. This was possible because I was also finishing my 6-year term as the Secretary General of IUPAB in the summer of 1984. Considering the critical reaction to the initial NMR structure determinations, I felt that it was important to document our work in a complete and detailed fashion. I thus had good reasons to honor my commitment of writing a monograph on the Baker Lectures, which I had delivered in 1983 at Cornell University. As I spent much of the time alone in Wengen, with my family joining me for weekends and vacation periods, work progressed well. “NMR of Proteins and Nucleic Acids” covers primarily work in my research group during the period 1977-84. It also turned out that directing my research group at a distance was surprisingly successful, and since the manuscripts were typed in Zürich from my handwritten notes, it helped that even ordinary mail was still reliably delivered within one day within Switzerland. It was therefore an easy decision for me to extend the stay in Wengen from the originally planned 6 months to 18 months. Besides the deskwork, important occupations in Wengen were skiing in the winter, and jogging and mountain climbing in the summer. According to my diaries I did not miss a single day of skiing from December 1, 1984 to April 10, 1985. This made up for having stayed away from the ski slopes during the 14 years from 1971 to 1984 because of my other professional activities. I also returned to the skiing outstation of the Federal Sports School in Mürren for a much-needed overhaul of my skiing technique, and participated in the organization of the famous Lauberhorn ski race in Wengen.  In the spring of 1986, after a second winter of skiing in Wengen, I had thoroughly cleaned up the backlog of unpublished material, in addition to having finished work on the Baker Lectures monograph. Protein structure determination by NMR had by then found its believers, as documented by the fact that the first printing of my new book was sold out within a few weeks. For us, a new chapter had to be opened, and we established contacts with biochemists and molecular biologists for the real test of the NMR technique in applications to biologically interesting systems. By 1990, a collaboration with Professor Walter Gehring of the Biocenter at the University of Basel yielded structure determinations of the *Antennapedia* homeodomain and its complex with the operator DNA. Using this structure as a platform, additional NMR experiments provided entirely novel insights into the role of hydration water for specific DNA recognition. A NMR structure determination of the cyclophilin A-cyclosporin A complex was pursued as a joint project with two former graduate students, Hans Senn, and Hans Widmer, and their research team at Sandoz AG. It had immediate practical impact, since the structure of the bound immunosuppressant turned out to be very different from the only other structural information available at the time, *i.e.*, crystal and NMR structures of free cyclosporin A. It was, for all involved, a completely unexpected and for many reasons surprising result!  In yet another exciting collaboration, with Professor Rudi Glockshuber at the ETH Zürich, we completed a structure determination for the C-terminal half of the mouse prion protein in April 1996, barely 10 days after the BSE-crisis in Great Britain broke into the open. With this timing, the prion protein structure had high visibility also in the popular media. In 1997 we succeeded to characterize the structure of the intact prion protein, and found that the N-terminal half of the molecule forms a highly flexible, extended “tail”. The prion protein thus presented a striking illustration of the unique power of NMR to characterize partially structured polypeptide chains. Others among the more than 70 protein structure determinations completed in my laboratory functionally relate to enzymology, toxicology, chaperone-mediated protein folding, and intercellular signaling.  The biological and biomedical projects pursued during the past 16 years with the use of the NMR technique have added and still add greatly to the quality of my professional life. In these endeavors, the quite extreme specialization needed to maintain a high standard of structure determination breaks open in that I learn about an ever-increasing range of biological systems and biomedical problems. I feel very fortunate that my field of specialization thus leads me to an education in biology from people who have high standards, and who sometimes even tend to consider me as one of their own. |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** |  |
| **Interview** |  |
| Q2 | **How did you start in this field?** |
|  | Kurt Wüthrich: I started in the field of magnetic resonance spectroscopy when I was 22 years old. |
| Q4 | **You are in the field of proteomics, which is a very new field in science?** |
|  | Kurt Wüthrich: We have been working with proteins. I’ve started to work with proteins in 1967 and the transition from working in structural biology with proteins to working in proteomics is as much a semantic transition, as it is also a transition which is substantial. |
| Q10 | **I could at least believe that you work with it because it is so beautiful, it’s like a piece of art. That is one protein?** |
|  | Kurt Wüthrich: Well, this is one system of protein with a very important reaction partner, in this case the reaction partner is shown in red, blue and grey colours. These are what we would refer to as functional colours whereas the receptor protein, that is the protein inside the cell, that would bind this smaller effector molecule is shown in light blue. |
| Q4 | **What does it do, this reaction part?** |
|  | Kurt Wüthrich: This is cyclosporin A. Cyclosporin A is a drug that prevents rejection of foreign tissue after an organ transplantation. It is sold under the name *Sandimmun*, it used to be a major product of the Sandoz pharmaceutical company. When we studied this structure, we had what is perhaps the biggest surprise I ever had in my career, we obtained the structure in which that molecule, after binding to its target in the cell looked when compared to its structure in the free state, looked that if a glove that has been ripped off your hand, with the inside coming out. A very big surprise which then gave important new information on possible modes of interaction of this drug molecule with its receptor and thus, in the next step, new guidelines for further research on this system. |
| Q10 | **How are they so beautiful, colourful, when you look at them?** |
|  | Kurt Wüthrich: This is what we add to our results. Proteins *per se* do not appear coloured to our eyes, except when they are combined with certain functional groups that are not of protein character and that may be visibly coloured. |
| Q14 | **One of the goals of proteomics is to make a full list of all the proteins, is it right?** |
|  | Kurt Wüthrich: This is what has originally been proposed as the goal of what is called structural genomics. I think we should no longer talk about structural genomics, we should talk about proteomics and structural proteomics. I believe that the goals of structural proteomics have been rephrased, in particular on the side of the commercial enterprises who have also entered this field in that one has rather gone away from the idea of establishing a complete atlas of all three-dimensional proteins folds but rather focuses on certain classes of proteins and performs in depth studies that would go far beyond full determination and would include information relating to the functional properties of these proteins. It has also been clearly shown that the high- throughput  technology, which is of course one of the key gadgets that have been introduced with structural proteomics, are particularly easy and efficient to be used for serial investigations of closely similar proteinic systems. For example, given protein receptor studied with a large library of small ligand molecules that bind to it in order to get lead information for drug design, for example. |
| Q4 | **How many proteins are there, if there are 30,000 genes. It’s just billions?** |
|  | Kurt Wüthrich: Well, I said an infinite number in principle. This of course is an exaggeration, but it can be a very large number. I mean, the proteins that are combined with carbohydrate moieties, they’re made typically from one gene, you may get tens of thousands of very slightly different carbohydrate moieties attached to the protein in the so-called glycol proteins. It is well known that the carbohydrate parts are highly heterogeneous so you may have very wide variety there. |
| Q14 | **My final question would be, what do you think will be the next big discovery in this field?** |
|  | Kurt Wüthrich: You see, in structural proteomics, we are faced with an enormous task of characterising not only one product per gene but a large multitude of gene products per gene and right now, it appears that we have to accumulate a large number of data. I mean in a typical proteomics project, we will no longer focus on one protein structure and try to make sense out of that structure, we would rather try to determine dozens or hundreds of structures and then from comparison of this data, derive novel information. This all looks extremely complicated, it looks as if an incredibly large amount of work will be needed and I think that a big breakthrough to be anticipated is that we will find simplicity in this very complex material that by getting a sufficiently large sample of experimental data, someone will all of a sudden again see common simplifying lines which might then enable us to handle the complexity of the proteome without undue demands on time, labour and money. |

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| **Chemistry\_2024-2000** | |
| **ID** | 0359 |
| **Biographical** | I was born in Taunton, Massachusetts on June 1, 1917, but I actually grew up in nearby New Bedford. My family background was heavily slanted toward business and seafaring matters. I can’t think of any relatives that ever went into science. My family gave me the best in education. To my father, business was the highest calling, but to my mother, medicine was the top profession. She would probably have gone to medical school if she had been born in a more enlightened era.  I went to boarding school at Berkshire in western Massachusetts, definitely the most beautiful part of the state. I’ll never forget the fall colors on the Berkshires. In those days I was terrible at athletics and never made a team, but quite easily led my class in academics. I was particularly good at math and science. I also got a good lesson in New England thrift. To get free ice for our physics experiments we had to wait until it snowed.  On graduating, I was easily admitted to Harvard. In that era all one had to do was pass the College Board exams. If any one in my family went to college that was where he went. My father spent a year there and quit to go into the textile business. At this point I was strongly advised that I was too young socially to go to college so I took a second senior year at Andover, another boarding school. At that time many students did this. At Andover I took my first chemistry course from a teacher named Bushy Graham and was fascinated by the subject. I remember him trying to explain Avagadro’s number and his discussion of the dangers of hydrogen and oxygen. At the end of the year, I took a competitive exam and won my first prize, the $50 Boylston prize in chemistry.  That summer I took a cruise on a 75-foot schooner with no engine, sailing from Gloucester, Massachusetts to Norway. We sailed around the Baltic ending up at Stockholm. I didn’t think of it at the time, but we spent most of three weeks on the north Atlantic with no contact at all with the outside world. Today one is always in touch with home base even if you go to the South Pole or the Moon. Memories of this sailing trip have always been vivid. On one instance we were mistakenly arrested in Tallin, Estonia and got a ride in the paddy wagon. Later we were released without comment. Little did I think that one day years later I would be returning to Stockholm to share the Nobel Prize in Chemistry.  At Harvard I majored in chemistry with a strong inclination toward math. I took the minimum of humanities. I was told I’d be a natural for physical chemistry but taking organic with Louis Fieser changed my mind. It was there I got my introduction to optical isomerism and the tetrahedral carbon atom. At Harvard competition was fierce and I always got a solid B, but not the straight A’s of many of my class mates. These were the days when most got a gentleman’s C.  On graduating in 1939 I was strongly advised to go elsewhere to graduate school. I went to Columbia with Professor Elderfield and worked on making simple analogs of the cardiac aglucones. These were tested at Eli Lilly for cardiac activity. Bob Elderfield was at his best when he talked steroids when he was at Rockefeller Institute. Paralleling Nobel’s experience I too had an explosion. Mine came when distilling diazomethane. No one was hurt, but a bottle of intermediate that I had labored on for months was destroyed.  In those days Professor Elderfield spent a lot of time away on the anti-malarial project in the military, and we were on our own a lot. Professor Nelson Leonard, long at the University of Illinois in Champagne, was in our research group. Later he consulted at Monsanto.  New York was an exciting place to be in those war years and my draft board forced Columbia to push me out sooner than would ordinarily happen. In those days industry would hire any chemist that could breathe. In 1942, I started in Dayton, Ohio at the Thomas and Hochwalt laboratories, which had recently joined Monsanto. Most of my assignments were pretty mundane, like making super pure hexamethylenetetramine to be used for making the explosive cyclonite.  In 1944, I was transferred to St. Louis to work on plasticizers and intermediates. We did make a lot of benzyl benzoate as a mite repellant for soldiers clothing. We later had a DDT project which never got into production until the war was over. More interesting, we had a synthetic process for vanillin but lost out to lignin as a way to get that desirable molecule. In those days we did get involved with the custom manufacture of the antibiotic chloramphenicol and made 10-15000 lbs. before it was taken off the market because a very small percentage of patients developed aplastic anemia. At the time my dog had a fungus on her chest that wouldn’t heal and resisted treatment. I made an ointment with our product and it cleared up in two days. She lived to 17 years.  Shortly after the war the discovery that cortisone might become a large volume pharmaceutical caused Monsanto to engage Professor Woodward with the hope of commercializing his synthetic approach. I was selected to join this effort since I had a steroid background.  Actually I got to spend nine months in his lab at Cambridge on this total synthesis. The experience working with the “great man” is one I’ll never forget. For the first three months in his lab he would come in at noon and say, “Let’s go to Schrafts.” We would spend an hour or more scribbling chemical structures on the menu or placemats. His phenomenal memory was beyond anything I’d ever seen. In those days he never kept a file or wrote a reference. He’d just say look on page so and so in Beilstein and you’ll find something on that. He lost some of this ability as he grew older and it bothered him. He really hoped Monsanto would commercialize his steroid synthesis, but the Mexican yam with its high content of diosgenin eventually killed our effort. Our program for cortisone got fairly well along. We made a few milligrams of racemic cortisone and we had resolved an early intermediate which we intended to carry through to the real thing. It was made too complex to compete with the lowly yam.  Later in the fifties I got involved in kinetic studies using my long forgotten math background. These studies led to improvements in several of our processes by doubling production with little or no additional capital. In those days, industry was hungry for chemicals and much effort was spent to get more out in the same equipment.  Monsanto had developed a separate line of advancement for those who wished to stay in technology and I rose to the top of that ladder before I even thought of asymmetric hydrogenations. I was one who liked to work with my hands as well as my brain. Chemical research in the lab was ideal for filling this need. The work on the asymmetric project, which started in the mid-sixties, is the subject of my lecture. Obviously, I kept active in this area until I retired in 1986, and continued in a consulting capacity for several years after.  On the home front we had purchased a cabin in Jackson Hole, Wyoming 25 years ago and have spent summers and some winter skiing time there ever since. It is there that our four children and four grand children often meet. On several occasions, Professor Kagan has visited us there and we’ve been able to talk asymmetric hydrogenations. I have always loved doing things outdoors, including fly-fishing, hiking and biking. When things are going wrong I find splitting wood quite therapeutic.  I received a number of awards for our work. |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** |  |
| **Interview** |  |
| Q4 | **William Knowles, Ryoji Noyori and Barry Sharpless, my congratulations for this year’s Nobel Prize in Chemistry. And also welcome to this Nobel interview. All three of you are organic chemists and this means that you are looking into the chemistry of life. How would you describe the work of an organic chemist? Is the work that you are doing in your laboratories trying to imitate what nature does in the real world? Is this the right description?** |
|  | Ryoji Noyori: Not really so.  William S. Knowles: We make big molecules, that’s what nature does and we try to copy nature. And I think big complicated molecules. |
| Q4 | **And you can find them in nature?** |
|  | William S. Knowles: Nature is full of them. We’re all great big molecules.  K. Barry Sharpless: I feel like we copy nature because we are nature. There’s a reverence for life’s chemistry that came from the origin of our field. In the beginning, Berzelius, here in Sweden, he didn’t really believe this. Stories about him were marvellous because he discovered selenium, which my first love is a research element. But I think he died believing in the vital force.  But his student, Wöhler, was the first person who made an organic compound. It was thought that you had to have an animal to make organic compounds. It was called vitalism or vis vitalis. So that monopoly was broken by Wöhler and he said I have to tell you Professor Berzelius that I found I can make urea without the help of a kidney or the dog or its kidney, or whatever. And that was the beginning of organic chemistry. We suddenly found we could actually make them.  Ryoji Noyori: And there are many important and useful compounds in nature. But that’s not enough. We need many other, more important artificial compounds, which can be synthesised by chemists. |
| Q15 | **We need artificial compounds for what?** |
