

Robert H. Wurtz, Ph.D.
Oral History Interview
December 1, 2015
Conducted by: E. Gordon Margolin

Margolin: We're about to start recording both on film and on audio, an oral interview with Dr. Robert H. Wurtz, who's a Ph.D. here at the NIH and who is an NIH distinguished investigator. We're sitting in the Office of NIH History, where this recording is being undertaken. I am Dr. Gordon Margolin. I'm a volunteer in this department. Today is December 1st, 2015. Let me tell you first a little bit about Dr. Wurtz before we start asking him questions. His research extends over about 50 years here at NIH, and explores the organization of the brain underlying visual perception, and the control of eye movement. He developed methods widely used to study these brain systems in awake behaving monkeys. The monkey is regarded as the best animal model available for the human visual system. He will tell us more in detail about how he did all this. This method however is very important because it makes possible analysis of the brain's integration of visual input from the eye with information about movement of the eye that is essential for the active vision of all primates. This interview is supplemented, in large part, by Dr. Wurtz's own autobiography which can be found as a PDF at SfN.org under AboutSfN, History of Neuroscience, Autobiographical Chapters, Volume7, Robert H. Wurtz. A copy of this autobiography will be attached to his document in the Office of NIH History.

Margolin: Dr. Wurtz, we'd be interested in hearing from you a little bit about your early life and some of your recollections which you now feel directed your career development that's been so prominent here at NIH.

Dr. Wurtz: Well, I grew up in Webster Groves, Missouri, which is a suburb of St. Louis, and my father was superintendent of a candy factory. I don't think his work had any influence on my scientific career. My mother had been the bookkeeper for the factory my father worked at, and they built a house in Webster Groves because they thought the school district was particularly good. I went to public schools through high school in Webster Groves, and I think their choice was very fortunate for me. I had many good teachers, but one in particular, Mary E. Moore, in the fifth and sixth grade, took particular interest in me and encouraged me to read, and I became particularly interested in history. This broadened my horizons in addition to making me seek out books to read. She also attempted to improve my miserable spelling and my hand writing: both attempts were a total failure. I still can't spell, and no one can read my writing. I have come to think both of these are neurological characteristics not just mental lethargy. I also had a teacher in junior high school and high school, Dorothy Weirick, who heard me give a speech in an election for President of the student body. She heard it and said I should really try out for the debate team, and I explained that I really couldn't because I had a severe stutter with anything I had not repeatedly practiced. "Well, that's okay, we can deal with that," she said, and in the course of debating I really did get control of the stutter. We won the Missouri state championship in my senior year. The point here is that two teachers identified my interests and my problems, took the

considerable effort to help me, and literally changed my life. Yet teachers are still underpaid and under recognized.

Another major influence when I was growing up was a group of close friends in high school. There's always the assertion that at a certain age your peers become much more influential on you than your parents, and that certainly happened to me. I became part of a group of eight, all of whom were interested in science. They were particularly influential in what I looked for in a college, which was important because no one in my family had ever gone to college before. The only thing that I knew is that the same class didn't meet every day. I benefitted from their interests and comradery, and we've stayed in touch throughout our entire lives. I didn't realize, until I went to the 50th reunion of my high school class, that it's not that we were among many science interested students, but that in our class, we were virtually the only ones; most of our classmates went on to be lawyers and businessmen, many very successful. It was an excellent high school for all. Anyway, the reason this is relevant is one of my friends, Chris Hohenemser, said, "Well, why don't you go to Swarthmore?" and while I thought that was a great idea I also thought that Swarthmore was much too far away from St. Louis, and he said, "Okay. Well then, why don't you go to Oberlin?" So, I went to Oberlin, and that turned out to be a very wise decision.

Margolin: I think your autobiography also says that your father had a rather significant influence on your thought processes.

Dr. Wurtz: Absolutely, I have foolishly skipped over that. Basically, my father had no education beyond sixth grade. But he educated himself particularly in literature, history and science. I think he could stand up to anyone who went to college, though he did not realize it and always felt he was not educated. It is a good illustration of how a good college education leads you to understand what you know and what you do not know. He had, however, developed management skills that provided him with a good job, but he absolutely hated the job. His dictum to me was, "You want to get a job that you're doing whether you are paid for it or not." He viewed college as mandatory and so did I. I looked on going to college as the way of finding out what I wanted to do, because when I left high school I had really no idea, except that science was very high on the list.

Margolin: That brings me to the next question. You went through a number of steps before you reached the career point, and that was really interesting how you put things together. Would you tell us a little bit about that?

Dr. Wurtz: Well, the steps were really a series of experiments, and I was in fact simply following my father's dictum of, "Find what you like to do." I went to listen to a lawyer, and that took care of that in one shot because he was only interested in making money. I took chemistry and it was taught by a wonderful professor, J Arthur Campbell, who emphasized that little memorization was not the goal; the periodic table was always going to be on the classroom wall. It was the first time I fully realized that my memory was not very good, but I could figure things out, and so chemistry seemed very attractive. I was also very interested in economics, for much the same reason. Later in my sophomore year I took psychology, which was a revelation, because it was taught from a Skinnerian view, which was frowned upon even then, but which showed that behavior could be

quantified, a science could be built around behavior, and both behavior can be changed by rewards and punishments. I had no appreciation of any of this. Another interesting course was an advanced course in biology, which mainly looked at nerve conduction and functions, but I think the combination of these latter two courses really nailed it for me: what I wanted to do was study the brain. But that was my junior year, and I had to remain a chemistry major to meet graduation requirements.

