The Science Studio
With Richard Axel

ROGER BINGHAM: My guest today on the Science Studio is Richard Axel, University Professor at Columbia University, an Investigator with the Howard Hughes Medical Institute, and the winner in 2004 of the Nobel Prize in Physiology or Medicine along with his former postdoctoral fellow Linda Buck. They got it for essentially figuring out how our sense of smell works or, as Axel puts it, how the brain knows what the nose is smelling. Richard, could you unpack that for me a little further?

RICHARD AXEL: Well smell is clearly, evolutionarily, the most primitive sense. For virtually all organisms, must have evolved a mechanism to experience their external world and most organisms, the simplest of organisms, bacteria, have no brain and no eyes and they need to sense chemicals in the environment because they provide an indication of the richness of the environment in terms of the provision of food, for example. They provide information about the quality of the environment, the harshness of the environment; they provide information about the gaseous content of the environment. That in its simplest form is smell. Bacteria have chemosensory receptors, odor receptors that reside on the surface of cells and in a relatively primitive way provide information about the external world, which results in changes, in intracellular changes that allow the organism to accommodate to its world.

Now as one moves up in evolution, one sees that system become increasingly more complex. But certainly, in a bacterium there may be upwards of a hundred different receptors that cross the membrane and sense the outside world. Now as we move into eukaryotes, simple eukaryotes such as yeast also maintain on their surface an array of receptors that provide information which allows for sexual reproduction. So yeast, for example, have pheromone receptors and those pheromone receptors, which interact with mating factors to allow for sexual reproduction, those pheromone receptors begin to take the molecular form of the odorant and pheromone receptors that we see in higher eukaryotes- mammals.

BINGHAM: One of the insights that you were following in the 80s, as I understand it, was that we obviously build representations of the outside world and that we use our senses to do that; smell is obviously a primary sense in structuring these representations. Does it take a lot of genetic components to create a sense of smell capable of doing that?

AXEL: Well you're talking about two different things. There are two problems. The first is the ability to sense the outside world. That's a problem in recognition. And the second problem is one of building a representation of that which you sense at the surface of a cell that is exposed to the outside world in your brain, to allow you

to translate the information in the world into something meaningful for the brain. We don't understand that second process. We're beginning to see what some of the rules are, but we don't understand. So we can talk extensively about the recognition problem and even more extensively about the problem of brain representations of the sensory world. And the reason is that we don't know very much about it, so we need to, so we can talk about it.

BINGHAM: One of the remarkable findings that come out of your work is that there are a thousand genes devoted to our sense of smell. With a human genome of about 30 thousand genes, that's three to five percent devoted to just one sense, which is an awful lot of genomic real estate. Could you comment on that?

AXEL: If you walk through a chemical storeroom or, interestingly, through a food market or simply on the streets of New York, the richness of odors that you can appreciate is unlimited. In one sense, I view it the way I view vision- if you look up at that bookcase, you're looking at a hundred thousand discrete forms and that is simply a meager image of what the brain is capable of perceiving. There is an unlimited number of forms in vision and the number of chemicals I believe that you can recognize is unlimited. And so it would be very hard to conceive of a mechanism for recognition that didn't involve a very large number of genes, and in fact, the approach that Linda Buck, a fellow in the lab, took for the isolation of the genes encoding the odorant receptors, had as one essential assumption in the identification scheme, that there be many genes. So we tacitly assume this. This principle of there being many genes encoding odorant receptors threads through all organisms. So the worm, the simple worm- Caenorhabditis elegans, has a total of sixteen olfactory sensory neurons, and those sixteen neurons express over a thousand odorant receptor genes. So a simple organism with a very primitive sensory system.

BINGHAM: It's very evocative, the way you talk about New York, the smells of the city and so on. I was just thinking, there was a novel written in 1985 called *Perfume*, which became a movie, I think last year, and there was a passage in there, let me just read it to you, which said: "In the period of which we speak," as you know, this was 1738 in Paris, "there reigned in the cities a stench barely conceivable to us modern men and women. The streets stank of manure, the courtyards of urine, the stairwells stank of moldering water" and on and on and on, this inventory of smells, and it's all there in Shakespeare as well, this use of language about, oh, my offense is rank, the use of smell words. It's obviously such an important part of our entire being, but it must have been very satisfying to you to actually have been working on something that had such human and personal importance.