|  | Ryoji Noyori: For pharmaceutical drugs, in many cases artificial. So we have to synthesise using our chemical knowledge. That is our aim.  K. Barry Sharpless: Most of the drugs on the market today are no longer natural compounds, the only one I can think of is morphine.  William S. Knowles: Aspirin. There isn’t enough aspirin available to provide the demand, we have to make aspirin. And that was a tough synthesis in its day. |
| Q18 | **You use the words ‘blind watch-maker’, Barry, can you just talk about that?** |
|  | K. Barry Sharpless: It’s a book by Richard Dawkins and I particularly enjoy reading his works. He wrote *The Selfish Gene* and *The Blind Watch-Maker*. *The Selfish Gene* really hits you in the face because it says that everything, the grass, the flowers, the poinsettia’s behind you are us, the weed in the field. A lot of us have the gene. Some of the proteins and the genetic compounds are in insects and us. There’s so much that’s there just as a piece of boiler plate material that’s been there for billions of years. We are survival machines for genetic material, if you look at it coldly. And the genetic material picks combinations of genes, travelling companions that have survival value. In a sense, the cold-blooded way of viewing this is our organism part, our system that’s closed and functioning, is just a way to push genetic material into the future.  And then coming along behind that, Dawkins wrote *The Blind Watch-Maker*, which is if you look at life it seems impossible to imagine it wasn’t somehow created from above because it’s too invested in so many complexities. How could you get there if you weren’t there? There’s a chicken and egg problem that’s massive. And the idea of *The Blind Watch-Maker*, Dawkins says well how else could you get there? We had four billion years and a planet for this system to evolve and if you just cobble together things, and when life discovers a new way, it never throws out totally the old stuff. You know, it’s not the nature of the way that organisms can function. They learn something, it’s not quite perfect, they learn something else. This whole thing is so then complicated that we don’t know how it really works and we can’t imagine, so that’s why it’s *The Blind Watch-Maker*. In a sense, the only way it could have gotten there is by the way it got there.  William S. Knowles: But it’s interesting, we are capable of making all the parts, we don’t know how to put them together for the living cell. We can’t think of any of the parts of the living cell that we can’t make. But we have no idea how to put them together to get something that works like that. No idea. |
| Q18 | **Do you think that this is a problem of science, that it’s so reductionistic, that you see only the small details, the atoms and molecules, or as you say even big molecules, but these are very, very tiny parts of the whole? How can you get this whole picture then?** |
|  | Ryoji Noyori: It’s difficult at this moment.  William S. Knowles: It’s beyond us at this moment. It may not be by the next 100th anniversary though. When one looks ahead it’s very dangerous to say that it’s not impossible.  K. Barry Sharpless: But you hit the nail in that reductionist is the problem humans have and we get attracted to things we can understand and we go in deep on solving puzzles, but we don’t notice, and we like to see things sitting still. If something is moving it’s blurry usually and that’s what our area is, the three of us, we work on catalysts. Everything that’s moving, by definition, and if you see it sitting still, you can’t gather the essential facts about it. So that’s kind of a nice metaphor for complexity. Catalysts in life are always moving. Life itself is not what we see here in front of you. If the energy is not pouring through the system, the message that’s being read out is there are selective catalysts in our bodies, they’re burning energy. If you froze me and sent me to the other side of the universe and I was just the corpse then, there is no easy way to tell what the function of this machine was.  Ryoji Noyori: Understanding is rather easy, however more important is the creation of new functions. That’s very difficult. |
| Q18 | **What does it mean, understand? Can we tell what is life?** |
|  | Ryoji Noyori: No, I mean if you go to school and you have a class and the teacher will tell something, and you understand it. And that’s easy. But is that really full understanding?  William S. Knowles: But your question can we understand and define what life is? And this would take a lecture. You can’t just sit down and define life, can you? I don’t think we can. We can define the characteristics of life and it’s about five or six characteristics that all life seems to have, but we have a hard time saying this is not life and this is life. But we seem to know this, don’t we? That’s funny.  K. Barry Sharpless: But I think that distinction is going to be more and more blurred. There’s this new school of thought, the born and the made are going to move together in the next thousand years. And I definitely think it’s got to happen. These people that have always this cell phone here, I mean why not have it somehow built in? Some people don’t function without one. So there’s going to be a way to integrate the born and the made a little bit.  It’s a little strange idea but no, this is the way the world seems to be heading. It’s almost like science fiction but its not because if you think about it, well one thing I read, if you get to another planet, you know how they test to see if there’s any amino acids or life there, if you saw a little box with four wheels on it, you wouldn’t have to search any further, you’d know there had been life on that planet. I mean there are certain complexities that only can exist through living things. I think the amazing thing is that we think we understand as much as we do.  Take one little cell, as far as I’m concerned, the medium is the message there. And people thing the genome is going to solve things, I think they’re absolutely crazy. And because this is a linear message and it’s all entangled in itself and you can probably get different functions out of that box that’s called a cell, thousands of different ways, you could tweak it in a thousand ways and every one of them would end up in the same function. That would be a drug function. So you think you had this target, but if you did three other things you would have the same result, you know? It’s just a matter of we don’t go at it that way, we go right there and we think we know that target is there, and we’re going to hit it. And then it doesn’t work when they do it and six things that were compensated and the thing doesn’t have a prayer from the beginning, but they assume it did.  Ryoji Noyori: The function or life itself is an integrative issue. And a global issue. And it’s very hard to make it, on the other hand you can understand in detail just by analysis.  K. Barry Sharpless: You can understand within our sciences about what we know and how we know it. But it’s not about any absolute knowledge, we just have ways of knowing things that enable us to carry forward with so called advances. But I do think that the life issue, the complexity, is a fascinating area. My favourite book these days is *Out of Control* by Kevin Kelly and that’s a book that really describes some things that all of us can learn from. |
| Q4 | **You mean it’s impossible to imitate the one hand of nature by chemistry?** |
|  | Ryoji Noyori: So the distinction between the right and the left, because the right and the left has the same physical energy or same free energy.  William S. Knowles: And it’s still that way. |
| Q2 | **But do you recognise this way of making discoveries, that you have a problem and you are somehow waiting how to solve it? The solution comes just by random. Is this called serendipity?** |
|  | William S. Knowles: I don’t like the word serendipity. I prefer luck. Because I think serendipity, in my mind, doesn’t seem to imply much intelligence. It seems there were these guys wandering around and lucky things happened to them. To me it doesn’t, I like to think I had luck, but I like there was a little intelligence behind this.  K. Barry Sharpless: I think you’re right, the serendipity one is a bit too much like really luck. Sometimes people are calling intuitive as well, which is related to this idea of they’re going to be able to take advantage of serendipity more because they’re actually open to it. And I think intuitive is a way that people who aren’t creative will describe creative people because they don’t see the method by which the information leads these people to the answer they get. I mean people that are intuitive often take in as much, if not more information, facts and feelings and connections than the people who are linear. So I think intuitive people actually are just using their information in a different way.  William S. Knowles: It’s also that, at least certainly the breakthroughs in science, you almost have to be active and your lucky break comes along. Never where or when you expect it, and the ones that succeed take advantage of that lucky break. And most people don’t bother to take advantage.  Ryoji Noyori: So we should be lucky. But I think discoveries are made accidentally, but that’s not real accident. |
| Q18 | **But it’s not only that you understand the parts, but you are also fascinated by this world. So I have a final question, you live with the molecules or the chemistry, you see the beauty and fascination of this world, but there is still all those people out there that cannot understand what you see is the most beautiful thing in the world. How do you manage to bridge over this gap? Do you see it as a problem?** |
|  | William S. Knowles: Not very well. This is a big frustration, bridging over the gap. We’ve talked a lot about that this week but we really haven’t come up with terribly good ideas for doing it, I don’t think. But it is desirable to bridge it.  K. Barry Sharpless: I do it as best I can through the sensual approach, that is chemistry organic is right in there for you because they almost all have a taste and a smell. And the big ones don’t smell but the little guys smell. So we notice flowers, fragrances, body odours, oils on your skin, all those things are easy for people to get interested in. But as far as life goes, I’ve found myself being attracted back, having the adventure we’ve had, finding we can be promiscuous and not be very selective but still get right and left. I find to get at the complexity of life maybe I need to use her proteins and things as reaction vessels themselves.  So I have an idea where I’m going to try and go back to mother. Mother inspired us, she’s the enzyme to do the right and left. It turns out that’s easier than many parts of making complex structures. So my thought is to go back and now use the real power of nature. Put the real message in completely. The actual encoding of all those touches, the molecules are touched, everyone’s touching each other. When we do it we use our hands. Our hands are very big and we’re actually pretending to run reactions at the molecular level by using our hands. That’s what it comes down to.  Ryoji Noyori: So the chemists are being interested in the structure of molecules. And now we can fully understand the structure, but that’s not enough. So important is the creation of functions from organic molecules, that’s integrated matter and very difficult to understand. I think that we should know more about biology and also physics. That’s really an integrated pro-gender issue.  K. Barry Sharpless: The function is really what we need to deliver faster, especially at affordable price, medicine and materials that people can build with. And we just don’t have much experience with speeding up. This speed is a thousand times less than it should be if we’re going to try to provide for the rest of the world at a decent level, like we have here in Sweden and Japan and the United States.  Ryoji Noyori: And I think the scientific research has been analytical. However that should be more scientific. So the integration of many simple elements generating anew our functions.  William S. Knowles: We can go on this discussion forever really. It’s absolutely fascinating. |

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| **Biographical** | I was born on September 3, 1938 in a suburb of Kobe (now Ashiya), Japan, the first son of Kaneki and Suzuko Noyori. Our family moved to Kobe soon afterwards. I grew up with two younger brothers and a sister in a pleasant city blessed by beautiful natural surroundings. Except for a short period at the end of World War II, I attended an elementary school affiliated to Kobe University from ages six to twelve, and then moved on to Nada Middle and High School from ages twelve to eighteen. I enjoyed many out-door activities in my youth.  My father, Kaneki, was a gifted research director of a chemical company, and his profession strongly influenced the path of my life. At home, we were surrounded by his scientific journals and books and various samples of plastics and synthetic fibers, and were frequently asked to test the quality of products which were under development for commercialization. When I entered middle school, my father took me to a public conference, the topic of which was “nylon”. The lecturer explained proudly that this new fiber could be synthesized from coal, air, and water (the then famous catchphrase of DuPont company). Although I knew nothing about industrial technology, I was deeply impressed by the power of chemistry. Chemistry can create important things from almost nothing! The event had an enormous impact on this 12-year-old schoolboy, because it was in 1951, shortly after World War II when Japan was so poor. We were very hungry. It was at this point that it became my dream to be a leading chemist to contribute to the society by inventing beneficial products.  My appetite for chemistry was further wetted through class work led by enthusiastic teachers in middle/high school including Dr. Kazuo Nakamoto (then Osaka University and afterward Illinois Institute of Technology and Marquette University) who gave me my first chemistry lesson. I also liked other sciences and mathematics. Together with regular schoolwork, “judo” (one of Japan’s traditional sports) was a major passion at this time. It was very popular amongst us because Nada School and Kodokan Judo School were founded by the same family. I highly appreciate the educational efforts of many schoolteachers as well as the warm friendship of classmates in those days, which strongly influenced the formation of my personal character.  In 1957, at the age of 18, I entered Kyoto University, which was known to be the most active institution in the research of polymer chemistry. Incidentally, this was the year when the USSR launched into space for the first time an artificial satellite, the Sputnik, thereby demonstrating the power of sciencebased technology. I recall that this success substantially shocked young science students in Japan. After three years, I started to study organic chemistry, rather than polymer chemistry, under the guidance of Professor Keiiti Sisido. The laboratory environment was very hospitable and I obtained my Bachelor degree in 1961. Upon completion of my Master’s degree in 1963, I was immediately appointed Instructor of Professor Hitosi Nozaki’s laboratories at Kyoto University and, in 1967, received my doctorate (DEng). My career path, that is the appointment to Instructor without a doctorate, is a little unusual but this is partly due to the difference in Japanese and Western education/teaching systems. Professor Nozaki strongly encouraged us to pursue new, original chemistry rather than tracing traditional subjects, while I served as a leader of his subgroup working on flourishing physical organic chemistry. It was under such conditions that in 1966 we discovered an interesting asymmetric catalysis that later became a life-long interest. This finding emerged during the course of an investigation of the transition metal effects in carbene reactions. Reaction of styrene and ethyl diazoacetate in the presence of a small amount of a chiral Schiff base-Cu(II) complex gave optically active cyclopropane derivatives, albeit with E.J. Corey at Harvard kindly agreed to accommodate me in his laboratories as a postdoctoral fellow. This plan, however, was postponed for reasons outlined below.  The situation changed drastically in the fall of 1967, when I received a totally unexpected offer from Nagoya University. I was asked to chair a newly created organic chemistry laboratory. This invitation surprised me. I was a mere 29-year-old Instructor at Kyoto enjoying daily research work with some young students. Nothing had prepared me to be a Professor at a major national university. Being too young and inexperienced to be a Full Professor, I was first appointed Associate Professor of Chemistry. In February, 1968, when I launched my own research group, Professor Yoshimasa Hirata, a senior faculty known for his outstanding accomplishments in natural products of organic chemistry, asked me to create a new stream of organic chemistry at Nagoya, different from his own field, thereby making the Chemistry Department more visible. I immediately decided to focus on organic synthesis using organometallic chemistry, which then comprised a branch of inorganic chemistry. Although not many researchers were aware of the high utility in organic synthesis, I was intuitively confident of the bright future of this scientific field. Professor Hirata consistently helped me in many aspects during his time at Nagoya University.  In 1969, as planned earlier, I went to Harvard. I was amazed by the enormous difference in the standard of living and science between the US and my mother country. Professor Corey was then already a leading organic chemist and I learned much from him. In addition, I became acquainted with many promising students and postdoctoral fellows including K. Barry Sharpless who was working with Professor [Konrad Bloch](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1964/index.html). Later many of these reliable friends, together with their scientific relatives, grew to become eminent researchers in the scientific community and helped me in many ways. Synthesis of prostaglandins (PGs) was my research theme in the Corey group. After completing several works, I was asked to selectively hydrogenate a PGF2a derivative that has two C = C bonds to a PGF1a compound possessing a single C = C bond. This was the start of my three-decade-long work on hydrogenation. My interest in homogenous hydrogenation was enhanced by reading almost all available literature on this very new topic and also through personal interaction with Assistant Professor John A. Osborn, who had joined Harvard Chemistry Department from Geoffrey Wilkinson’s laboratory at Imperial College, London. Osborn, an authority of Rh-catalyzed homogeneous hydrogenation, taught me many aspects of organometallic chemistry. It was in 1968, when W.S. Knowles and L. Horner reported independently the first homogeneous asymmetric hydrogenation using chiral phosphine-Rh catalyts, albeit in low optical yields. The fruitful Harvard experience, coupled with our earlier asymmetric cyclopropanation in 1966, led to my life-long research on asymmetric hydrogenation.  