Having decided on studying the brain, the next question was, do you go to graduate school or medical school? I made the initial decision to go to medical school. I was going to Harvard. Oberlin had very good relations with Harvard Medical School, so it was convenient to do that. By the midpoint of the senior year, I increasingly had doubts that I really wanted to treat individual patients, whereas if I did research I could solve a problem for everybody for all time. It had caught the research bug, I guess.

I changed my mind, and decided that I really should go to graduate school, and I knew of a professor at the University of Michigan, James Olds, who I'll talk about a little bit more in a moment, and he said he would accept me in his lab. The only problem is, the graduate school deadlines had long since passed, but the department chairman waived that rule, and I was accepted at Michigan and did my Ph.D. at Michigan.

Margolin: How long did you stay there as a graduate student?

Dr. Wurtz: At Michigan? I stayed for four years. I worked with Olds, and he was incredibly influential on me. I did not really appreciate until long after I had left his lab that he was the one who made me into an experimental scientist. He took me aside, to start with, and said, "You know, at Oberlin you wanted to study hard and get high grades." That wasn't quite true, but I got the point. He said, "Here, forget it. Forget courses. What you're going to learn is going to be in the laboratory." He was absolutely right. It is something that I never forgot. He also said, "If you're doing one experiment, and you see another possibility that looks more exciting, switch to do the most exciting one. Always do the most interesting experiment you possibly can."

Finally, Olds was very influential in that he protected me from the psychology department. When I went to graduate school, I had only two courses in psychology, so I didn't know much psychology. In the first year, they gave all incoming students exams in ten areas, and I failed six or seven of them. My psychology advisor rightly said, "You've got to learn lots more psychology, so what on earth are you doing auditing biochemistry and taking physiology." And I'd already signed up next for neurophysiology and neuroanatomy. Olds came to my rescue and said, "Look, we're studying how the brain produces behavior, and you have to know the brain as well as behavior," and so I developed a neuroscience education before neuroscience existed, but I had to sculpt it out myself. Olds protected and strongly supported my interest in doing so. He was the defining influence on the rest of my scientific life.

Margolin: I gather that psychology and scientific approaches were not really compatible at that time. They were totally separate.

Dr. Wurtz: Well, it really depends on the area of psychology. Sensory psychology had been a scientific area for a hundred years. The Germans pioneered it, and it, to this day, it is a very exact science. Other areas, like social relations, at least not then, were not exact sciences. It was useful to know about such other areas of psychology, but it was much more important to learn more about physiology and neuroanatomy.

Margolin: That was an interesting trip you took to get to where you are, I must admit that. How did that bring you to NIH, and what were your thoughts about coming here and your thoughts about this institution in general?

Dr. Wurtz: After Michigan, I knew to concentrate on laboratory work, but I decided that what I was doing in graduate school was not the best way available to study the brain. I was passing electric current through the brain in order to produce rewards and punishments, which are the experiments for which Olds was famous. But a leading neuroscientist, Vernon Mountcastle, came to Michigan and gave a lecture describing recordings from single cells in the brain, and how these cells carried information from sensory receptors to the brain. I thought, "Whoa, he's recording the electricity from the brain, and I'm just electrocuting it."

I decided that I had to change my research direction, and at the same time I didn't quite know what direction to take. I moved temporarily to St. Louis in part because my father was seriously ill and in part because I took a part time position with the Committee for Nuclear Information. The committee was a group of scientists whose goal was to inform the public what the scientific facts about nuclear war and nuclear fallout were so that they could make informed decisions. Of course, I wasn't a nuclear physicist, but with a college chemistry major and introductory physics you can understand what the scientific basis of issues were. My reason for doing so was that at the time nuclear fallout was being produced by atmospheric bomb tests and the nuclear arms stockpile was rapidly growing. Why study brains when they all might shortly be incinerated. It was satisfying for a year, but I didn't think I was really accomplishing very much, and fallout decreased dramatically after Kennedy ended nuclear testing (along with much discussion about the risks of nuclear war). So I went back to full time research. At Washington U, I learned how to do single-cell recording, which I was particularly interested in, and on the side I learned how to use computers. MIT had a program, paid for by the NIH, that provided LINC computers to some 15-20 laboratories, and the neurology-neurosurgery lab was one of them. The goal was to distribute the Laboratory INstrument Computers to a group of universities to encourage scientists to integrate them into their labs I was able to use one at Wash. U. The LINC showed me first, how powerful a computer was and how it could revolutionize brain research, and two, how deep the time sink required for machine code programming was. At Washington U, I wound up doing an experiment on synaptic learning using single cell recording in a sea slug, the *Aplysia*. Once again, I thought I knew a lot about behavior, but I didn't know much about physiology, and so I was starting to look around for a place to learn more single-cell physiology. I had a colleague at Wash. U., Emilio Bizzi, who had moved to the NIH who thought the NIH was a wonderful place to learn what I wanted to know.