AXEL: Yes, but we were aware of that before our observations. As I said earlier, indeed, all of the senses impact, in somewhat different ways one might argue, on

our internal state and our emotive state. Indeed we associate smells with different things. For me, the smell of the city is more attractive than the smell of the country; it's my world. And this brings up sort of a very interesting notion that perhaps was supported by Proust, and that was that odor is really an evocative sense. That odors can bring forth vast memories, so of course in Proust, the smell of a madeleine en combret, brought forth 7 volumes of remembrances of things past.
Now thankfully, odors don't elicit that voluminous a memory in all of us, but you might ask yourself, why is it that odor is for some individuals so evocative of memories? And I've tried to think about this, and one reason I believe is that it is impossible for you to describe an odor to anyone else such that they will know what you're talking about. There is no language to describe an odor as there is a language to describe a visual scene. In fact there are pictures, there is music, which is written, but there is no language for odors. There is no communicable description of an odor.

BINGHAM: So, you might say: "It is a bit strawberry like" or "a bit vanilla like," but that's actually a taste.

AXEL: But that of course doesn't help you. So what you do is, because you can't describe it in any kind of language, you associate it. The scent of a woman, which is indescribable, conjures forth for you memorable moments.

BINGHAM: In your autobiographical essay for the Nobel Prize foundation, the first line is, New York City is my world. You obviously have a wonderful feel for the city, you loved growing up there. Could you give me some sense of what that was like? What your family is like? How you got from there to here?

AXEL: I came from a rather modest family of Eastern European immigrant parents. My father was a tailor. My parents were not educated people; they were very intelligent people and extremely warm, but I was the first among the few people in my family to have completed high school or to go to college. In college it was unclear which direction I would turn. I was a chemistry major and an English major. Like many young people in the sixties: "Should I go this way or should I go that way?"

The direction I went was determined by the rather unfortunate Vietnam War. I was drafted and very quickly applied to medical school in the hope of a deferment. So I went to medical school. I told the story yesterday of finding myself in a place where I was not competent. I was asked by the Dean to never practice medicine on live patients. So I did an internship in pathology and was asked by the chairman to never practice medicine on dead patients, so there was really rather little left for me but to go into science. Science in the early seventies really followed the enormous initial discoveries in molecular biology. So I turned to molecular biology.

BINGHAM: When you write about New York, it's wonderful sort of elegiac, evocative writing; growing up there, doing jobs, working as a waiter in Greenwich Village. You're obviously a tall man; you talk about having played basketball, you're on the courts a lot. People sometimes think that scientists of your stature, caliber, must have had a very bookish upbringing, but that's not the case, is it? You did the sort of thing that other people do as well.

AXEL: I certainly did the things that other people do and it really was a learning experience to live in this world. New York is a marvelous city. It is a city that is so suffused with the different cultures of its immigrant population that provides the city with a diversity that leads to enormous excitement. I found the culture and background of this world in New York City to be so overpoweringly influential on my world. But of course I did all these things, but you must remember that I wasn't good at it. So I played basketball because I went to a high school for students that scored well on examinations, Stuyvesant. So I was the star center for Stuyvesant, because the school was composed of the sons of Marxist immigrants, none of whom were terribly good basketball players. So there is a story which I recounted where I came up in my junior year against a fellow named Lou Alcindor who was playing for Paul Memorial and he was 7 feet tall and I was the center against him. He scored 54 points against me in a high school basketball game. I recall when I first got the ball after he had scored 14 points, I faked to the right, and I faked to the left, and he looked at me and he said "What you gonna do Einstein?" He turned out to be Kareem Abdul Jabbar, arguably the greatest basketball player that ever lived, and I study olfaction. Who hath the greater degree of ecstasy?