After returning to Nagoya in 1970, I began to study organic synthesis and homogeneous catalysis via organometallic chemistry, while in August 1972, at the age of 33, I was promoted to Full Professor. In the hope of development of efficient asymmetric hydrogenation and other reactions, we became interested in BINAP [2,2′-bis(diphenylphosphino)-1,1′-binaphthyl], a novel C2 chiral diphosphine possessing a beautiful molecular shape. Synthesis of the optically pure diphosphine was unexpectedly difficult. It was in 1974, that I started stereospecific synthesis from optically pure 2,2′-diamino-1,1′-binaphthyl with my long-term collaborator, the late Professor Hidemasa Takaya, who was with me at Nagoya and afterwards moved to the Institute of Molecular Science and Kyoto University. After two years, we managed to obtain optically active BINAP, however, the result was disappointingly irreproducible. In 1978, we reached a reliable method for resolution of racemic BINAP with a chiral amine-Pd complex. Unfortunately, the results of BINAP-Rh(I) catalyzed asymmetric hydrogenation of dehydro amino acids were highly variable depending on the reaction conditions. Eventually, in 1980 after a six-year endeavour, thanks to the unswerving efforts of my young colleagues and students, we were able to publish our first work on asymmetric synthesis of amino acids via this BINAP chemistry.  The success in our asymmetric hydrogenation largely relies on the invention of BINAP and the use of Ru element, which behaves differently from conventional Rh. A major breakthrough in asymmetric hydrogenation came in 1986, when we developed BINAP-Ru(II) dicarboxylate complexes that enjoy a much greater scope of olefinic substrates. Furthermore, in 1987-1988, 179 we developed a versatile general asymmetric hydrogenation of functionalized ketones with BINAP-Ru(II) dihalide complexes. The scope of this method is far reaching. These asymmetric hydrogenation methods allow for the synthesis of a wide array of terpenes, vitamins, b-lactam antibiotics, a– and b-amino acids, alkaloids, prostaglandins, and other compounds of biological and physiological interest. BINAP chemistry has been applied to the large-scale production of the synthetic intermediates of antibiotic carbapenems (Takasago International Co.) and levofloxacin, a quinolone antibacterial agent (Takasago International Co./Daiichi Pharmaceutical Co.). The efficiency of BINAP chemistry rivals or in certain cases even exceeds that of enzymes. In addition, a team of the Noyori Molecular Catalysis Project (ERATO, 1991-1996) discovered the catalysts of type RuCl2(diphosphine)(diamine) leading to another major breakthrough in hydrogenation. The reaction of unsaturated ketones occurs preferentially the C = O function leaving the olefinic linkage intact. The combined use of the BINAP ligand and a chiral diamine effects asymmetric hydrogenation of a range of aromatic, hetero-aromatic, and olefinic ketones. The reaction is very rapid, productive and stereoselective, providing the most practical method for converting simple ketones to chiral secondary alcohols.  BINAP-Rh(I) complexes are useful for asymmetric isomerization of allylic amines to enamines of high enantiomeric purity. In the early 1980s, a fruitful academic/industry collaboration was made between the groups at Osaka University (S. Otsuka and H. Tani), Nagoya University, Institute of Molecular Science (H. Takaya), Shizuoka University (J. Tanaka and K. Takabe), and Takasago International Co., realizing the industrial production of (-)-menthol and other optically active terpenes.  In 1995-1996, we invented a range of Ru(II) catalysts modified with a chiral b-amino alcohol or 1,2-diamine derivative that effects asymmetric transfer hydrogenation of ketones and imines using 2-propanol or formic acid as hydrogen donors. More recently, the reaction has proven to proceed via a nonclassical metal – ligand bifunctional mechanism. My interest in asymmetric chemistry is broad. In 1986, we found a highly enantioselecive addition of dialkylzincs to aldehydes using a small quantity of a camphor-derived chiral amino alcohol, where the alkylation products with high enantiomeric excesses are accessible with a partially resolved chiral ancillary. We could fully elucidate the origin of this striking chiral amplification phenomenon at the molecular structure level. My stay at Harvard in 1969-1970 spurred me to develop an efficient way to synthesize prostaglandins (PGs). In this connection, a series of selective synthetic methods was explored in our laboratories. Our binaphthol-modified lithium aluminum hydride reagent (1979) was applied to the commercial Corey PG synthesis (Ono Pharmaceutical Co.). Furthermore, we realized the long-sought three-component PG synthesis in 1985, which now plays an important role in biochemical and physiological studies of PGs.  Chemical synthesis provides a logical basis for molecular science and related technologies which require a high degree of structural precision. I have 180 tried to select general and fundamental research subjects in this important field. A clear-cut solution to a long-persistent problem, when accomplished, often results in an enormous scientific or technological impact. Asymmetric hydrogenation is a typical example. BINAP chemistry is now utilized worldwide in research laboratories and also at the industrial level. In fact, the selective synthesis of single enantiomers using well-designed chiral molecular catalysts has now become common practice. This fascinating field is still growing rapidly, and recent advances have dramatically changed the way of chemical synthesis, opening tremendous potential for molecular technologies.  Our broad research activity goes beyond asymmetric synthesis. In 1994, we discovered the remarkable utility of supercritical carbon dioxide as a medium for homogeneous catalysis. Thus Ru-catalyzed hydrogenation produces formic acid, methyl formate, and dimethylformamide with an extremely high turnover number. More recently, we devised practical, environmentally sound methods for olefin epoxidation and alcohol oxidation using aqueous H2O2, whose utility is highlighted by the direct conversion of cyclohexene to adipic acid (1996-1998). The stereospecific living polymerization of phenylacetylenes was achieved by using a structurally defined tetracoordinate Rh complex (1994). We also developed an efficient synthesis of solid-anchored DNA oligomers using organopalladium chemistry (1990). In my early days at Nagoya, we invented the iron carbonyl-polybromo ketone reaction which allows the construction of five- and seven-member carbocycles in a 3 + 2 and 3 + 4 manner, respectively. In the late 1970s, we exercised initiative in the catalytic use of organosilicon compounds for organic synthesis.  Organometallic chemistry is a scientific space leading to an enormous technical impact and even more general social benefits. I am very pleased to be involved in contributing to the progress of this significant scientific realm. The above described scientific accomplishments are not my own, but the credit in fact belongs to my research family at Nagoya University and many collaborators at other institutions. My initial ideas in solving problems were not always appropriate and, sometimes even nonsensical. However, my serendipitous collaborators incubated such research themes through careful experiments and much deliberation, and eventually reached new chemical concepts and useful methodologies. Their intellect, sense, and skills are highly appreciated. In addition, through my frequent traveling abroad as a visiting professor or invited lecturer at research institutions and conferences, I have met many superb colleagues from the international scientific community. Their encouragement as well as the exposure to different cultures and environments have deeply affected my way of thinking. Furthermore, for over three decades, my scientific work has been supported generously and consistently by the Ministry of Education, Culture, Sports, Science and Technology of Japan as well as the Research Development Corporation of Japan, various private foundations, and numerous industrial companies.  My activities are not limited to education and research. I have served on the editorial boards of some thirty international journals including the editorship of *Advanced Synthesis & Catalysis* (Wiley/VCH) which emphasizes the “practical elegance” of chemical synthesis. Furthermore, I have been involved in much administrative work, for example, as Science Advisor (1992-1996) and Member of the Scientific Council (1996-present) of the Ministry of Education, Culture, Sports, Science and Technology; Dean of the Graduate School of Science at Nagoya University (1997-1999); and President of the Society of Synthetic Organic Chemistry, Japan (1997-1999). Such official duties significantly hamper my research activity but are unavoidable for a senior scientist.  In 1972, I married Hiroko Oshima (a daughter of a Professor of Medicine at Tokyo University) who was studying the immunology of cancer at a research institute in Tokyo. Since then, she has played the most important part in our private life at Nagoya. We have two children. Our first son, Eiji (born in 1973), is an active staff writer of a newspaper company, and our second son, Koji (born in 1978), studies painting at an art university in Tokyo. |
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| Q4 | **William Knowles, Ryoji Noyori and Barry Sharpless, my congratulations for this year’s Nobel Prize in Chemistry. And also welcome to this Nobel interview. All three of you are organic chemists and this means that you are looking into the chemistry of life. How would you describe the work of an organic chemist? Is the work that you are doing in your laboratories trying to imitate what nature does in the real world? Is this the right description?** |
|  | Ryoji Noyori: Not really so.  William S. Knowles: We make big molecules, that’s what nature does and we try to copy nature. And I think big complicated molecules. |
| Q4 | **And you can find them in nature?** |
|  | William S. Knowles: Nature is full of them. We’re all great big molecules.  K. Barry Sharpless: I feel like we copy nature because we are nature. There’s a reverence for life’s chemistry that came from the origin of our field. In the beginning, Berzelius, here in Sweden, he didn’t really believe this. Stories about him were marvellous because he discovered selenium, which my first love is a research element. But I think he died believing in the vital force.  But his student, Wöhler, was the first person who made an organic compound. It was thought that you had to have an animal to make organic compounds. It was called vitalism or vis vitalis. So that monopoly was broken by Wöhler and he said I have to tell you Professor Berzelius that I found I can make urea without the help of a kidney or the dog or its kidney, or whatever. And that was the beginning of organic chemistry. We suddenly found we could actually make them.  Ryoji Noyori: And there are many important and useful compounds in nature. But that’s not enough. We need many other, more important artificial compounds, which can be synthesised by chemists. |
| Q15 | **We need artificial compounds for what?** |
|  | Ryoji Noyori: For pharmaceutical drugs, in many cases artificial. So we have to synthesise using our chemical knowledge. That is our aim.  K. Barry Sharpless: Most of the drugs on the market today are no longer natural compounds, the only one I can think of is morphine.  William S. Knowles: Aspirin. There isn’t enough aspirin available to provide the demand, we have to make aspirin. And that was a tough synthesis in its day. |
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|  | Ryoji Noyori: It’s difficult at this moment.  William S. Knowles: It’s beyond us at this moment. It may not be by the next 100th anniversary though. When one looks ahead it’s very dangerous to say that it’s not impossible.  K. Barry Sharpless: But you hit the nail in that reductionist is the problem humans have and we get attracted to things we can understand and we go in deep on solving puzzles, but we don’t notice, and we like to see things sitting still. If something is moving it’s blurry usually and that’s what our area is, the three of us, we work on catalysts. Everything that’s moving, by definition, and if you see it sitting still, you can’t gather the essential facts about it. So that’s kind of a nice metaphor for complexity. Catalysts in life are always moving. Life itself is not what we see here in front of you. If the energy is not pouring through the system, the message that’s being read out is there are selective catalysts in our bodies, they’re burning energy. If you froze me and sent me to the other side of the universe and I was just the corpse then, there is no easy way to tell what the function of this machine was.  Ryoji Noyori: Understanding is rather easy, however more important is the creation of new functions. That’s very difficult. |
| Q2 | **What does it mean, understand? Can we tell what is life?** |
|  | Ryoji Noyori: No, I mean if you go to school and you have a class and the teacher will tell something, and you understand it. And that’s easy. But is that really full understanding?  William S. Knowles: But your question can we understand and define what life is? And this would take a lecture. You can’t just sit down and define life, can you? I don’t think we can. We can define the characteristics of life and it’s about five or six characteristics that all life seems to have, but we have a hard time saying this is not life and this is life. But we seem to know this, don’t we? That’s funny.  K. Barry Sharpless: But I think that distinction is going to be more and more blurred. There’s this new school of thought, the born and the made are going to move together in the next thousand years. And I definitely think it’s got to happen. These people that have always this cell phone here, I mean why not have it somehow built in? Some people don’t function without one. So there’s going to be a way to integrate the born and the made a little bit.  It’s a little strange idea but no, this is the way the world seems to be heading. It’s almost like science fiction but its not because if you think about it, well one thing I read, if you get to another planet, you know how they test to see if there’s any amino acids or life there, if you saw a little box with four wheels on it, you wouldn’t have to search any further, you’d know there had been life on that planet. I mean there are certain complexities that only can exist through living things. I think the amazing thing is that we think we understand as much as we do.  Take one little cell, as far as I’m concerned, the medium is the message there. And people thing the genome is going to solve things, I think they’re absolutely crazy. And because this is a linear message and it’s all entangled in itself and you can probably get different functions out of that box that’s called a cell, thousands of different ways, you could tweak it in a thousand ways and every one of them would end up in the same function. That would be a drug function. So you think you had this target, but if you did three other things you would have the same result, you know? It’s just a matter of we don’t go at it that way, we go right there and we think we know that target is there, and we’re going to hit it. And then it doesn’t work when they do it and six things that were compensated and the thing doesn’t have a prayer from the beginning, but they assume it did.  Ryoji Noyori: The function or life itself is an integrative issue. And a global issue. And it’s very hard to make it, on the other hand you can understand in detail just by analysis.  K. Barry Sharpless: You can understand within our sciences about what we know and how we know it. But it’s not about any absolute knowledge, we just have ways of knowing things that enable us to carry forward with so called advances. But I do think that the life issue, the complexity, is a fascinating area. My favourite book these days is *Out of Control* by Kevin Kelly and that’s a book that really describes some things that all of us can learn from. |
| Q2 | **So what was the idea?** |
|  | William S. Knowles: I think that every organic chemist has felt frustrated about having to resolve racemic mixtures. And this has limited what organic chemists have done. They say, oh god, I’ve got to resolve that, I don’t want to do that if I don’t really have to. And it’s a chore. And so I think they’ve all felt there should be a nicer way to get around this, but you have to wait until some good idea comes along. You see what others have done and they’re not really getting very far on the thing, there was a big Japanese programme with Akaburi on this rule, all aware of this I’m sure, but it didn’t look as if I could add anything to what they had done.  It didn’t look a thing, then suddenly something comes along and they say, well Jesus, this is a great new approach to this. Be worth trying. And that’s exactly what it was. But I wasn’t really thinking of any particularly molecule, I’d have settled for any molecule that I do around this, it wouldn’t make any difference. Any sort of what we call a pro-chiral molecule, pro-chiral molecule is your hydrogenates, you get a new asymmetric centre, racemic form. And so I would’ve settled for any one. Actually I chose one that never did work with us very well.  Ryoji Noyori: 150 years ago, Pasteur mentioned the dissymmetry is only in the strict boundary between the biological system and chemical or physical system. And he mentioned that it’s impossible to generate that dissymmetry by using a chemical or physical force. |
| Q4 | **You mean it’s impossible to imitate the one hand of nature by chemistry?** |
|  | Ryoji Noyori: So the distinction between the right and the left, because the right and the left has the same physical energy or same free energy.  William S. Knowles: And it’s still that way. |
| Q2 | **But do you recognise this way of making discoveries, that you have a problem and you are somehow waiting how to solve it? The solution comes just by random. Is this called serendipity?** |
|  | William S. Knowles: I don’t like the word serendipity. I prefer luck. Because I think serendipity, in my mind, doesn’t seem to imply much intelligence. It seems there were these guys wandering around and lucky things happened to them. To me it doesn’t, I like to think I had luck, but I like there was a little intelligence behind this.  K. Barry Sharpless: I think you’re right, the serendipity one is a bit too much like really luck. Sometimes people are calling intuitive as well, which is related to this idea of they’re going to be able to take advantage of serendipity more because they’re actually open to it. And I think intuitive is a way that people who aren’t creative will describe creative people because they don’t see the method by which the information leads these people to the answer they get. I mean people that are intuitive often take in as much, if not more information, facts and feelings and connections than the people who are linear. So I think intuitive people actually are just using their information in a different way.  William S. Knowles: It’s also that, at least certainly the breakthroughs in science, you almost have to be active and your lucky break comes along. Never where or when you expect it, and the ones that succeed take advantage of that lucky break. And most people don’t bother to take advantage.  Ryoji Noyori: So we should be lucky. But I think discoveries are made accidentally, but that’s not real accident. |