With the blessings of those who I was working with in St. Louis, I came on an eight-month visit to the NIH. I was in the Mental Health Institute, in the Laboratory of Neurophysiology, but my

appointment was in the Neurology Institute. It was at the time when the intramural program in nervous system was well-integrated across institutes. I did learn much more about Aplysia and how to do single-cell recording. I also discussed going to work with Eric Kandel, to continue work on Aplysia, but I missed the richer behavior in mammals and decided to concentrate on the animal model most similar to humans, the old world monkey. But Eric remained a lifelong advisor and friend.

About that time, a position opened in Mental Health in Dr. Ichiji Tasaki's laboratory. He was chief of the Laboratory of Neurobiology, and I applied for that position. I got it in part because Tasaki had spent the early post-war years in St. Louis and was personal friends with all the people who were recommending me. You'll see a certain pattern, that what I at the time thought was good luck was, in fact, support by the senior scientists who I had had contact with. It wasn't luck at all. It was their support that did it. I moved to Dr. Tasaki's lab with the agreement that I could do anything I wanted except bother him. He worked on nerve conduction and he was fully engaged in it. He was happy to answer questions, but he didn't want to be bothered if it could be avoided.

At that point I had decided to concentrate on the visual system because Hubel and Wiesel at Harvard had shown that while the retina sends information to the brain about little spots of light, by the time neurons recorded in the primary visual cortex responded, they did so preferentially not to little spots, but to oriented slits. A given cell responded to an oriented slit of light at one location but not at another – their sensitivity was localized to one region of the visual field. It was a riveting finding because it showed how the brain could move from one level of analysis to another level, and it was really the only place where that had been shown so clearly. I had had the opportunity to watch an experiment in their lab because I had met David Hubel when he gave a lecture at the Woods Hole Biological Laboratory where I had spent a summer while I still a graduate student. But their work was in anesthetized animals, and I thought that a critical next step would be to see what would happen if the brain were actually using this visual information. I decided that I could determine this in monkeys because I was confident that I could train the monkeys so I could control its eye movements. My enthusiasm was of course reinforced by my brief visit to their laboratory, and I of course benefitted from David and Torsten support and friendship over the subsequent years.

Margolin: Let me interrupt and ask, why did you choose monkeys?

Dr. Wurtz: Monkeys have a visual system that is as close to our visual system as you can possibly get, except for the great apes. If you didn't have monkeys you'd have to invent them in order to have a good model for human vision. In addition to that, which I realized only later, their eye movement system is virtually identical in monkeys and humans. So if I recorded a monkey's eye movements and my own eye movements, and I gave the records to you, you'd be hard put to be able to tell the difference between them. So the reason for concentrating on the monkey is that it has that comparability to human systems, it has rich behavior, and it's trainable. It's very hard to train a sea slug, but it's very easy, or, let me say, straightforward, to train a monkey. I joined Tasaki's lab in July of 1966. I needed to set up a monkey holding facility, train a monkey on the task, and build the apparatus to do the training so that I could first see if the task worked. Then I

needed to gather the equipment for the recording from neurons, and obviously I had to have the monkey do the task do before I did the recording. Actually, things went very well. One of the tremendous advantages of the NIH was that a lot of equipment I didn't have, I could go around and borrow. You know, if you say you're going to borrow something for three months and you do return it, scientists are almost always willing to help.

Margolin: You crossed over among a bunch of different institutes.

Dr. Wurtz: Oh, yes. I borrowed from labs in both mental health and neurology – this is before the eye institute existed.

So, the task that I trained the monkeys to do was to look at a small spot of light, and detect when the spot had a slight change in shape or intensity. If it indicated that it saw the change, it received a reward. The monkeys easily did the task to get the reward. I had them do this task because for the few seconds that they were looking at the spot they were not making large eye movements. The eye was nearly as stable in the awake monkey as it was in the anesthetized monkey and so for these few seconds I could study the awake functioning cortex in the same way it had been studied in anesthetized monkeys.

The first question I wanted to investigate was whether the primary visual cortex solved the problem referred to as the construction of visual stability. As we've been talking, we've probably made five to ten thousand eye movements because we make rapid two to three eye movements every second. So if the eye were a movie camera, and I showed you the sequence of images it recorded, you would see the visual scene jumping as the eye was directed toward one place to another, so much so that we'd probably all get sick from watching it. But, the brain has some mechanism to compensate for that continual jumping of the visual scene. So the first question I asked was how did those neurons in the very first levels of visual cortex deal with that? Because the eye movements wreck such havoc on our vision, I thought the nervous system would deal with that problem immediately.

So after starting in July 1966, I had a monkey trained and things working well enough to start recording neurons the week before Thanksgiving. On the day before Thanksgiving, I found cells in the primary visual cortex that responded best to a slit with a given orientation. At that point I knew that I could replicate the work in awake monkeys that Hubel and Wiesel had done in the anesthetized cats and monkeys. I had a very pleasant Thanksgiving that year. I took the records to Tasaki who, while he worked on nerve impulses in the squid, was fully knowledgeable about the visual system. He was pleased to see the results and told me to go ahead and buy the 565 Tektronix oscilloscope that I had wanted at the start. The oscilloscope that I bought is the one that I just transferred to the NIH museum.