BINGHAM: You developed a great love in the early years for the arts, the opera as well. I'm reminded of the first deputy director of the Salk Institute here, it was a man named Jacob Bronowski, who was well known for doing a television series called *The Ascent of Man*, and for bringing together the arts and the sciences, the two cultures. Is that something that is very important to you?

AXEL: Important for what? It's important for me to experience the richness of the arts. The relationship of science and art is a talked out arena. The reality is that each of the endeavors requires creativity. But I think beyond that the comparisons become difficult. I mean after all William Blake said "that which was proven was once only imagined." That's very true in science. There is an imaginative period, a creative period, which in the arts plays out in the creation of a work. Whereas in science, beyond the creative moments, the rest really requires a rigor and dedication that I think quite distinguishes the doing of science from the doing of art. There are other things that of course distinguish it, and this isn't necessarily bad. In science, were there no Jim Watson or Francis Crick, we would know the structure of DNA. In the arts, were there no Rembrandt or there no Picasso, we would not have the De Mousel. So there is a uniqueness to the contributions of art that isn't apparent in science. Yes it may take a bit longer, had the giants in science

not existed, but this information would be here, in much the same way that without Shakespeare there is no Lear and will never be a Lear.

BINGHAM: You mentioned Jim Watson and Francis Crick. I think there's a public perception that the way science is done, the way to win a Nobel Prize is you go down to the pub, have a few beers, fiddle with a tinker toy model, have a eureka experience, and bingo, you have the double helix. At the other end of the spectrum, of course, is the work of somebody like Roger Guillemin, another Nobel laureate here at the Salk Institute, whose work involved grinding up literally hundreds of thousands, perhaps millions of sheep brains to get even a small amount of the brain hormone he required. Where on the spectrum does your work lie?

AXEL: Well the identification of the odorant receptors themselves required really a concerted effort for almost five years by a student, a postdoctoral fellow in the lab, Linda Buck. You know how a lab in the modern world functions. I might have conversations with my students about what is an exciting arena and how one might approach its solution and then the student goes off and with constant conversations does their work. As it is written in the Bible, the work of the righteous is done by others. So Linda worked on this for five years and the receptors were revealed. Now the receptor genes themselves provided only a solution to the first question, that is, how you recognize the information in the environment. But a little bit of looking at these receptors and the way in which they were expressed in the sensory cells in the nose also began to tell us how it is that the system is organized. It sort of fell forth from looking at the way the genes were expressed that we began to get some insight into how the information in the periphery was actually being relayed to the brain in a form that would allow for discrimination. Now we're not yet there but the very beginnings of that model came very quickly upon the identification of the receptors. I'm rather eclectic and work on a number of things and olfaction has held my interest more so than any of the other fields of molecular neuroscience I've engaged in.

BINGHAM: Probably because of what you were saying earlier about the memory component as well, it occurs to me that Eric Kandel, another Nobel laureate who works on memory, is at Columbia at the moment, so your paths must cross quite a bit. Could you talk a little bit about that?

AXEL: Yes Eric Kandel and I are extremely close. In fact the whole neuroscience community at Columbia is unique in the affiliative nature of the group. I have not observed this anywhere else in the world. It's a marvelous culture and its best or well illustrated by my association with Eric. In my early years I was a molecular biologist without any insight into neurobiology at all. I participated in the revolution of recombinant DNA. I learned how to cut and paste and sequence DNA sequences and introduce these sequences into cells and organisms. It was all

a lot of fun. While Eric was at the same time quite unfamiliar with molecules and certainly not at all familiar with DNA or RNA, and he was working out in precise detail the functional anatomy of a neural circuit in a simple organism that had the capacity to learn. It was in 1980 that I came together at a faculty meeting. Faculty meetings at Columbia tended to be intensely boring. I knew that Eric was interested in memory and I said "Eric we need to work on the molecular biology of memory". We began to talk and we actually worked together for a while and Eric taught me neurobiology. Now could you imagine a greater person to provide insight into neurobiology, and at the same time I taught him molecular biology. One of my students worked together with Eric and I, Richard Scheller. Richard is a neurobiologist who now is the vice president of Genentech and in charge of research. It was a spectacular time when the two of us sat and talked and tried to understand one another, and of course what could be more pleasurable than for me to learn that Eric won the Nobel Prize in 2000 for his studies on the molecular biology of memory. And of course I joined him in Stockholm and then four years later, he joined me.