| Q2 | **But what does intuition mean in that, that you look at the right things?** |
|  | K. Barry Sharpless: You worked it, you kind of get attracted to the areas where you have a better chance. In this book, Kevin Kelly’s book, it’s kind of interesting, life itself is attracted to instabilities though. I mean it’s obviously connected, in my belief, all these things connect back to facts in the end. That the DNA does contain the information that leads these systems to where they go, but it almost seems like life systems want to be near the edge of chaos because his image is riding a wave, you know, surfer riding a wave.  If you’re up high on the wave and the wave goes forever and you can stay in the zone and you have movement, you have power, potential energy. If you get over the top of the wave, you could die. But if you’re down back on the wave in a trough, you can’t move. And move means evolve. You have to be having movement and life is attracted to instability and creative discoveries come from points of instability in chaos. You have chaos in catalysis. And catalysis is life really. You need to be near this slippery area, partly because you need speed. Speed is really crucial.  Ryoji Noyori: So the discovery is a matter about kinetics rather than thermal dynamics. We need some thermal dynamics and then we need some basic knowledge. But that’s not enough. |
| Q18 | **But it’s not only that you understand the parts, but you are also fascinated by this world. So I have a final question, you live with the molecules or the chemistry, you see the beauty and fascination of this world, but there is still all those people out there that cannot understand what you see is the most beautiful thing in the world. How do you manage to bridge over this gap? Do you see it as a problem?** |
|  | William S. Knowles: Not very well. This is a big frustration, bridging over the gap. We’ve talked a lot about that this week but we really haven’t come up with terribly good ideas for doing it, I don’t think. But it is desirable to bridge it.  K. Barry Sharpless: I do it as best I can through the sensual approach, that is chemistry organic is right in there for you because they almost all have a taste and a smell. And the big ones don’t smell but the little guys smell. So we notice flowers, fragrances, body odours, oils on your skin, all those things are easy for people to get interested in. But as far as life goes, I’ve found myself being attracted back, having the adventure we’ve had, finding we can be promiscuous and not be very selective but still get right and left. I find to get at the complexity of life maybe I need to use her proteins and things as reaction vessels themselves.  So I have an idea where I’m going to try and go back to mother. Mother inspired us, she’s the enzyme to do the right and left. It turns out that’s easier than many parts of making complex structures. So my thought is to go back and now use the real power of nature. Put the real message in completely. The actual encoding of all those touches, the molecules are touched, everyone’s touching each other. When we do it we use our hands. Our hands are very big and we’re actually pretending to run reactions at the molecular level by using our hands. That’s what it comes down to.  Ryoji Noyori: So the chemists are being interested in the structure of molecules. And now we can fully understand the structure, but that’s not enough. So important is the creation of functions from organic molecules, that’s integrated matter and very difficult to understand. I think that we should know more about biology and also physics. That’s really an integrated pro-gender issue.  K. Barry Sharpless: The function is really what we need to deliver faster, especially at affordable price, medicine and materials that people can build with. And we just don’t have much experience with speeding up. This speed is a thousand times less than it should be if we’re going to try to provide for the rest of the world at a decent level, like we have here in Sweden and Japan and the United States.  Ryoji Noyori: And I think the scientific research has been analytical. However that should be more scientific. So the integration of many simple elements generating anew our functions.  William S. Knowles: We can go on this discussion forever really. It’s absolutely fascinating. |

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| **Chemistry\_2024-2000** | |
| **ID** | 0361 |
| **Biographical** | From 6th through 12th grades I attended a Quaker school on the Philadelphia city line. Twice a week the entire school attended Quaker Meeting, silent gatherings except when someone received a personal call to speak.  I never got a call, but nonetheless my head was full: I thought about fishing and boats. Or else I thought about when next I could get from Philadelphia to our cottage on the New Jersey Shore in order to go out fishing in a boat. Beneath my picture in one high school yearbook it says, “I’m going to the Shore”.  While I had an overwhelming passion for fishing, school I merely enjoyed and I never planned to be a scientist. In fact, passion, not planning, is the engine driving all my thought and action. The almost unimaginably good fortune of my youth was that other people made such very, very good plans and choices for me.  My parents selected the excellent Friends Central School where, fortuitously, Clayton Farraday was both a science teacher and the school’s beloved Mr. Chips. The counselors there decided, wisely, that I should attend a college rather than a large university, and I departed Philadelphia for Dartmouth College in the fall of 1959. Though literature courses there were my favorites, I was a pre-medical student solely because my parents always hoped that I’d become an MD like my father. Pre-meds majored in chemistry or biology, and between the two I leaned toward chemistry. I didn’t get really interested, however, until I had two semesters of organic my sophomore year from a young chemistry professor who chose me to do research in his lab. When I graduated Dartmouth a few years later, in 1963, the same prof called my next move, a PhD in organic chemistry instead of medical school. He even chose the graduate school I attended and my research supervisor there. Such a strong intervention in a student’s life is no doubt unusual, but the precipitating events were unusual, too.  Generally speaking, colleges have the best undergraduate teaching, and universities, whose labs are filled by graduate and post-graduate students, have the best research. When I arrived at Dartmouth College in 1959, the chemistry department had a graduate program, which meant great teachers who were just as good at research. However, the program was small, and only a master’s degree was awarded, so consequently professors were perpetually hungry for more manpower for their labs, more “hands”. Undergraduates who performed well in lab courses were actively recruited to do “real” graduate- level research.  Thomas A. Spencer, a brand-new assistant professor of chemistry, arrived at Dartmouth when I did, and I was part of his research group for three years. Because Tom was (and still is) so smart and such a good chemist, he could recognize not just talent, but the potential to do something significant; because Tom was also born a great teacher, he was obliged to give a swift kick to my comfortable obliviousness. Fishing, now in the form of working all summer on charter boats, continued as my abiding passion, which meant I continued to need a wise person to make good decisions for me. If some variables in my adult life were changed, I might still have made it onto these pages, but it never would have happened without Tom Spencer.  Since some family background and professional activities (and lots more about fishing) are in the Nobel lecture that follows, and since the standard biographical folderol is most easily found online at www.scripps.edu/ chem/sharpless/, I hope to provide a more interesting read with the highly subjective and largely unorthodox personal information that follows.  I met my future wife, Jan Dueser, at a beach party at San Gregorio, west across the foothills from Stanford University. I was a first-year graduate student, and she was a Stanford sophomore and, on that day, my roommate’s date. I admired her touch football form, and she entrusted me with her delicate wristwatch, which I lost in the sand. We were married about a year-and-a-half later, on April 28, 1965, my 24th birthday, at the Palo Alto courthouse. David Schooley, a fellow chemistry grad student and now a professor at University of Nevada, Reno, was our best man.  Jan and I practiced with dogs before we had children; chemists still ask about our first, the black and enormous Lionel, a regular laboratory and classroom visitor at MIT. Our daughter Hannah (whose nickname “Pippi”, comes from “pipette”, not from Miss Longstocking) was born in 1976, and is a middle school teacher in Boston. To chemists who’ve attended my seminars, she is permanently six years old, the familiar Alice in Wonderland who gazes at the huge book of Looking Glass Sugars. William (“Will”) and Isaac (“Ike”) followed Hannah at two-year intervals. Both of our sons are still college undergraduates. None of our children has much interest in science, and I’m sorry, but not disappointed, that that is so.  My passion for chemistry was preceded by a passion for fishing.  With no children at home any more, dogs are, once again, our companions of choice – for play, for exercise and for hanging out with in bed. I haven’t gone fishing for probably over thirty years, but the ocean is still programmed into me like the birth stream of a salmon. One of the glories of moving to Scripps in 1990 has been seeing the Pacific Ocean every day, and, when its temperature reaches 70° (July or August), swimming in it every day as well. In windy New England I wind-surfed and we loved our little catamaran; San Diego’s sail-less ocean vistas still seem weird.  My most important award, the greatest honor I’ve ever received, and the grandest and most memorable occasions I’ve ever witnessed, are, of course, benefits of sharing the 2001 Nobel Prize in Chemistry. But other honors have peerless characteristics as well, notably:  The heaviest object in our bank deposit box is the 1995 King Faisal Prize for Science medal; the most beautiful one is the 1988 Prelog Medal from the Swiss Federal Institute of Technology (ETH). Its exquisite relief rendering of Old Vlado’s profile rivals the most beautiful portraits found on coins from antiquity, and the gold has a gorgeous, pliant, velvety warmth that has to be seen to be believed (by appointment only). A friend once asked, quite appropriately, if the portrait was of Alexander the Great.  Three unique objects, and I treasure each one, celebrate the day in 1995 when I received an honorary doctorate from Stockholm’s Royal Institute of Technology. My only top hat, frequently brought out for guests to admire, bears the Institute’s seal; my only ring, always admired when I wear it, is a heavy gold band surrounded by a garland of leaves and acorns in deep relief. These two I share with all the Institute’s doctoral recipients, but I also have a large brass cannon shell casing, fired during the cannon salute that accompanied the conferring of the degree and the ceremonial placing of the hat on my head. The shell sits on my desk at home.  Only one award commemoration of mine is lettered on real vellum, and it is the largest one, as well: in both English and Hebrew the 1998 Harvey Science and Technology Prize of the Israel Institute of Technology, Haifa’s Technion, is proclaimed.  In the category “news received most delightfully”, the winner is… an April, 1984, telephone call Jan took in a Jacksonville, Florida, hotel room all five of us were sharing while I attended a meeting. On the line from Washington, D.C. was my MIT colleague George Büchi, the most generous and thoughtful colleague I have ever known. George said he was calling because it was announced just minutes before that I had been elected to membership in the National Academy of Sciences. When Jan replied that she’d pass the message on, George said, no, she must go immediately to the meeting room and give me the message. Our children were too young to be left alone, especially since the meeting room was next to a swimming pool. I was giving my talk when I saw Jan and the three children, and all of them on tiptoes, enter the room and move along the back in the semi-darkness. She was looking for a familiar face, and she whispered the message when she found one. I stopped talking as Jan’s informant walked to the front of the room and asked for the lights to be brought up so he could make an important announcement. Why the audience was so enthusiastic I wasn’t quite sure. Not only did I not know I’d been nominated, I didn’t even know one had to be nominated. I thought the National Academy was something like a high-level appointed government advisory committee. Learning otherwise was a wonderful surprise.  Inaugural events always have special significance and vivid memories; these “firsts” mean a lot to me:  Receiving the first Paul Janssen Prize for Creativity in Organic Synthesis, presented by HRH Prince (now King) Albert of Belgium. Security forces were everywhere that day in 1986, and I asked Prince Albert if having to travel with such a large group wasn’t inconvenient. No, he replied, all those soldiers were required because I was an American – he didn’t need them.  Being Texas A & M’s first Barton Lecturer, 1997. Nothing is dearer me than having been selected by Sir Derek, my career-long scientific role model and mentor, to deliver the first edition of a lectureship endowed in his honor, the only Barton Lecture to take place before his death in 1998.  Launching the University of Sydney’s Cornforth Foundation for Chemistry (which honors both Rita and Kappa) with the inaugural [Cornforth](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1975/index.html) lecture in 2002. Like Sir Derek, Sir John is one of our gods; I stand awed at having participated in these events honoring them.  And, finally, if I had a crown, its jewels would be the 75-or-so former Sharpless Group members who are research professors. The training received in the group is neither predictable nor quantifiable; likewise, it is not intended to produce a product that, for example, industry wants. Since nothing original is intentionally discovered by scientists who cannot tolerate (indeed, they should welcome it) a high degree of uncertainty, group membership does not guarantee results. Because of the nature of our research, however, group members preselect themselves and possess a remarkably high degree of independence of thought as well as scientific motives tilted toward discovery, not reward. As a group, they hold superior standards for judging the significance of research, and I share with all them all of the glory that is a Nobel Prize. |
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| Q4 | **You use the words ‘blind watch-maker’, Barry, can you just talk about that?** |
|  | K. Barry Sharpless: It’s a book by Richard Dawkins and I particularly enjoy reading his works. He wrote *The Selfish Gene* and *The Blind Watch-Maker*. *The Selfish Gene* really hits you in the face because it says that everything, the grass, the flowers, the poinsettia’s behind you are us, the weed in the field. A lot of us have the gene. Some of the proteins and the genetic compounds are in insects and us. There’s so much that’s there just as a piece of boiler plate material that’s been there for billions of years. We are survival machines for genetic material, if you look at it coldly. And the genetic material picks combinations of genes, travelling companions that have survival value. In a sense, the cold-blooded way of viewing this is our organism part, our system that’s closed and functioning, is just a way to push genetic material into the future.  And then coming along behind that, Dawkins wrote *The Blind Watch-Maker*, which is if you look at life it seems impossible to imagine it wasn’t somehow created from above because it’s too invested in so many complexities. How could you get there if you weren’t there? There’s a chicken and egg problem that’s massive. And the idea of *The Blind Watch-Maker*, Dawkins says well how else could you get there? We had four billion years and a planet for this system to evolve and if you just cobble together things, and when life discovers a new way, it never throws out totally the old stuff. You know, it’s not the nature of the way that organisms can function. They learn something, it’s not quite perfect, they learn something else. This whole thing is so then complicated that we don’t know how it really works and we can’t imagine, so that’s why it’s *The Blind Watch-Maker*. In a sense, the only way it could have gotten there is by the way it got there.  William S. Knowles: But it’s interesting, we are capable of making all the parts, we don’t know how to put them together for the living cell. We can’t think of any of the parts of the living cell that we can’t make. But we have no idea how to put them together to get something that works like that. No idea. |
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|  | Ryoji Noyori: It’s difficult at this moment.  William S. Knowles: It’s beyond us at this moment. It may not be by the next 100th anniversary though. When one looks ahead it’s very dangerous to say that it’s not impossible.  K. Barry Sharpless: But you hit the nail in that reductionist is the problem humans have and we get attracted to things we can understand and we go in deep on solving puzzles, but we don’t notice, and we like to see things sitting still. If something is moving it’s blurry usually and that’s what our area is, the three of us, we work on catalysts. Everything that’s moving, by definition, and if you see it sitting still, you can’t gather the essential facts about it. So that’s kind of a nice metaphor for complexity. Catalysts in life are always moving. Life itself is not what we see here in front of you. If the energy is not pouring through the system, the message that’s being read out is there are selective catalysts in our bodies, they’re burning energy. If you froze me and sent me to the other side of the universe and I was just the corpse then, there is no easy way to tell what the function of this machine was.  Ryoji Noyori: Understanding is rather easy, however more important is the creation of new functions. That’s very difficult. |
| Q2 | **What does it mean, understand? Can we tell what is life?** |