Margolin: Is that what you called the grass camera?

Dr. Wurtz: No the oscilloscope produced the images of neuronal activity on its cathode ray screen, and the Grass camera (also transferred to the museum) photographed a series of these images onto film.

Margolin: I see.

Dr. Wurtz: It was the way we went about doing it in those days. Truly primitive. Also, in the rack of equipment transferred to the museum was a row of digital modules. Those digital modules, named Digibits, could be wired to control the onset of visual stimuli and produce the rewards for the monkey. The sequence had to be mechanized because there were 300 to 500 trials per recording session.

Margolin: Okay. This led you into a lot more detailed study of the individual system.

Dr. Wurtz: Yes. The salient point is that my goal of seeing how neurons in the visual cortex compensated for eye movements was total and complete failure. There was little indication of any compensation, certainly not enough to compensate for the effects of the frequent rapid eye movements. That was a major disappointment. What was striking, however, is that the visual cortex of the awake monkey acted pretty much like the visual system of the anesthetized, paralyzed monkey, which indicated that the beautiful experiments of Hubel and Wiesel were not some aberrant result related to anesthesia. In addition, the experiment established a basic technique that has now been used throughout the visual system to study the neuronal mechanisms of vision and cognition at higher levels of the brain. The way experiments are done on the visual system has totally flipped. Once in a while you'll see a study done under anesthesia, which is perfectly reasonable for certain studies, but the vast majority are done in the awake animals. Furthermore, the technique has made possible studies of neuronal activity related to cognitive functions, at higher levels of the nervous system, and for more complex questions than just visual processing.

Because the mechanisms for visual stability were not clearly present in primary visual cortex, it seemed reasonable to examine a phylogenetically older visual pathway in the primate. In all mammals there is a visual pathway that doesn't go to the cortex, but goes down to the brain stem to a region named the superior colliculus. I therefore started recording in the superior colliculus, and I was joined by my first post-doctorate fellow who was a new MD from Harvard serving at the NIH instead of being sent to Vietnam. In my view, possibly the only benefit of the Vietnam war was that Michael Goldberg came to work at the NIH. But that aside, this turned out to be very good luck on my part because he was very talented, enthusiastic and we became equal collaborators within a few months. He's now a professor at Columbia, a member of the National Academy and former president of the Society for Neuroscience.

Margolin: How did you get deep into the brain?

Dr. Wurtz: In all of these experiments there is no discomfort to the monkey as it is doing its task. In fact, the monkeys do the tasks as if they were doing video games – they will frequently continue doing the task even when they are not getting their reward. The reason for this is that in all of the monkey experiments an opening is put in the skull when the monkey is under general anesthesia. It is roughly comparable to the placement of fillings in teeth; both the filling in teeth and the window in the bone of the skull are placed under anesthesia, but they are used after the subject is no longer under anesthesia. The brain has no sensation within it so the tiny wire used for the electrodes slides into the superficial cerebral cortex or to the deep superior colliculus with equal ease.

I skipped over the more general methods required for doing these experiments so I want to digress briefly describe them and mention those who showed me how to use them. Mort Mishkin and Hal Rosvold showed me the surgical procedures and the care of the monkeys. My next-door neighbor in NIH building nine was Edward Evarts. Ed had perfected the system for studying single unit responses in awake monkeys. I just adapted all his techniques to record from the visual system. In fact, Evarts would tell me, "Well, go over to the NIH instrument shop and get this, this, this and this." He just gave me a shopping list although it would take them a month to make this, this, this, and this. But Ed was incredibly helpful. I couldn't have done the setup of the experiment as fast as I did were it not for his help. I think he was skeptical whether this was going to work or not, but so was I.

Now to return to the superior colliculus, and the difficulties we had in getting started there. Here the problem was that little was known about the superior colliculus in the monkey and we had difficulty determining when we were and were not in the superior colliculus. At one point, Goldberg commented that "The superior colliculus has one of each neuron type in the entire brain and it's put all together for neurophysiologists to practice on." Because we didn't know quite where we were most of the time, it took us a good while because we were, we had to make marks in the brain with the electrodes and then put the euthanize the monkey and do histology on the brain to locate the marks. But we eventually worked out the layers. The top layer was visual neurons. The next layer was eye movement neurons along with neurons showing the interactions such as those whose response was stronger when the monkey was getting ready to make an eye movement to a target.

We also found neurons whose visual responses were modified during rapid eye movements, exactly what I was looking for in visual cortex. We were so overwhelmed by the other interactions of visual and motor processing, we did not study this in detail until many years later. In 2002, Marc Sommer identified a pathway that carried the eye movement information to frontal cortex. Here the interactions I expected to see in the early visual pathway became apparent at one of the highest levels of visual processing in the primate brain.

The significance of these superior colliculus experiments was that they incorporated analysis of both vision and of eye movements; the superior colliculus seemed to be a crossing point of the visual system and the rapid eye movement systems. In lower vertebrates like frogs it's all they've got. In primates including monkeys and humans, the higher levels of processing have been taken over by cortex.