BINGHAM: You've obviously had a very fulfilling career. Could you imagine what you might have done if you had not been a scientist?

AXEL: I could've been bored. You know one doesn't know those things, both in science and in life. One is opportunistic in some sense. One latches onto that which one loves and then pursues it with vigor and excitement and a rigor and dedication. What would I do? Well I'm much happier being a scientist than I would be as a professor of English, which is something that had entertained my mind because I prefer exploring rather than critically evaluating.

BINGHAM: Is there anybody historical, dead, alive, that you would have liked to have had a conversation with, asked some questions of?

AXEL: Yes, there are many people who I would have liked to have a conversation with. But, I feel very fortunate. I'm exposed to extremely smart people both in science and outside of science with whom I do have conversations. I live in the world of the arts and writing and it's just been a real pleasure. Sure one would like to have the opportunity to talk to any interesting person, be he a cook in a delicatessen or a great writer in his loft overlooking the sea.

BINGHAM: I was just thinking suppose you had a time warp and you could have gone to Gregor Mendel and said "do you know how many genes it takes for sense of smell?"

AXEL: If I had my choice I think I might choose Descartes. I think that this whole issue of perception has been considered over time since the very earliest of philosophers. Plato's cave scenario really questions what I call this tension between

image and object between physical reality and the brain's perception of physical reality. It's something that we in neuroscience think about and should think about quite a bit. The reality is that history, philosophy has a long history of thinking about perception while ignoring the brain. Now, we're in a really unique situation where we can actually study these disciplines, which were formerly in the hands of philosophers and psychologists who consider the brain a black box, and now we can open that box and begin to look at it. So It's a very exciting time in neuroscience right now.

BINGHAM: I noticed that in your banquet speech at the Nobel Awards you gave a presentation and mentioned the conflict between intellect and political and religious authority, and how those issues were intensifying. And you actually quoted Jacob Bronowski. Is this something you think about on a regular basis?

AXEL: Well I think it's particularly important the issue of academic freedom and intellectually freedom and it's a freedom that I think has in the current time in the United States in compromise. I do believe that we as scientists are being restricted in our efforts based upon what I believe is religious ideology. The stem cell debate is one particularly clear example. I experienced the debate over recombinant DNA, which had perhaps a more measured period of controversy, but again there are numerous instances in science when apocalypse was predicted and nothing happened. There is little question that science comes without value. That is a piece of science has the potential to be enormously valuable and has the potential for harm, but we are a long way down the road in a generation of science and science has and inexorably will affect our lives and it's the scientists obligation and the publics obligation to recognize this and see to it that science although not restricted in its endeavor be used for the benefit of man, and in fact Bronowski thought of this quite more eloquently than I can.

BINGHAM: Each year the literary agent John Brockman asks a group of people a question, and in 2007 the question was "What are you optimistic about?" Could I ask you the same question, what are you optimistic about?

AXEL: Well I think I've already intimated my optimism about the movement of neuroscience. Neuroscience is really gaining a momentum. The integration of disciplines is bringing cognitive psychology with molecular biology, electrophysiology, and the introduction of extremely powerful technologies that I just observed downstairs in Terry's lab. These really provide me with an excitement that we can understand something. Now we aren't going to understand how an odor evokes the memory of events in ones life in my lifetime. But we are going to begin to make substantive contributions to our understanding of perception, memory, and ultimately cognition. We are hopefully going to be able to understand how it is that these processes which after all can only involve neurons since that is all there is in your brain. How it is that these processes are transformed

in disease states. This is going to be a rather- it is, it has been, its going to be an even more exciting time. And if I can continue to do this and still go to the opera I'll be a happy man.

BINGHAM: Richard Axel, thank you.