|  | Ryoji Noyori: No, I mean if you go to school and you have a class and the teacher will tell something, and you understand it. And that’s easy. But is that really full understanding?  William S. Knowles: But your question can we understand and define what life is? And this would take a lecture. You can’t just sit down and define life, can you? I don’t think we can. We can define the characteristics of life and it’s about five or six characteristics that all life seems to have, but we have a hard time saying this is not life and this is life. But we seem to know this, don’t we? That’s funny.  K. Barry Sharpless: But I think that distinction is going to be more and more blurred. There’s this new school of thought, the born and the made are going to move together in the next thousand years. And I definitely think it’s got to happen. These people that have always this cell phone here, I mean why not have it somehow built in? Some people don’t function without one. So there’s going to be a way to integrate the born and the made a little bit.  It’s a little strange idea but no, this is the way the world seems to be heading. It’s almost like science fiction but its not because if you think about it, well one thing I read, if you get to another planet, you know how they test to see if there’s any amino acids or life there, if you saw a little box with four wheels on it, you wouldn’t have to search any further, you’d know there had been life on that planet. I mean there are certain complexities that only can exist through living things. I think the amazing thing is that we think we understand as much as we do.  Take one little cell, as far as I’m concerned, the medium is the message there. And people thing the genome is going to solve things, I think they’re absolutely crazy. And because this is a linear message and it’s all entangled in itself and you can probably get different functions out of that box that’s called a cell, thousands of different ways, you could tweak it in a thousand ways and every one of them would end up in the same function. That would be a drug function. So you think you had this target, but if you did three other things you would have the same result, you know? It’s just a matter of we don’t go at it that way, we go right there and we think we know that target is there, and we’re going to hit it. And then it doesn’t work when they do it and six things that were compensated and the thing doesn’t have a prayer from the beginning, but they assume it did.  Ryoji Noyori: The function or life itself is an integrative issue. And a global issue. And it’s very hard to make it, on the other hand you can understand in detail just by analysis.  K. Barry Sharpless: You can understand within our sciences about what we know and how we know it. But it’s not about any absolute knowledge, we just have ways of knowing things that enable us to carry forward with so called advances. But I do think that the life issue, the complexity, is a fascinating area. My favourite book these days is *Out of Control* by Kevin Kelly and that’s a book that really describes some things that all of us can learn from. |
| Q2 | **But do you recognise this way of making discoveries, that you have a problem and you are somehow waiting how to solve it? The solution comes just by random. Is this called serendipity?** |
|  | William S. Knowles: I don’t like the word serendipity. I prefer luck. Because I think serendipity, in my mind, doesn’t seem to imply much intelligence. It seems there were these guys wandering around and lucky things happened to them. To me it doesn’t, I like to think I had luck, but I like there was a little intelligence behind this.  K. Barry Sharpless: I think you’re right, the serendipity one is a bit too much like really luck. Sometimes people are calling intuitive as well, which is related to this idea of they’re going to be able to take advantage of serendipity more because they’re actually open to it. And I think intuitive is a way that people who aren’t creative will describe creative people because they don’t see the method by which the information leads these people to the answer they get. I mean people that are intuitive often take in as much, if not more information, facts and feelings and connections than the people who are linear. So I think intuitive people actually are just using their information in a different way.  William S. Knowles: It’s also that, at least certainly the breakthroughs in science, you almost have to be active and your lucky break comes along. Never where or when you expect it, and the ones that succeed take advantage of that lucky break. And most people don’t bother to take advantage.  Ryoji Noyori: So we should be lucky. But I think discoveries are made accidentally, but that’s not real accident. |
| Q2 | **But what does intuition mean in that, that you look at the right things?** |
|  | K. Barry Sharpless: You worked it, you kind of get attracted to the areas where you have a better chance. In this book, Kevin Kelly’s book, it’s kind of interesting, life itself is attracted to instabilities though. I mean it’s obviously connected, in my belief, all these things connect back to facts in the end. That the DNA does contain the information that leads these systems to where they go, but it almost seems like life systems want to be near the edge of chaos because his image is riding a wave, you know, surfer riding a wave.  If you’re up high on the wave and the wave goes forever and you can stay in the zone and you have movement, you have power, potential energy. If you get over the top of the wave, you could die. But if you’re down back on the wave in a trough, you can’t move. And move means evolve. You have to be having movement and life is attracted to instability and creative discoveries come from points of instability in chaos. You have chaos in catalysis. And catalysis is life really. You need to be near this slippery area, partly because you need speed. Speed is really crucial.  Ryoji Noyori: So the discovery is a matter about kinetics rather than thermal dynamics. We need some thermal dynamics and then we need some basic knowledge. But that’s not enough. |
| Q18 | **But it’s not only that you understand the parts, but you are also fascinated by this world. So I have a final question, you live with the molecules or the chemistry, you see the beauty and fascination of this world, but there is still all those people out there that cannot understand what you see is the most beautiful thing in the world. How do you manage to bridge over this gap? Do you see it as a problem?** |
|  | William S. Knowles: Not very well. This is a big frustration, bridging over the gap. We’ve talked a lot about that this week but we really haven’t come up with terribly good ideas for doing it, I don’t think. But it is desirable to bridge it.  K. Barry Sharpless: I do it as best I can through the sensual approach, that is chemistry organic is right in there for you because they almost all have a taste and a smell. And the big ones don’t smell but the little guys smell. So we notice flowers, fragrances, body odours, oils on your skin, all those things are easy for people to get interested in. But as far as life goes, I’ve found myself being attracted back, having the adventure we’ve had, finding we can be promiscuous and not be very selective but still get right and left. I find to get at the complexity of life maybe I need to use her proteins and things as reaction vessels themselves.  So I have an idea where I’m going to try and go back to mother. Mother inspired us, she’s the enzyme to do the right and left. It turns out that’s easier than many parts of making complex structures. So my thought is to go back and now use the real power of nature. Put the real message in completely. The actual encoding of all those touches, the molecules are touched, everyone’s touching each other. When we do it we use our hands. Our hands are very big and we’re actually pretending to run reactions at the molecular level by using our hands. That’s what it comes down to.  Ryoji Noyori: So the chemists are being interested in the structure of molecules. And now we can fully understand the structure, but that’s not enough. So important is the creation of functions from organic molecules, that’s integrated matter and very difficult to understand. I think that we should know more about biology and also physics. That’s really an integrated pro-gender issue.  K. Barry Sharpless: The function is really what we need to deliver faster, especially at affordable price, medicine and materials that people can build with. And we just don’t have much experience with speeding up. This speed is a thousand times less than it should be if we’re going to try to provide for the rest of the world at a decent level, like we have here in Sweden and Japan and the United States.  Ryoji Noyori: And I think the scientific research has been analytical. However that should be more scientific. So the integration of many simple elements generating anew our functions.  William S. Knowles: We can go on this discussion forever really. It’s absolutely fascinating. |

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| **Biographical** | I was born on a bitter cold morning (20º F below zero) in Sioux City (Iowa) on January 22, 1936. I was told that when my father went out in the cold that morning to go to the hospital to visit his wife and newborn first son, his car would not start. Despite advice to the contrary, he walked to the hospital; his ears were frostbitten on the way.  The Heeger family came to Sioux City (Iowa) from Russia as Jewish immigrants in 1904 when my father was a small boy (age 4). My mother was born in Omaha (Nebraska); she was a first generation child of Jewish immigrants. My mother and father were married in the midst of the Great Depression.  My early years were spent in Akron (Iowa), a small midwestern town of 1000 people, approximately 35 miles from Sioux City. I went to elementary school in Akron. My brother, Gerald, was born in Akron. My father was the manager and, subsequently the owner, of a general store that served the local farming community. I have a strong memory of the day I was told that my father had a weak heart and that he had to go to the hospital. He died when I was nine years old on the same day that Franklin Roosevelt died; it was his 45th birthday.  After my father’s death, we moved to Omaha, so my mother could be closer to her family. She raised us as a single parent in a house that we shared with her sister and her sister’s children.  One of my earliest memories (long before my father died), is of my mother telling me of the importance of getting a university education. When she graduated from high school, she received a scholarship to go on to university but went to work instead; she was needed by her parents to help support the family. It was always clear to me that it was my responsibility to go to university; prior to my generation no one on either side of my family had an education that went beyond high school. I and my brother were the first in our family to receive the PhD degree.  My high school years were fun and frustrating, typical of the teen years. The most important accomplishment was meeting my wife, Ruth. I have loved her for nearly fifty years, and she remains my best friend.  I was always a good student, but I do not remember science being especially easy. On the contrary, I recall that in high school, physics was somewhat mysterious. I was impatient to get on with my education, to get on with more important things, and therefore completed high school one year early.  My undergraduate years at the University of Nebraska were a special time in my life; the combination of partying and intellectual awakening that is what the undergraduate years are supposed to be. I went to the University with the goal of becoming an engineer; I had no concept that one could pursue science as a career. After one semester, I was convinced that engineering was not for me, and I completed my undergraduate studies with a dual major in Physics and Mathematics. The highlight was a course (in my senior year) in Modern Physics taught by Theodore Jorgensen. Professor Jorgensen introduced me to quantum physics and twentieth century science. I was honored by the University of Nebraska in 1998 with a Doctor of Science (h.c.) and had the pleasure of giving a Physics colloquium at that time. Ted Jorgensen came to the lecture; he was 92 and working hard on revising his book on the Physics of Golf.  Again, I was impatient to get on with “real physics”. I started the path toward my PhD in Physics at UC Berkeley while working part time for Lockheed Space and Missile Division in Palo Alto, CA. On Monday, Wednesday and Friday, I would wake up early and drive the Bayshore Freeway to Berkeley to attend classes. After sitting in class all morning, I had lunch and then got back on the freeway to return to work in Palo Alto. Naturally, after such a morning I fell asleep at the wheel almost every trip. Thus, it was not a terribly difficult decision; Ruth and I moved into student housing at Berkeley, and I started research on a full time basis.  When I started at Berkeley, my goal was to do a theoretical thesis under Charles Kittel. Thus, when the decision was made to go for my degree on a full-time basis, I went first to Kittel and asked if I could work for him. Kittel had just returned from a trip to Moscow where he met Landau, and he told me that Landau required that a prospective student had to pass a rigorous examination before he would agree to take the student into his research group. Kittel indicated that I should take the PhD qualifier and come back to him after I had done so. When I came back to discuss my future with him, Kittel told me that he would take me on. He said, however, that although I could do a thesis under his direction in solid state theory, he did not think I would be a first-rate theorist. He recommended instead that I consider working with someone who does experimental work in close interaction with theory. This was perhaps the best advice that anyone ever gave me – and I followed his advice. I joined the research group of Alan Portis.  I remember with clarity my first day in the laboratory. I was doing “original research”; at last I was involved with real physics. After only one day of carrying out magnetic measurements on an insulating antiferromagnet, KMnF3, I wrote a theory of antiferroelectric antiferromagnets and presented it to Portis with great pride. He was patient with me then and again a few days later when I apologized and told him my theory was nonsense. Through my interactions with Portis (I recall spending many hours talking with him in his office), I learned how to think about physics; more important, I began to learn about good taste in the choice of problems.  After completing my degree, I went directly to join the Physics Department at the University of Pennsylvania where I remained for over twenty years. It was an exciting period for condensed matter physics at PENN. Eli Burstein had made major progress in building the solid state group; he convinced Robert Schrieffer to come to Penn, and he and Schrieffer attracted an outstanding group of young people. Beginning with my experimental studies of magnetic impurities in metals and the Kondo Effect, I learned many-body physics from Schrieffer.  Anthony Garito introduced me to tetracyanoquinodimethane (TCNQ); I brought him into my research group for post-doctoral research. We worked together from 1970 through 1975 on the metal-physics of TTF-TCNQ and on the discovery of the Peierls instability in quasi-one-dimensional p-stacked molecular crystals. Although the direct observation of the incommensurate Peierls distortion with wave number q = 2kF proved that we were on the right track, this was a time of controversy and stress.  In 1975, the first papers on the novel metallic polymer, poly(sulfur-nitride), (SN)x appeared in the literature. I was intrigued by this unusual quasi-1d metal and wanted to get into the game. I learned that Alan MacDiarmid, a professor in the Chemistry Department at PENN, had a background in sulfurnitride chemistry, and I made an appointment to see him with the goal of convincing him to collaborate with me and to synthesize (SN)x. I recall that we met late in the afternoon of an autumn day. After quite a long discussion during which I made little progress toward my goal, I realized that while I was saying ” (SN)x“, he was hearing ” (Sn)x“. Needless to say, he was not impressed with my enthusiasm for (Sn)x being a metal; any chemist knew that tin was a metal!  Once MacDiarmid and I got past this initial language problem, a true collaboration began. We realized that it was a long reach across the Chemistry-Physics boundary, and we were determined to learn from one another. Although we collaborated during the week, we typically met on Saturday mornings with no agenda; just to try to learn from one another. At that time, I was fascinated with the metal-insulator transition as envisioned by Mott. I recall that I tried to convey my interest in this problem to MacDiarmid by asking him to consider a linear chain of hydrogen atoms as a model system. He balked right away; a linear chain of hydrogen atoms did not exist. After discussion, we focused in on the abstraction of a chain of p-bonded -CH- units as an example of a system that would have one unpaired electron per repeat unit. Shortly thereafter, MacDiarmid went to Japan for a visit. MacDiarmid is a very visual person. He loved the golden color of films and crystals of (SN)x, and he showed samples and photos of this golden material during his lectures. After one such lecture, a Japanese scientist came up to him during the coffee break and told MacDiarmid that he, too, had some shiny films. Thus, MacDiarmid was introduced to Hideki Shirakawa and to polyacteylene.  When MacDiarmid returned from Japan, he told me with great excitement about (CH)x. With the help of a small addition to an ONR grant from the Program Officer, Kenneth Wynne, we were able to bring Hideki Shirakawa to PENN as a Visiting Scientist. The initial discovery of the remarkable increase in electrical conductivity of (CH)x and the identification of that increase as resulting from a transition from insulator (semiconductor) to metal followed in a very short time.  The soliton in polyacetylene was born with the observation of an electron spin resonance (esr) signal in the pure material where there should not have been one. Building on the earlier work by Michael Rice on phase-solitons, I realized that if one drew a domain wall between the two identical forms with opposite bond alternation, one would have an unpaired spin and postulated that the origin of the esr signal might be a bond-alternation domain wall. Curt Fincher, then a graduate student in my research group, had recently discovered the doping-enhanced infrared vibrational modes which became a signature of the doping. In a luncheon seminar before the solid state group at PENN, I argued that these doping-induced IR modes might arise from the enhanced electric field at IR frequencies that would result if a charged bond-alternation domain wall were to move back and forth driven by the external field of the incident IR radiation. Schrieffer listened closely and made some comments about “kinks” at the end of my talk. A few days later he showed me how the mid-gap state would arise from the formation of such a bond-alternation domain wall and how that mid-gap state would have a reversed spin/charge relation relative to that of fermions. Wu-Pei Su then worked this out in detail, and the SSH papers were written.  