After the work on the superior colliculus, almost everything we did was not vision and not motor, it was visual motor. I certainly look on these systems as not two systems but one system. The motor is there to move the eyes where you want to see something, without the motor system you won't be able to clearly see the object of interest.

Margolin: This led you to other parts of the brain which you have obviously identified in the same system.

Dr. Wurtz: Yes. One is a brain region known as the basal ganglia that feeds into the superior colliculus. Okihide Hikosaka, a subsequent collaborator, found that its tonic output inhibits the superior

colliculus and then releases the colliculus briefly. This inhibition and release has turned out to be a major way in which the basal ganglia influence other brain regions. We also investigated regions of visual cortex beyond the first visual area including area MT that is devoted to visual motion analysis and depth vision, and the frontal eye field in frontal cortex that carries out higher level visual processing that leads to eye movements. As noted briefly above, we also followed a pathway from the superior colliculus to cortex that carries a copy of the rapid eye movement activity to cortex (a corollary discharge), probably contributes to produces the visual stability I was interested in in 1966. We must mercifully skip over these and other experimental sequels here.

Margolin: Are you saying that sticking with the visual motor studies led you to a much broader understanding of brain function and applicable perhaps to a great deal of other effort in brain research?

Dr. Wurtz: Yes. I would say now, most use of this visual and oculomotor system is not to investigate the visual and oculomotor system but to use it to investigate, say, reward in the basal ganglia or the result of punishment in the basal ganglia. My colleague, Okihide Hikosaka, does just that. In his experiments he uses the visual motor system to study other topics because it's a system that's well enough understood that it can be used as an entry to understanding other not as well understood systems in the brain. There's motivation that it's applied to, visual attention, memory and I would say all of these areas have progressed more rapidly using the visual oculomotor system than it has using other sensory systems. It's been a window into higher processes.

Margolin: You were the one that did all that?

Dr. Wurtz: What I did was the basic technique. Many, many people have done these other experiments, obviously.

Margolin: Yeah, but obviously it all came out of your basic studies.

Dr. Wurtz: Well yes frequently true. It's very satisfying to go to a session at the Neuroscience Society meeting and see almost every report in the session using awake monkeys.

Margolin: It's a remarkable journey and remarkable progress and obviously it's going to continue to influence studies on the brain.

Dr. Wurtz: Yes. It influences the study of not only the monkey brain but also the human brain because it is such a good model of human behavior. It's not human behavior but is close in so many respects and it's much closer to humans than are other animals such as particularly rodents.

Margolin: Can any of this be reproduced in studying human beings?

Dr. Wurtz: The way I would go about answering this question is by comparing what we can do in experiments on monkeys with what we can do in humans. In monkeys, we essentially have two steps. In the first, we try to figure out how increases or decreases in neuronal activity in a particular area is correlated with the monkey's behavior. We try to establish the circuits among the neurons we study and develop models that explain the correlation. In the second step, we

perturb the system of neurons to see if that changes the monkey's behavior. After all, in the first step, the correlations might be spurious; neurons correlated to and eye movement might be equally correlated with a toe movement. To perturb the neurons we usually use small injections of chemicals among the neurons to alter their activity; for example if inactivation of the neurons does change the behavior, it provides strong evidence that activity of the neurons are related to the behavior.

A major way of studying humans is by using the expanding number of imaging techniques, particularly fMRI. With imaging you can only address the first question, the correlation of brain activity in a given brain area and behavior. This is not as precise as neuronal recording because there is little hope of identifying a neuronal circuit, or the precise location of the neurons. In addition, the image is based on activity of at least thousands of neurons and an MRI is actually not measuring cell activity but rather is measuring change of blood flow related to cell activity. But this is the human brain, and what we can see is incredible. The second step is currently not possible because we have no way of inactivating a local area of identified neurons in the human brain; no one would be willing to do the invasive experiments in humans that are possible and painless in monkeys. The current best solution is to determine the neuronal basis of the behavior using the perturbation experiments in monkeys and testing predictions derived from these experiments using human imaging and behavior. The combination of monkey and human experiments has proved to be a powerful tool, and one that is only possible by the extensive study of the monkey model of human brain function.

Margolin: How applicable will the circuits in the brain be to studies on other disease like Parkinsonism, Alzheimer's and so forth.

Dr. Wurtz: Good question. The applicability to human disease depends on understanding the brain circuits in the monkey model and how these are altered by the disease. Parkinson's disease is in fact a superb example of moving from the monkey model to a treatment for a devastating aspect of Parkinson's disease, uncontrollable tremor. A colleague of mine, Mahlon DeLong, began to work in Ed Evarts' laboratory here at NIH and studied the neurons in the area of the brain that was known to be implicated in Parkinson's disease, the basal ganglia we have already mentioned. He outlined the organization of neurons in the basal ganglia and adjacent thalamus and developed hypotheses about how they might be connected to the control of skeletal movements. One possibility he recognized was that if the activity in one part of the circuit were altered that reduction might reduce tremor. In collaboration with other clinicians, he found that brain stimulation in specific locations in the basal ganglia and thalamic circuitry reduced tremor and some cases dramatically eliminated the tremor. This opened the field of what is referred to as deep brain stimulation which has now been used to treat the tremor in many Parkinson's disease patients. This work is the model for translation from monkeys to humans of information that forms the basis for the development of treatment of a human disease. Success clearly is dependent on determining the circuit organization in the monkey brain; the greater the knowledge the higher the likelihood that related human diseases can be treated.