I was drawn to Santa Barbara by the promise of a singular opportunity to build a special Physics Department, by the promise of continuing my close collaboration with Bob Schrieffer, by the opportunity to work with Fred Wudl, and – frankly – by the lure of this beautiful place. Wudl, then a synthetic chemist at Bell Laboratories, and I were recruited to UC Santa Barbara together and enjoyed a close and productive collaboration over a period of 15 years.  Daniel Moses and I have worked together for twenty years, initially at PENN and then at UCSB. Dan dragged me into ultra-fast pulsed laser spectroscopy and into fast-transient photoconductivity as probes of the excited states of semiconducting polymers. Dan continues in his efforts to resolve the remaining fundamental scientific issues in the field of semiconducting polymers with creativity and with determination.  In 1986, in the process of building the Macromolecular division of our newly formed Materials Department, we convinced Paul Smith to leave DuPont Central Research and come to UCSB. Whereas I and Alan MacDiarmid and most of the early players in the conducting polymer field were amateurs in the field of polymer science, Paul was a professional. He quickly hammered into my head the importance of making conducting polymers processible, and he had the annoying habit of asking me embarrassing questions such as “What is the intrinsic electrical conductivity of a conducting polymer?”. Anything I know about the processing and mechanical properties of polymers, I learned from Paul.  In 1990, Paul Smith and I decided that conducting polymers as materials had developed to a level of maturity that commercial products were possible. With this as a goal, we founded UNLAX Corporation. Fortunately, on a trip to China in 1986, I met Yong Cao and immediately realized that he was a remarkable scientist. I was able to bring him to Santa Barbara in 1987. Initially, he worked with Paul and with me at UCSB. When we founded UNIAX, Yong Cao was the first employee. His creativity, determination and scientific strength were critical to our scientific progress and to the success of UNIAX. During the 1990’s, UNIAX played a leading role in developing the science and technology of conducting polymers with many important contributions.  The twenty-five years since the discovery of conducting polymers have taken me on a great ride; always on the frontier and always with the challenge of exciting discoveries. In 1990, the discovery of polymer LEDs by Richard Friend and colleagues at Cambridge gave the field a boost with the promise of important technology and with the excitement of an entirely new set of phenomena to study. In 1992, while doing post-doctoral research in my group at UCSB, Serdar Saricifici discovered ultrafast photo-induced electron transfer from semiconducting polymers to acceptors such as C60. This discovery resulted in the development of polymer photodetectors and photovoltaic cells that offer promise for use in a variety of applications. In 1996, the discovery of amplified spontaneous emission and lasing (simultaneously by our group, by Richard Friend’s group at Cambridge and by Valy Vardeny’s group at Utah) opened yet another potentially important direction. And it goes on.  None of this could have been accomplished without the hard work, dedication and creativity of the students and post-docs with whom I have had the pleasure of working over the past forty years. I thank them all.  I have enjoyed the life of a scientist while sharing both the exciting days and the disappointments with Ruth. She has filled my life with love and surrounded me with beauty. She has also gallantly put up with my eccentricities for more than forty years. We have succeeded in starting an academic dynasty; our two sons, Peter and David are both academics. Peter is a professor and medical doctor who is doing research on immunology at Case Western Reserve University. David is a professor and neuroscientist at Stanford University where he studies human vision. I have had the great pleasure of collaborating and publishing articles (as co-author) with both of my sons. Now I am looking forward to the emergence of my four grandchildren, Brett, Jordan, Julia and Alice, as the next generation of the Heeger family. Of all the congratulations that I have received as a result of the Nobel Prize, I took greatest pleasure from their pride in their grandfather. |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** |  |
| **Interview** |  |
| Q2 | **What were the obstacles?** |
|  | Alan Heeger: The obstacles are very, very real. Part of the obstacles are of course these language issues and the different concepts, but I think in this case it was more than that. I mean, we were taking on a really difficult problem with hindsight. We were either courageous or foolish because it was a very difficult problem and if you look back at it at that time and say how would you get through this? Even in the 1990s, which is now, let’s say, 20 years after the original discoveries, there were many people in the scientific community, our colleagues, who seriously doubted that you could ever achieve the purity in the materials that you would need to make, for example, semiconductor devices. Turns out that you can, turns out that you can do so for very fundamental reasons but we didn’t know that early on and so you just go ahead, it’ll work out. |
| Q10 | **So how did you manage? How did you manage to get funding, for example?** |
|  | Alan MacDiarmid: The funding aspect is, as we have been discussing recently during this Nobel week, I think, very important indeed and, Hideki and Alan, just last week I was looking at our original letter when we submitted our first communication, and we sent a copy of this letter to Dr Ken Wynn at the Office of Naval Research. Here we apologised for the fact that most of the work – we actually had this in the second to last paragraph in the letter written 23 years ago – we apologised for the fact that most of the work had been done on moonlighting, moonlighting on other grants. But we then said that the other grants were acknowledged and of course by moonlighting, one refers to the fact where one is actually doing research which is not necessarily encompassed in a given subject matter for which we are receiving funding.  Alan Heeger: But the agencies which supplied those funds were very pleased. I mean, success is success. The early work that we did together was indeed spectacular, although, I must say, the first papers were not easily accepted by the appropriate journals, but once it got out, I mean, it was clearly an exciting time and funding was not a problem. I think, as I recall, the biggest issue in that context, in a slightly larger context, was that there was immediately a positive response by industry. They saw the potential, the dream of a new class of materials which would have the electrical and optical properties of metals but retain the processing advantages and mechanical properties of plastics, but it wasn’t true then. It was still a dream. It was 20 years away or whatever and so there was this initial big push, I would say, or at least start-up of quite a lot of activity in industrial laboratories and they quickly became disillusioned. It was only because the funding agencies that were supporting the universities and supported our programmes and our colleagues around the world that we got through this valley, because it did take, let’s say, 15 years before we began to see materials that might someday be really useful.  Alan MacDiarmid: I think in this respect, to stress again the difficulty we had in convincing some of our colleagues that one could work in an area of dirty nasty organic polymers, not nice crystal and materials. There’s one person, a colleague we were discussing within the very early days, concerning collaborative interaction and I remember well this person said something which represented the opinion of many. He said Alan, you know, all of this is a junk effect, don’t touch it. Then I said to this person, well, if you know what the junk is and you know how to put it in controllably and you know how to take it out controllably, could you not possibly call it a doping effect? But I think this overall fell in the past, in the whole area of electronic materials. The physicists, both academic and those in industry, had been dealing with nice, clean crystal inorganic materials and now you came to a yucky polymer, not nicely crystal and just urgh, you wouldn’t touch it.  Hideki Shirakawa: Speaking about the founding, Japan has a really different system as far as the university concerns. The faculty in the National University has received maybe one or two million yen per year without any proposer so within that money we can do without any restriction. I mean, that as I …  Alan Heeger: As you want.  Hideki Shirakawa: As I want to.  Alan MacDiarmid: That’s good.  Hideki Shirakawa: In that sense, the basic research can do.  Alan MacDiarmid: That is still the case, Hideki?  Hideki Shirakawa: Yes, it’s still, yes.  Alan MacDiarmid: That’s excellent. |
| Q2 | **That’s what I wonder, how do you actually do a discovery? Is it a trial and error process? How do you come into the discovery?** |
|  | Alan Heeger: No, no, discovery is discovery. You don’t predict it, right, and it comes in its time. You can be aware of events in a field so that perhaps you’re prepared. You can be aware that something’s going on over here that will stimulate your mind, but discovery is discovery. What can one say?  Hideki Shirakawa: And it’s very difficult to predict.  Alan MacDiarmid: Or if you put it in other terms, that if you plot, say, a straight line, here you have known data and then from the known data, then in principle you can extrapolate to the future new types of phenomena based on that known data but it’s an extrapolation of the curve; but the real exciting things are where, rather than extrapolation of the curve, you have a point way over here which is not on the curve, which is not data which you do not necessarily expect from the data and information which is already known. But once you get that new point and look at it for a while, then you can look back and say yes, of course, this is exactly what you’d expect. But at the time you get it, you don’t.  Alan Heeger: And the other aspect, I suppose, of discovery is to come to a conclusion on the basis of too few facts to really get you that conclusion that enables you then to say, well let’s try that, ok? And then you have a discovery, ok? In that sense, you can’t deduce the result from the facts that you have but by being creative, you can say well, put these ideas together in your mind and it makes something whole to you. Of course, it’s still a hypothesis and then it works and then you’re off and running?  Alan MacDiarmid: Or it doesn’t work and then you modify the hypothesis accordingly. |
| Q7 | **What is the characteristics of a good scientist? Is it high IQ or being creative, as you say?** |
|  | Hideki Shirakawa: Their personality should be very curious, ask why, ask what happens and have many interests in everything.  Alan MacDiarmid: Or in other words, I feel one has to live it, eat it, dream it, sleep it, has to be complete immersion and I like to try to point out to some of my students at times that the creative scientist is just as much an artist as a person composing a symphony or painting a beautiful painting and I say have you ever heard of a composer who has started composing his symphony at 9 o’clock in the morning and composes it to 12 noon and then goes out and has lunch with his friends and plays cards and then starts composing his symphony again at 1 o’clock in the afternoon and continues through ‘til 5 o’clock in the afternoon and then goes back home and watches television and opens a can of beer and then starts the next morning composing his symphony? Of course the answer is no. The same thing with a research scientist. You can’t get it out of your mind. It envelopes your whole personality. You have to keep pushing it until you come to the end of a certain segment.  Alan Heeger: Persistence is important. Of course, intelligence and IQ are important, of course, but I was going to say unfortunately or, whatever, I know many people who have far higher IQs that I envy so persistence is very important and also an ability to just focus. The autobiographies that you read about, for example, Einstein as the classic scientist suggest that he could just focus on a problem and just not let go of it for a time and with an intensity that is just far more than most of us can do and evidently that has something to do with success in science. |
| Q6 | **I know that you both, two Alans, are known for being workaholic, I would say. Do you have any other passions besides science?** |
|  | Alan Heeger: Many things. I love the theatre. We have a wonderful theatre group in Santa Barbara and I’m on the board of directors of that theatre group and support it and Ruth and I always like to go to London and to New York to the theatre. I love music. We’re great opera fans. We were at the opera the night before we left to come to Stockholm, but the real passion, I must say, is downhill skiing so I’ve gotten my whole family to be similarly enthusiastic about skiing and in fact we’re all going next week for a holiday to relax from this very hard-working Nobel week for a week of downhill skiing, so as a sport that’s the one that I like.  Alan MacDiarmid: You see, Alan’s skiing is snow skiing. Ours is water-skiing. We have a house beside the largest lake in Pennsylvania in the Pocono mountains and all of my children and my wife and grandchildren, we like to get up very early in the morning, about 6 o’clock when the lake is absolutely flat, before other people have gone out onto the lake, and then we go water-skiing together and we do slalom skiing, also one ski skiing and it’s really fun, I find. This last summer, for example, to be actually out water-skiing not only with my children but with my grandchildren.  Alan Heeger: Oh yes, that’s great fun. How about you Hideki, are you a sportsman?  Hideki Shirakawa: In my case my way to relax is to grow plants and also I keep my garden.  Alan MacDiarmid: I’ve seen your lovely cactus in your garden when I visited.  Alan Heeger: I remember you took cactus plants with you from Philadelphia 25 years ago. Do they still exist?  Hideki Shirakawa: Still exist, yes. Not to large but maybe this size.  Alan Heeger: In Santa Barbara, I planted cactus in one year. The next year, the next year, they really grow. |

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| **Chemistry\_2024-2000** | |
| **ID** | 0363 |
| **Biographical** | I was born a Kiwi (a New Zealander) in Masterton, New Zealand on April 14, 1927, and still am a Kiwi by New Zealand law, although I became a naturalized United States citizen many years ago in order to have the right to vote in US elections and, hence, voice my political opinions in a meaningful way. My father, an engineer, was unemployed for four years during the Great Depression which hit New Zealand rather severely in the early 1930s. Since jobs were believed to be more plentiful in the vicinity of Wellington, the capital city of New Zealand, located at the bottom of the North Island, we moved to Lower Hutt a few miles from Wellington. There my two older brothers and my elder sister were able to find jobs while I and my younger sister were still at primary school.  My mother and father set the stage for nurturing a warm, loving united, mutually supportive family who always pulled together and also helped others outside the family in need when necessary. Although we did not have too much food, my mother was always inviting other, less fortunate people to meals. On such occasions, my older brothers and sister would frequently remind me and my younger sister at meals not to ask for more food by saying to us out loud at the table, “FHB,” which meant, “Family Hold Back,” i.e., don’t eat too much! We had no phone or refrigerator. In one of the houses we lived in Lower Hutt, our hot water came from water pipes embedded in the brick at the back of the open fireplace in the living room. This resulted in our weekly bath night – where the younger children used the bath water from the older children, to which we were allowed to add more hot water if any still remained! For most of my time at primary school, I went to school barefooted, like most of the other kids. The soles of our feet literally became leather!  Even though I have been away from New Zealand for about 50 years, my brothers and sisters and I (my parents passed on several years ago) are still very closely connected to each other. Throughout the decades we have telephoned each other about every ten days and we all keep up to date with what we are each doing. Shortly after learning of my being a recipient of the Nobel Prize I was speaking to one of my brothers in New Zealand by phone and I said how lucky I was to have been raised in a poor family which was also a close loving family. The fact that we were poor made us self reliant and conscious of the value of money. The fact that we were closely knit taught us the important aspects of interpersonal relationships. Everyone expects “the important things” in life that such as birthday and Christmas presents, but it is the “little unimportant” actions which actually are the real important things. These put the flesh on the skeleton of any relationship. Several hundred of these each week – the unimportant, the unexpected, the unnecessary, “the little things”, are the things that really count. We are lucky to have been brought up in this environment, but there is a statement on the wall of my study at home in suburban Philadelphia which reads, “I am a very lucky person and the harder I work the luckier I seem to be”!  It is my home life while growing up through high school, which I consider to have been the single most important factor in any success which I may have had in life. As my parents always said, “…an ‘A’s grade in a class is not a sign of success.” Success is knowing that you have done your best and have exploited your God-given or gene-given abilities to the next maximum extent. More than this, no one can do.  For a period in grade school, I attended a two-room school in Keri Keri (town population, 600) where most of my school chums were Maori boys and girls from whom I learned so much. During much of my time at grade school I had an early morning, pre-school job delivering milk on my bicycle for Mr. Bradley, who had a few cows in a nearby paddock. My mother was superb – she would get up with me while it was still dark to make me hot tea to send me on my way. When I started high school it was necessary to give up my Milk route. Instead, I delivered the “Evening Post” newspaper on my bicycle after school.   |  | | --- | |  | |  |   When my father retired (on a very small pension) and moved away from Wellington, it was necessary for me to leave Hutt Valley High School after only three years at the age of 16 and take a low-paying, part-time job as “lab boy”/janitor in the chemistry department at Victoria University College, as it was then known. The total student population was 1200; the Chemistry Department had a faculty of 2! I boarded with friends of my parents and, as a part-time student, took only two courses – one in chemistry and one in mathematics. During this time I became a resident at Weir House, the University dormitory for men. This I found to be one of the most enjoyable and maturing times of my life where I made many good friends from the other ninety residents, with some of whom I still keep in close contact. I remained a part-time student throughout my B.Sc. and M.Sc. studies at Victoria University College. After completing my B.Sc. degree I graduated to the position of demonstrator. Since the age of 17 I have supported myself financially, assisted later only by scholarships and fellowships for which I am most grateful.  My interest in chemistry was kindled when I was about ten years old at which time I found one of my father’s old chemistry text books dating back to the late 1800’s when he was studying engineering. I spent hours pouring over the pages in complete confusion but with burning curiosity! Some clarification of a type occurred when I rode my bicycle to the public library in Lower Hutt and entered the children’s section. There, on the right hand side on the bottom shelf, in the new books section, was a book with a bright blue cover. It was called, “The Boy Chemist.” I took it out and continually renewed it by borrowing it for over a year and carried out most of the experiments in it. One of my duties as lab boy, when I was not washing dirty labware or sweeping floors, was to prepare demonstration chemicals for Mr. A.D. “Bobbie” Monro, the lecturer in first-year chemistry. On one occasion he asked me to prepare some S4N4 – beautiful bright orange crystals. When it became time for me to start my M.Sc. thesis, I asked Mr. Monro if I could look at some of its chemistry. He agreed. This resulted in my first publication in 1949. Its derivatives were highly colored. Color continued to be one of the driving forces in my future career in chemistry. I love color. Little did I know that thirty years later this was going to be a key factor which would shape my professional life.  In 1950, I had the good fortune to receive a Fullbright fellowship from the U.S. State Department to do a Ph.D. at the University of Wisconsin in the USA where I studied under Professor Norris F. Hall, majoring in Inorganic Chemistry, studying the rate of exchange in 14C-tagged complex metal cyanides. It was at the University of Wisconsin that I became president of the International Club – the largest student organization on campus and had the crucial chance meeting of my life when I met my future wife, Marian Mathieu, at an International Club dance. During this time I was elected by the Department of Chemistry to the position of Knapp Research Fellow and had the privilege of living rent free in the beautiful old ex-governor’s mansion on the shores of Lake Mendota.  When I was still at the University of Wisconsin I was successful in obtaining a New Zealand Shell graduate scholarship to study silicon hydrides at Cambridge University, England under the directorship of Professor H.J. Emeléus. It was there that Marian and I were married in the chapel at my college, Sidney Sussex College.  After a brief appointment as a junior faculty member at Queens College of the University of St. Andrews, Scotland, I accepted a junior position on the faculty of the Department of Chemistry at the University of Pennsylvania where I have been for the past 45 years and became father of three daughters and a son and grandparent of nine lovely boys and girls. I grew to love teaching and the stimulation of young fresh inquiring minds. I am still fully engaged in teaching as well as research and indeed have requested to teach a section of first-year chemistry at Penn later this year.  I had the good fortune to meet my future friend and colleague, Professor Alan J. Heeger, Professor of Physics at the University of Pennsylvania. On one occasion he came to my office and informed me that Mort Labes, Professor of Chemistry at Temple University, had published a paper on a highly conducting material. I asked Heeger its formula and he replied, “sss-nnn-ex”. Being an inorganic chemist, I wrote down on a piece of paper, “(Sn)x” and said, “Of course you expect it to be conducting, it’s a metal!” To which Heeger replied on paper, “No, not (Sn)x, but (SN)x! This was the beginning of our each learning each other’s scientific language. I told him that I had made the precursor to (SN)x, i. e. S4N4 during my M.Sc. thesis work in New Zealand. He asked me if I could make some (SN)x – as golden crystals. We were ultimately successful, and co-published many papers together, on this conducting polymer.  When I was a Visiting Professor at Kyoto University in Japan, lecturing on molecular silicon compounds, I visited Tokyo Institute of Technology in 1975 and described our work on (SN)x, Hideki Shirakawa and I met over a cup of green tea after a lecture I gave and as I was showing a sample of our golden (SN)x, he showed me a sample of his silvery (CH)x.  I asked him how he had made this silvery film of polyacetylene and he replied that this occurred because of a misunderstanding between the Japanese language and that of a foreign student who had just joined his group. Shirakawa had been polymerizing ordinary acetylene welding gas using a Ziegler-Natta catalyst and had been obtaining a rather uninteresting black-brown powder. He told the new student to repeat this work using a concentration of the catalyst which was milli-molar. A few days later the student came back and said that the stirring bar would not go around in the flask. Shirakawa went to the laboratory and, sure enough, instead of the black brown powder, there were lumps of silvery-pinkish jelly floating around. Shirakawa asked what the student had done and the student replied that he had done exactly as Shirakawa had told him; he had made the catalyst with a concentration of “x-molar”- in other words, he had made the catalyst 1000 times more concentrated than Shirakawa had told him! Shirakawa was most intrigued by this observation, since as all good chemists know, a catalyst should only increase the rate of a chemical reaction and should not alter the nature of the product. This then started Shirakawa investigating this silvery form of polyacetylene. I asked Shirakawa if he could join me for a year at the University of Pennsylvania since I was already interested in conducting materials such as the golden (SN)x films. He stated that he could and when he arrived we tried to make the silvery polyacetylene, (CH)x, more pure and, hence, increase its conductivity. However, we found that the purer we made the (CH)x, by elemental analysis, the lower was its conductivity! Since we had found previously that by adding bromine to the golden (SN)x material, we could increase its conductivity tenfold, we thought that perhaps the impurity in the polyacetylene was acting as a dopant and was actually increasing the conductivity of the polyacetylene, rather than decreasing it. We therefore decided to add some bromine to the silvery (CH)x films and immediately, within a few minutes at room temperature, the conductivity increased many millions of times. We then collaborated with my colleague, Professor Alan Heeger, who was well-versed in the physics of conducting materials. The rest is history! When Alan left Penn almost 10 years ago, my ongoing collaboration with my good friend Professor Art Epstein (Physics Dept, Ohio State Univ.) continued at an even more rapid pace.  One of the transparencies I showed at the very end of my Nobel Lecture in Stockholm on December 8, 2000 is given below. Every word carries real meaning and emotion from my heart.  I wish to extend my personal thanks to:   |  |  | | --- | --- | | • | My *(late)* wife, **Marian**, for her dedicated support and love during our 36 years of marriage. | | • | My loving partner **Gayl Gentile** for her untiring personal and professional support throughout the past 9 years. | | • | My mother, **Ruby** and father, **Archibald MacDiarmid** for providing a loving and solid home foundation on which to base my life. | | • | My brothers and sisters, **Colin, Roderick, Sheila, Alice** for their ceaseless, loving emotional support during the past 73 years! | | • | To my children, **Heather, Dawn, Duncan and Gail,** for their understanding and forbearance in my not spending as much time with them as I might have during their childhood years. | | • | To my delightful grandchildren who never cease to be a pleasure with their many questions and boundless enthusiasm. |   We all owe so much to those who have gone before us – “we stand on the shoulders of giants.”  Copies of the very last transparencies given in my Nobel Lecture are reproduced below. They carry a very special message to all of us.  S*eeking the Great****White Bird****of Absolute Truth*  The dependency of any one person’s research on the labors of scores of earlier scientific pioneers is illustrated very beautifully by a few sentences of this variation from a book by Olive Schreiner, written at the turn of the century, entitled, “The Story of an African Farm.” I would like to share with you this adapted portion.  The story concerns a young hunter who, in his youth, heard about the great white bird of “absolute truth” which lived at the very top of a high mountain far in the east. He had spent all his life seeking it without success – and now he was growing old.  The old thin hands cut the stone ill and jaggedly, for the fingers were stiff and bent. The beauty and strength of the man were gone.  At last, an old, wizened, shrunken face looked out above the rocks. He saw the eternal mountains still rising to the white clouds high above him.  The old hunter folded his tired hands and lay down by the precipice where he had worked away his life.  I have sought,” he said, “for long years I have labored; but I have not found her. By the rough and twisted path hewn by countless others before me, I have slowly and laboriously climbed. I have not rested. I have not repined. And I have not seen her; now my strength is gone. Where I lie down, worn out, other men will stand, young and fresh. By the steps that I, and those before me, have cut, they will climb; by the stairs that we have built, they will mount. They will never know those who made them, their names are forgotten in the mists of time. At the clumsy work they will laugh; when the stones roll, they will curse us; but they will mount, and on our work they will climb, and by our stair! They will find her, and through us!”  The tears rolled from beneath the shrivelled eyelids. If truth had appeared above him in the clouds now, he could not have seen her, the mist of death was in his eyes.  **… Then slowly from the white sky above, through the still air, came something falling … falling … falling. Softly it fluttered down and dropped on to the breast of the dying man. He felt it with his hands –**  *– it was –*  *– a feather.* |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** |  |
| **Interview** |  |
| Q10 | **So how did you manage? How did you manage to get funding, for example?** |
|  | Alan MacDiarmid: The funding aspect is, as we have been discussing recently during this Nobel week, I think, very important indeed and, Hideki and Alan, just last week I was looking at our original letter when we submitted our first communication, and we sent a copy of this letter to Dr Ken Wynn at the Office of Naval Research. Here we apologised for the fact that most of the work – we actually had this in the second to last paragraph in the letter written 23 years ago – we apologised for the fact that most of the work had been done on moonlighting, moonlighting on other grants. But we then said that the other grants were acknowledged and of course by moonlighting, one refers to the fact where one is actually doing research which is not necessarily encompassed in a given subject matter for which we are receiving funding.  Alan Heeger: But the agencies which supplied those funds were very pleased. I mean, success is success. The early work that we did together was indeed spectacular, although, I must say, the first papers were not easily accepted by the appropriate journals, but once it got out, I mean, it was clearly an exciting time and funding was not a problem. I think, as I recall, the biggest issue in that context, in a slightly larger context, was that there was immediately a positive response by industry. They saw the potential, the dream of a new class of materials which would have the electrical and optical properties of metals but retain the processing advantages and mechanical properties of plastics, but it wasn’t true then. It was still a dream. It was 20 years away or whatever and so there was this initial big push, I would say, or at least start-up of quite a lot of activity in industrial laboratories and they quickly became disillusioned. It was only because the funding agencies that were supporting the universities and supported our programmes and our colleagues around the world that we got through this valley, because it did take, let’s say, 15 years before we began to see materials that might someday be really useful.  Alan MacDiarmid: I think in this respect, to stress again the difficulty we had in convincing some of our colleagues that one could work in an area of dirty nasty organic polymers, not nice crystal and materials. There’s one person, a colleague we were discussing within the very early days, concerning collaborative interaction and I remember well this person said something which represented the opinion of many. He said Alan, you know, all of this is a junk effect, don’t touch it. Then I said to this person, well, if you know what the junk is and you know how to put it in controllably and you know how to take it out controllably, could you not possibly call it a doping effect? But I think this overall fell in the past, in the whole area of electronic materials. The physicists, both academic and those in industry, had been dealing with nice, clean crystal inorganic materials and now you came to a yucky polymer, not nicely crystal and just urgh, you wouldn’t touch it.  Hideki Shirakawa: Speaking about the founding, Japan has a really different system as far as the university concerns. The faculty in the National University has received maybe one or two million yen per year without any proposer so within that money we can do without any restriction. I mean, that as I …  Alan Heeger: As you want.  Hideki Shirakawa: As I want to.  Alan MacDiarmid: That’s good.  Hideki Shirakawa: In that sense, the basic research can do.  Alan MacDiarmid: That is still the case, Hideki?  Hideki Shirakawa: Yes, it’s still, yes.  Alan MacDiarmid: That’s excellent. |
| Q2 | **That’s what I wonder, how do you actually do a discovery? Is it a trial and error process? How do you come into the discovery?** |
|  | Alan Heeger: No, no, discovery is discovery. You don’t predict it, right, and it comes in its time. You can be aware of events in a field so that perhaps you’re prepared. You can be aware that something’s going on over here that will stimulate your mind, but discovery is discovery. What can one say?  Hideki Shirakawa: And it’s very difficult to predict.  Alan MacDiarmid: Or if you put it in other terms, that if you plot, say, a straight line, here you have known data and then from the known data, then in principle you can extrapolate to the future new types of phenomena based on that known data but it’s an extrapolation of the curve; but the real exciting things are where, rather than extrapolation of the curve, you have a point way over here which is not on the curve, which is not data which you do not necessarily expect from the data and information which is already known. But once you get that new point and look at it for a while, then you can look back and say yes, of course, this is exactly what you’d expect. But at the time you get it, you don’t.  Alan Heeger: And the other aspect, I suppose, of discovery is to come to a conclusion on the basis of too few facts to really get you that conclusion that enables you then to say, well let’s try that, ok? And then you have a discovery, ok? In that sense, you can’t deduce the result from the facts that you have but by being creative, you can say well, put these ideas together in your mind and it makes something whole to you. Of course, it’s still a hypothesis and then it works and then you’re off and running?  Alan MacDiarmid: Or it doesn’t work and then you modify the hypothesis accordingly. |
| Q7 | **What is the characteristics of a good scientist? Is it high IQ or being creative, as you say?** |
|  | Hideki Shirakawa: Their personality should be very curious, ask why, ask what happens and have many interests in everything.  Alan MacDiarmid: Or in other words, I feel one has to live it, eat it, dream it, sleep it, has to be complete immersion and I like to try to point out to some of my students at times that the creative scientist is just as much an artist as a person composing a symphony or painting a beautiful painting and I say have you ever heard of a composer who has started composing his symphony at 9 o’clock in the morning and composes it to 12 noon and then goes out and has lunch with his friends and plays cards and then starts composing his symphony again at 1 o’clock in the afternoon and continues through ‘til 5 o’clock in the afternoon and then goes back home and watches television and opens a can of beer and then starts the next morning composing his symphony? Of course the answer is no. The same thing with a research scientist. You can’t get it out of your mind. It envelopes your whole personality. You have to keep pushing it until you come to the end of a certain segment.  Alan Heeger: Persistence is important. Of course, intelligence and IQ are important, of course, but I was going to say unfortunately or, whatever, I know many people who have far higher IQs that I envy so persistence is very important and also an ability to just focus. The autobiographies that you read about, for example, Einstein as the classic scientist suggest that he could just focus on a problem and just not let go of it for a time and with an intensity that is just far more than most of us can do and evidently that has something to do with success in science. |
| Q6 | **I know that you both, two Alans, are known for being workaholic, I would say. Do you have any other passions besides science?** |
|  | Alan MacDiarmid: I like to work hard and play hard. Not very much in between, it’s either work or play and whatever I do, I like to put my full energy into it. |

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| **Chemistry\_2024-2000** | |
| **ID** | 0364 |