Margolin: In science we sort of pick little bits at a time and make discoveries as we go along so that the original bits lend more and more credence.

Dr. Wurtz: The other aspect to keep in mind is, okay what's the alternative to accumulating little bits at a time and building knowledge of the circuits underlying disease. You can do what people have been doing for thousands of years or you can search for new ways to treat the disease.

Margolin: Right.

Dr. Wurtz: I think the greater the understanding of the circuit and the system the better your ability to make hypotheses about what could be going wrong in humans and what you can do to fix it. It's really not a choice, it's just the way the world works.

Margolin: The world of the brain is a very complicated world.

Dr. Wurtz: I don't think anyone would dispute that. It's the most complicated device in our known universe.

Margolin: Let me divert just a moment to a couple of questions. You had contributed to the museum here some other items, a PDP-11 and a safety helmet. Can you tell us how those were used so we can get it on record here?

Dr. Wurtz: Sure. The safety helmet is trivial, it's to keep monkey saliva from splashing you in the eyes and face. That's for our protection, not for the monkeys.

As to the computer, it was from a series of computers used in the lab. The frustrations with Digibits balanced out my fear of shifting from science to programming, and we were able to buy a PDP12 computer in 1971 which was a combination of the LINC computer I mentioned earlier and an early PDP computer of Digital Equipment Corporation. Goldberg and I switched to the PDP 12 after finishing the superior colliculus work and the rest of the time, true to form, was spent programming the PDP12 rather than doing experiments before Goldberg returned to being a physician. The PDP11 was a much simpler computer and it was the successor to the PDP12 that was used throughout our labs and by almost everyone who had a computer at the NIH. The PDP11 transferred to the history museum was one from my labs. The story of lab computer evolution is a story all to itself; it has more steps as any of the experiments I have described.

Margolin: It was a basic computer that you used in many of your early studies?

Dr. Wurtz: It was the workhorse of the lab's experiments from the 1970s until the switch over to PCs beginning in the 1980s.

Margolin: Oh, okay. Let's go on a little bit. You were responsible in large part for the organization of a Laboratory of Sensorimotor Research.

Dr. Wurtz: Right, I was the founding chief.

Margolin: Can you tell us what that is and what that meant?

Dr. Wurtz: Sure. After it became clear in the early 70s that the monkey visual and oculomotor systems were good models for humans, the director of the National Eye Institute, Carl Kupfer, came to the conclusion that it would be useful for the Institute to have a laboratory that was devoted to studying the visual and the oculomotor system. This concentration would be closely coupled

with the neuro-ophthalmology group in the Institute headed by David Cogan. Up until that point I had been in Mental Health. After discussions with Dr Kupfer, I organized the Laboratory of Sensorimotor Research (LSR) with a group of scientists who would study the visual and oculomotor systems, primarily in the monkey, and also collaborate on clinical studies by neuro-ophthalmologists. I picked a three-word title for the LSR because I thought three word titles were remembered; I think I may have made up the single word, sensorimotor.

It was really the first lab devoted to studying the visual and oculomotor system in monkeys in the world. Most of the people were recruited mainly from other parts of the NIH because it was at a time when the NIH salaries were so low that the only ones you could recruit were those already on a government salary. But I think I managed to bring together an outstanding group of scientists: Bob Wurtz, Michael (Mickey) Goldberg, David Robinson Fred Miles, and Lance Optican. My philosophy of organization was borrowed from Steve Kuffer at Harvard; recruit the best scientists you can and then leave them alone. The lab became very well-known for the work of these people but more importantly, we attracted postdoctoral fellows who I think were the best and the brightest. They in turn formed their own labs that have also become prominent.

Margolin: You served as the head of the Sensorimotor Research Lab from '78 to 2002.

Dr. Wurtz: Yes, that's right, 10 years longer than I should have.

Margolin: It's a continuing and active form since then?

Dr. Wurtz: Yes. One of the scientists I recruited is now laboratory chief, Bruce Cumming, and all but two of the members have been replaced by a new generation. As part of the old generation I'm entitled to say that I think it's a better lab now than it's ever been. I think it's flourished. At the time of its formation there were doubts on the part of ophthalmologists that studying frontal cortex really is a part of ophthalmology. In the first 10 years of the lab that was a substantial problem, but I think once we established that we were actually learning a lot about the visual system and the oculomotor system, the complaint died away.

Margolin: It sounds like you were not only a basic scientist but a great educator of other researchers.

Dr. Wurtz: I think most of us didn't look on it as education. People came and we worked on experiments together but that's the only way to learn.

Margolin: The growth of knowledge, obviously, is education.

Dr. Wurtz: Yes, that's true. I think knowledge was our only product, but in producing it we also provided some outstanding scientists to neuroscience.

Margolin: In all of this, I'll say commotion between the various institutes and the various doctors and the clinic and the lab and so forth, what would you say about the overview as you've lived through it? At NIH what's gone on here, the benefits, the detractions of spending your lifetime in this organization.