| **Biographical** | For the ten years from the third grade of elementary school to the end of high school, I lived in the small city of Takayama, a town of less than sixty thousand, located in the middle of Honshu, Japan. Even though it was far away from Japan’s principal cities, Takayama has been called a “little Kyoto” because of the similarity of its landform to Kyoto, the city sits in a basin surrounded by mountains with a river flowing through it, and because of its long-established cultural heritage and tradition. In this small town, rich in natural beauty, I spent my days enthusiastically collecting insects and plants, and making radios. My affinity for science was awakened and grew during in these ten years.  Long after I became a polymer scientist, I occasionally remembered a short composition I had written during my last year in junior high school. At that time students compiled a commemorative collection of compositions describing our future dreams. As I recalled, I wrote something about my wish to be a scientist in the future and to conduct research on plastics useful for ordinary people. I cannot be sure what I wrote exactly because I lost the book of essays during repeated moves afterwards. I had long regretted this loss because I wanted to know more about why and how a junior high school boy decided on a future research career in plastics.  Much to my surprise, I found that the full composition I had lost was printed in every Japanese newspaper the day after the Royal Swedish Academy of Sciences announced its award of the Nobel Prize in Chemistry for 2000 to two friends and myself. After 45 years, I could finally read the complete composition again. I was deeply impressed with the great power of the Nobel Prize.  I was born in Tokyo in August 1936, the third child of Hatsutarou, a medical doctor, and Fuyuno, a daughter of a chief priest of a Buddhist temple. After me, a sister and a brother were born, joining my elder brother, my elder sister and me. After I was born, my family moved many times, following my father’s work, but we finally settled in Takayama, my mother’s hometown, in 1944 during the confusion toward the end of the war.  My higher education began when I entered Tokyo Institute of Technology in April 1957. In March 1966, I completed my doctoral course and received the degree of Doctor of Engineering. In the same year, I married Chiyoko Shibuya, and we were later blessed with two sons, Chihiro and Yasuki.  There were three specific fields I wished to study at university. One was polymer chemistry, just as I had written in my junior high school composition. The other possibilities were horticulture and electronics. I had decided to major in polymer chemistry only if I successfully passed the entrance examination for Tokyo Institute of Technology. In April 1957, after entering Tokyo Institute of Technology, I mainly studied applied chemistry during my undergraduate career. In Japanese universities, an undergraduate major in an science course has to belong to one of the laboratories in his department during his final year in order to work on a graduation thesis. I was interested in synthesizing new polymers, so I applied to a laboratory conducting synthesis research. But since there were too many applicants who wanted to enter into the laboratory I had chosen, I had to switch to a laboratory working on polymer physics. Initially I was reluctant to work in this field, but actually, I realize that my experiences in this laboratory were of great importance to me when I worked with polyacetylene later on.  I finally began working on polymer synthesis, my original interest, in my graduate program, but I started the work on polyacetylene, the work for which I now share the Nobel Prize, just after I received my doctorate and I became a research associate in April 1966. The initial purpose of this study was to determine the polymierization mechanism of polyacetylene using the [Ziegler-Natta](https://www.nobelprize.org/prizes/chemistry/1963/summary/) catalysts. In the fall of 1967, only a short time after we started polyacetylene film through an unforeseeable experimental failure.  With the conventional method of polymerization, chemists had obtained polyacetylene in the form of black powder; however, one day, when a visiting scientist tried to make polyacetylene in the usual way, he only produced some ragged pieces of a film. In order to clarify the reason for the failure, I inspected various polymerization conditions again and again. I finally found that the concentration of the catalyst was the decisive factor for making the film. In any chemical reaction, a very small quantity of the catalyst, about mmol would be sufficient, but the result I got was for a quantity of mol, a thousand times higher than I had intended. It was an extraordinary unit for a catalyst. I might have missed the “m” for “mmol” in my experimental instructions, or the visitor might have misread it. For whatever reason, he had added the catalyst of some molar quantities in the reaction vessel. The catalyst concentration of a thousand-fold higher than I had planned apparently accelerated the rate of the polymerization reaction about a thousand times. Roughly speaking, as soon as acetylene gas was put into the catalyst, the reaction occurred so quickly that the gas was just polymerized on the surface of the catalyst as a thin film.  But we noticed another important factor besides the concentration of the catalyst. Polyacetylene has a property of being insoluble in any solvent, a property which contributed to the formation of the film. Even more surprising, when we observed the film through a transmission electron microscope, we saw that the film was composed of long entangled micro-fibers of polyacetylene. These two properties are essential for the formation of any film, and they were inherent in polyacetylene.  One more important factor contributed to the formation of the film was the Ziegler-Natta catalyst we had used. Most of the Ziegler-Natta catalysts tend to form precipitates which give an inhomogeneous solution. From such an inhomogeneous catalyst, it is very difficult to form polyacetylene film. But the Ziegler-Natta catalyst we had used in our experiment was a unique one. It had good solubility in organic solvents to give a homogeneous solution and it also had high activity to give a high molecular weight and crystalline form of polyacetylene. I could say that nature had prepared us for the way to make polyacetylene film. Later, through the measurements of various absorption spectra of this thin film, we determined the molecular structure of polyacetylene, and thus, we fulfilled the initial purpose of our work.  By chance, this glittering, silvery film, caught the eyes of Professor Alan G. MacDiarmid, one of the co-recipients of the prize, and he invited me to work with him in the U.S.A. In September 1976, I went to the University of Pennsylvania, where Professor Alan J. Heeger, another co-recipient, was also working, and I spent one year there.  I still vividly remember the day of November 23, 1976. With Dr. C.K. Chiang, a postdoctoral fellow who was working under Professor Heeger, I was measuring the electric conductivity of polyacetylene by the four-probe method, adding bromine. At exactly the moment we added bromine, the conductivity jumped so rapidly that he couldn’t switch the range of the electrometers. Actually, the conductivity was ten million times higher than before adding bromine. This day marked the first time we observed the doping effect, although it was a pity that the expensive equipment was broken. The discovery of chemical doping is one of the representative results of our collaboration in this period.  After returning to Japan, I continued to work on polyacetylene. What I did first was to shed light on the chemical reaction associated with the doping phenomena. In cooperation with many co-workers, I investigated various spectra of the doped polyacetylene films: infrared absorption, [Raman](https://www.nobelprize.org/prizes/physics/1930/raman/facts/) scattering, ultraviolet-visible absorption, the [Mössbauer](https://www.nobelprize.org/prizes/physics/1961/mossbauer/facts/) effect, and EXAFS. As a result, we found that the emergence of electrical conductivity on the doped polyacetylene was due to the creation of carbocations or positively charged solitons associated with withdrawing of p electrons from polyacetylene by the dopant when iodine was used as an acceptor dopant.  In November 1979, I moved from Tokyo Institute of Technology to the Institute of Materials Science, University of Tsukuba, where I was appointed Associate Professor. In October 1982, I was promoted to full professor and worked on polyacetylene and other conducting polymers. Since my retirement from University of Tsukuba at the end of March 2000, I have withdrawn from scientific research and other educational activities.  Let me mention two of my major contributions to polyacetylene research during my time at Tsukuba. One is the preparation of oriented films. The significance of polyacetylene being a typical quasi-one dimensional material was recognized very early. In this sense, an oriented film was indispensable to study the intrinsic one-dimensional properties. The polyacetylene films synthesized until then were an isotropic material in which the fibrils were entangled in three-dimensional disorder. I came up with the idea to directly synthesize the uniaxially oriented films by using liquid crystal as a solvent. The same idea was proposed by a scientist from a company. We found that an equimolar mixture of nematic liquid crystals bearing a phenylcyclohexyl moiety was useful for that purpose. We succeeded in simultaneously polymerizing acetylene and synthesizing uniaxially oriented polyacetylene films by orienting the catalyst solution of liquid crystal solvent under flow condition or magnetic field. Further development of this technique enabled us to synthesize helical polyacetylene that consists of clockwise or counterclockwise helical structure of fibrils, by use of chiral nematic liquid crystals. The chiral helicity of the films may be useful for electromagnetic and optical applications.  The other contribution is the synthesis of liquid crystalline conjugated polymers by replacing the hydrogen atom bonded to polyacetylene with a substituent having liquid crystalline nature as the side chain. As these polymers have large substituents, the doping effect is poor. However, these polymers can be modified by introducing various substituents with interesting optical and thermal properties. In addition, they can orient spontaneously in a given range of temperature. |
| **Autobiographical** |  |
| **Podcast** |  |
| **Telephone**  **interview** |  |
| **Interview** |  |
| Q10 | **So how did you manage? How did you manage to get funding, for example?** |
|  | Alan MacDiarmid: The funding aspect is, as we have been discussing recently during this Nobel week, I think, very important indeed and, Hideki and Alan, just last week I was looking at our original letter when we submitted our first communication, and we sent a copy of this letter to Dr Ken Wynn at the Office of Naval Research. Here we apologised for the fact that most of the work – we actually had this in the second to last paragraph in the letter written 23 years ago – we apologised for the fact that most of the work had been done on moonlighting, moonlighting on other grants. But we then said that the other grants were acknowledged and of course by moonlighting, one refers to the fact where one is actually doing research which is not necessarily encompassed in a given subject matter for which we are receiving funding.  Alan Heeger: But the agencies which supplied those funds were very pleased. I mean, success is success. The early work that we did together was indeed spectacular, although, I must say, the first papers were not easily accepted by the appropriate journals, but once it got out, I mean, it was clearly an exciting time and funding was not a problem. I think, as I recall, the biggest issue in that context, in a slightly larger context, was that there was immediately a positive response by industry. They saw the potential, the dream of a new class of materials which would have the electrical and optical properties of metals but retain the processing advantages and mechanical properties of plastics, but it wasn’t true then. It was still a dream. It was 20 years away or whatever and so there was this initial big push, I would say, or at least start-up of quite a lot of activity in industrial laboratories and they quickly became disillusioned. It was only because the funding agencies that were supporting the universities and supported our programmes and our colleagues around the world that we got through this valley, because it did take, let’s say, 15 years before we began to see materials that might someday be really useful.  Alan MacDiarmid: I think in this respect, to stress again the difficulty we had in convincing some of our colleagues that one could work in an area of dirty nasty organic polymers, not nice crystal and materials. There’s one person, a colleague we were discussing within the very early days, concerning collaborative interaction and I remember well this person said something which represented the opinion of many. He said Alan, you know, all of this is a junk effect, don’t touch it. Then I said to this person, well, if you know what the junk is and you know how to put it in controllably and you know how to take it out controllably, could you not possibly call it a doping effect? But I think this overall fell in the past, in the whole area of electronic materials. The physicists, both academic and those in industry, had been dealing with nice, clean crystal inorganic materials and now you came to a yucky polymer, not nicely crystal and just urgh, you wouldn’t touch it.  Hideki Shirakawa: Speaking about the founding, Japan has a really different system as far as the university concerns. The faculty in the National University has received maybe one or two million yen per year without any proposer so within that money we can do without any restriction. I mean, that as I …  Alan Heeger: As you want.  Hideki Shirakawa: As I want to.  Alan MacDiarmid: That’s good.  Hideki Shirakawa: In that sense, the basic research can do.  Alan MacDiarmid: That is still the case, Hideki?  Hideki Shirakawa: Yes, it’s still, yes.  Alan MacDiarmid: That’s excellent. |
| Q2 | **That’s what I wonder, how do you actually do a discovery? Is it a trial and error process? How do you come into the discovery?** |
|  | Alan Heeger: No, no, discovery is discovery. You don’t predict it, right, and it comes in its time. You can be aware of events in a field so that perhaps you’re prepared. You can be aware that something’s going on over here that will stimulate your mind, but discovery is discovery. What can one say?  Hideki Shirakawa: And it’s very difficult to predict.  Alan MacDiarmid: Or if you put it in other terms, that if you plot, say, a straight line, here you have known data and then from the known data, then in principle you can extrapolate to the future new types of phenomena based on that known data but it’s an extrapolation of the curve; but the real exciting things are where, rather than extrapolation of the curve, you have a point way over here which is not on the curve, which is not data which you do not necessarily expect from the data and information which is already known. But once you get that new point and look at it for a while, then you can look back and say yes, of course, this is exactly what you’d expect. But at the time you get it, you don’t.  Alan Heeger: And the other aspect, I suppose, of discovery is to come to a conclusion on the basis of too few facts to really get you that conclusion that enables you then to say, well let’s try that, ok? And then you have a discovery, ok? In that sense, you can’t deduce the result from the facts that you have but by being creative, you can say well, put these ideas together in your mind and it makes something whole to you. Of course, it’s still a hypothesis and then it works and then you’re off and running?  Alan MacDiarmid: Or it doesn’t work and then you modify the hypothesis accordingly. |
| Q7 | **What is the characteristics of a good scientist? Is it high IQ or being creative, as you say?** |
|  | Hideki Shirakawa: Their personality should be very curious, ask why, ask what happens and have many interests in everything.  Alan MacDiarmid: Or in other words, I feel one has to live it, eat it, dream it, sleep it, has to be complete immersion and I like to try to point out to some of my students at times that the creative scientist is just as much an artist as a person composing a symphony or painting a beautiful painting and I say have you ever heard of a composer who has started composing his symphony at 9 o’clock in the morning and composes it to 12 noon and then goes out and has lunch with his friends and plays cards and then starts composing his symphony again at 1 o’clock in the afternoon and continues through ‘til 5 o’clock in the afternoon and then goes back home and watches television and opens a can of beer and then starts the next morning composing his symphony? Of course the answer is no. The same thing with a research scientist. You can’t get it out of your mind. It envelopes your whole personality. You have to keep pushing it until you come to the end of a certain segment.  Alan Heeger: Persistence is important. Of course, intelligence and IQ are important, of course, but I was going to say unfortunately or, whatever, I know many people who have far higher IQs that I envy so persistence is very important and also an ability to just focus. The autobiographies that you read about, for example, Einstein as the classic scientist suggest that he could just focus on a problem and just not let go of it for a time and with an intensity that is just far more than most of us can do and evidently that has something to do with success in science. |
| Q6 | **I know that you both, two Alans, are known for being workaholic, I would say. Do you have any other passions besides science?** |
|  | Alan Heeger: Many things. I love the theatre. We have a wonderful theatre group in Santa Barbara and I’m on the board of directors of that theatre group and support it and Ruth and I always like to go to London and to New York to the theatre. I love music. We’re great opera fans. We were at the opera the night before we left to come to Stockholm, but the real passion, I must say, is downhill skiing so I’ve gotten my whole family to be similarly enthusiastic about skiing and in fact we’re all going next week for a holiday to relax from this very hard-working Nobel week for a week of downhill skiing, so as a sport that’s the one that I like.  Alan MacDiarmid: You see, Alan’s skiing is snow skiing. Ours is water-skiing. We have a house beside the largest lake in Pennsylvania in the Pocono mountains and all of my children and my wife and grandchildren, we like to get up very early in the morning, about 6 o’clock when the lake is absolutely flat, before other people have gone out onto the lake, and then we go water-skiing together and we do slalom skiing, also one ski skiing and it’s really fun, I find. This last summer, for example, to be actually out water-skiing not only with my children but with my grandchildren.  Alan Heeger: Oh yes, that’s great fun. How about you Hideki, are you a sportsman?  Hideki Shirakawa: In my case my way to relax is to grow plants and also I keep my garden.  Alan MacDiarmid: I’ve seen your lovely cactus in your garden when I visited.  Alan Heeger: I remember you took cactus plants with you from Philadelphia 25 years ago. Do they still exist?  Hideki Shirakawa: Still exist, yes. Not to large but maybe this size.  Alan Heeger: In Santa Barbara, I planted cactus in one year. The next year, the next year, they really grow. |