Dr. Wurtz: There are huge advantages at the NIH. The biggest advantage at the NIH is your time is your own; minimum committees and assignments. A second advantage that I don't think is recognized frequently enough is that you can have laboratories like ours that have a group of people concentrating on one topic. At universities you have to have a distribution because they have to teach different areas. That concentration makes a huge difference because that's the way in which when I develop something new instantly the machine shop makes it for everyone in the lab. When someone else develops a new computer program it's on the computer, anyone can use it. And of course, you do not spend time writing grants that you do not get.

The other advantage is that I think the intramural program has the best method of funding in the world, namely we are judged primarily on what we have done. In contrast, the extramural program judges by what is promised for the future. In one case, it is the scientific results that are evaluated, in the other it is scientific promises that are being evaluated. Finally, I think the intramural program is much more flexible than the extramural program. My first doctoral fellow, Goldberg, laughed, and said, "Well, you would never have gotten your grant: you never had used monkeys, you had never trained monkeys, you had never recorded cells from monkeys and you didn't know much about the visual system." All absolutely true, but even with many failures along the way the work provided considerable progress. Study sections provide a conservative anchor that weighs down innovative proposals. We always tell post-doctoral fellows when they leave the LSR, not to propose something novel, propose something that is continuation of what you are doing. The worst advice you can ever give to a scientist, but to get a grant it's probably the best advice.

The intramural program's problem is that when you're in the lab it's fantastic. Don't ever walk out of the lab, however, because when you do the travel restrictions, ethical restrictions and ever growing bureaucracy. This is not all the NIH's doing, of course; the HHS plays a major role.

Margolin: You indicated to me before that going from goal to achievement is not a straight line, that there are a lot of ups and downs and a lot of crooked pathways, that's all possible at a place like NIH.

Dr. Wurtz: Yes. For example, in my 50 years here no one has ever suggested to me what research I should do, which permits long term planning. The reason a long term view is beneficial is that frequently the goal is quite distant, whether I know it or not. For example, I have already talked about the failure in my first monkey experiment to see neuronal correlates of visual stability. We returned to this question in earnest after about forty years when a post-doctoral fellow, Mark Sommer, expanded on our previous findings in the superior colliculus. These findings showed that the activity of some superior colliculus visual neurons were modified by rapid eye movements and that this modification could result from input from the eye movement related neurons in the deeper layers of the superior colliculus. What Marc found was a pathway going from these deeper superior colliculus neurons, not out to the muscles to drive the eyes, but up to the frontal cortex. This copy of what goes out to muscles is called a corollary discharge and had been seen primarily in lower animals but definitely not in monkeys in relation to rapid eye movements. Marc was able to show that the eye movement information sent to frontal cortex modified the response of the cortical neurons to visual stimuli. Marc had found the interaction of

visual and eye movement activity in one of the highest visual processing areas in the brain that I expected to find in the very lowest visual area, primary visual cortex over forty years earlier.

We've just recently been able to show that this corollary discharge reaching frontal cortex from the superior colliculus influences perception by indicating where the eye is directed, that is, where you're looking. Speaking of 'aha' moments, we had a monkey with a partially inactivated corollary discharge that is looking here right at the camera but when we ask him where he thinks he's looking (using a task I will not go into) he says it's over here. Knowing where the monkey thinks he is looking is the first step in solving the problem of visual stability. How this is organized to provide visual stability is another step but it's the critical first step and it came over forty years after the question was first asked. If you asked me about my goal in 1966 I would have described something close to the results of the experiment that I actually did in 2015. The NIH is tolerant of such deviations.

Margolin: That's a great example of what you've lived through and how you've reached it.

Dr. Wurtz: Also, it's an example of something else. That experiment took three and a half years. If I had been in the extramural program I think I would have lost at least one grant because I had nothing to show for it until after about four years. In humans you can tell them what to do but for the monkey you must reward it for solving the problem you want him to solve. It takes six to nine months to train the monkey to do the task we used, and then you've got to find this tiny area in the brain to inactivate, and then you've got to get the monkey to do the task and inactivate the brain at the same time. It takes time and patience.

Margolin: Switching gears, you told me that for the present and for the future, probably monkeys aren't going to be the main animal and that use of the mouse is expanding. Tell us a little bit about the mouse and the monkey.

Dr. Wurtz: A good biologist will always study a system that's most appropriate to the question he's asking. I think in many cases the monkey is the most appropriate animal model for humans, but the monkey work is very slow-going. There are experiments in monkeys that would take years but would take only months in a mouse. But the problem is, that comparing the mouse brain to a human brain requires a big jump across species whereas comparing a monkey brain to a human brain is comparing a primate to a primate. For brain systems that I study, comparing brains and behavior within primates is critical. Primates have a specialized retina; it has a high resolution fovea at the center of the retina and it has elaborate eye movement systems to move that fovea to objects of interest, that is to objects in the visual field that draw the primate's attention, be it a monkey or a human. A mouse simply does not have this visual and motor machinery. Not surprisingly, the anatomy of the monkey brain also has greater similarities to the human brain than does the mouse brain. The frontal cortex is greatly expanded in primates and the brain circuits connected to this and other regions of the cortex have similarities in monkey and humans but that is not the case in mouse and humans. So at the level of systems, the monkey is a much better match to humans than is the mouse in both the organization of behavior and the anatomy of the brain.

So my take on the issue is that the closer an experiment is centered on the behavior and the anatomical systems within the brain, the more important it is to use the animal model closest to humans, the monkey not the mouse. This becomes particularly important in relations to some human diseases that are beginning to be understood as disfunction of circuits within the brain: the closer the structure of the circuits in the animal model are to humans the better. But it might also be that for diseases that are specifically related to functions governed by the activity within the cell, the mouse is as good a model as the monkey, or an even better model in that the experiments can be performed more expeditiously. It might also be that the rodent brain is simpler and in some ways easier to understand so that the overall organization of a system is more easily seen in the mouse, but of course the overall organization may not be the same in humans and mice.. So in the end, it does come down to the biological rule: study the animal that is best for the problem. My conclusion is simply that for higher order behaviors, circuits are critical and the monkey and human have the closest structure and function.

Margolin: Another thing I'd like to talk about is you've been the awardee of many different awards and recognitions. I can't even begin to enumerate them, they're in your autobiography. Is there any one that you would like to speak about that you are particularly proud of?

Dr. Wurtz: This is a "which of your children are your favorites" question, I am grateful for each because they all recognize different achievements, but I can name a few. First, is election to the National Academy of Sciences, which was 25 years ago. Those who do the selection are themselves outstanding scientists who I have admired, and they do so largely on scientific grounds. When I see from the inside the complexity of the election process, I still feel lucky to be a member. Second, I am grateful for the Gruber prize and Dan David Prize because they are international prizes open to all scientists and so represent science throughout the world. Finally, I have to say that election to President of the Society for Neuroscience was very satisfying because I went to the first meeting of the Society where there were 500 people at the Shoreham Hotel in Washington D. C., I had watched it develop, and I then had the opportunity to contribute to that development.

Margolin: I think you reflected in your autobiography that the word 'neuroscience' wasn't in the vocabulary when you first started.

Dr. Wurtz: Oh, absolutely not. It's relatively recent. The society was named neuroscience but its common usage has been only in the last 10 years or so. Now if you say neuroscience on television I think most people know what it means and it's used more frequently just in the news. It's an immense change.

Margolin: It wasn't an organized body of knowledge at one time. You helped pull it together.

Dr. Wurtz: Maybe a little bit but there were the other thousands of contributors.

Margolin: Your humility comes through very clearly but obviously your contributions to this whole area were fantastic. You just told us a fabulous story of development and growth and recognition and accomplishment. I'm just sitting here just overwhelmed by your background. I certainly appreciate your giving all this. Do you have any final comments you'd like to make about this

whole experience and what you've done and what you still look forward to for the future of science?

Dr. Wurtz: That is a great question, but it requires prediction and as Niels Bohr sagely commented, prediction is very hard especially for the future. In considering any prediction here, it is essential to realize that neuroscience incorporates levels of organization in the brain extending from circuits in the brain that produce behavior down to molecular genetic mechanisms that govern cells and their development. If you ask someone at each level of this continuum, I suspect that you'll get a different answer to your question. Mine is at the systems and behavior level, and even here I do not try to predict the future; the best I can do is an extrapolation from what is happening now.

I think now, the exciting direction is the continuation of circuit identifications within the brain, those that underlie behavioral functions and the disorders that result from the failure of those functions. I think of these systems as connecting a series of neurons that can be represented by a wiring diagram, but that might not be the case. Behavior might instead be the result of populations of neurons organized in ways currently largely unknown. Or it might be a circuit organization at some levels (possibly earlier ones) and populations at higher orders. The contribution of circuits and populations may well be a central issue in future research – it is a major frontier. In addition, the tools to explore these systems questions are expanding, particularly with multichannel recording for recording from many neurons at the same time and optogenetic driven activation and inactivation to perturb the hypothesized circuits to see if behavior is altered.

Mr. Grasso: Will you continue to be doing work in this area now that you're emeritus, or are declaring Emeritus?

Dr. Wurtz: Yes, but what I'll do beyond this is mainly writing and organizing support for neuroscience.

Mr. Grasso: With all your complaints about your spelling and your handwriting, you're going to be a writer.

Dr. Wurtz: I type and I have spell check. I'm saved by technology.

Margolin: Good. If you are speaking with an investigator 20 years hence, is there something that you would like to explain? We're all looking forward with excitement about all the changes that are possible, and the things that are built on the foundations that exist at the moment. What words would you have for an investigator down the road?

Dr. Wurtz: I would say that in systems neuroscience, I think we will see an understanding at least in outline of some of the major circuits or population mechanisms in the brain underlying behavior that are identified by the use of the emerging new tools including multichannel recording and optogenetic based perturbation. For sure I envy anyone starting to work in the next 20 years given the new tools and continuing challenges.

Margolin: Good. Thank you.

Speaker 3: Any more questions?

Margolin: No, I think that you've hit everything.

Speaker 3: Thanks, Bob. Thank you so much.

Margolin: Okay.

End of Transcript