

Rowland

We're visiting today with Dr. Joseph Gibbs. Dr. Gibbs and I are old friends, but I'd like to start at the beginning. Joe, could you tell me about your background and how you got to NINDS in the first place?

Gibbs

My background in science, in research, began in 1951 at the Walter Reed Army Institute of Research in Clinical Pathology. Where I worked on the development of a complement fixation test for leptospirosis and then I did some other work on Eastern Equine Encephalitis, Venezuelan, a number of the arboviruses-developing vaccines in the old Veterinary Division. I stayed there for three years, and then I was asked by Dr. Joe Smadel if I would take a position in the Department of Hazardous Operations, to develop a vaccine against Rift Valley Fever, which I did do and it turned out to be a very effective vaccine. I left Walter Reed in 1959 and came here to the NIH to work in the National Institute of Allergy and Infectious diseases, in the arthropod-borne virus section of the Laboratory of Tropical Virology. The thought was that we would come here, work here on campus for a year and then go down to Panama where we had a laboratory.

Rowland

In the Institute of Allergy and Infectious diseases? You had just done something for Rift Valley?

Gibbs

The intent of the laboratory I was in was that you would come here, work for a year, and then go to Panama and work for 2 years and then come back here. That system never worked out. We had some problems in the laboratory in the arthropod borne virus section and I wound up being the Acting Chief of that section in very short order. I enjoyed doing work in arthropod-borne viruses;

they are exciting things to work on. Things had gotten so bad administratively that I decided I would leave. I was offered a fellowship in Balang, Brazil with the Rockefeller crowd.

I went over to see Smadel (Joseph). He was still on campus here, and he just looked at me when I walked in the door and he said, "You're not going to Brazil!". I said, "If I don't go to Brazil, where will I go"? He said, "You're going to go with Carleton, and you're going to provide some stability to an otherwise, unstable place". I said, "What does that mean"? And he said, "You're going to go there and you're going to open a laboratory and the basic issue in the laboratory is to find out whether or not you can transmit Kuru. Is it an infectious disease or not"?

I thought it over, and sure hated to give up arthropod-borne viruses. I met Carleton again. I had known him at Walter Reed and we had met on a number of occasions. I talked to Carleton about it and I said, "Look, if I come with you, can I work on arthropod borne viruses as well"? "Oh, yeah, sure"! You know Carleton. He lets you work on anything. I decided this is what I would do, what Smadel told me: "Neither you nor me nor anybody else knows anything about what causes Kuru. But, my gut reaction is that you will have either golden positive or golden negative results in five years. That's not too long to put in your career". So, I took the job and I had to start from scratch. They had nothing in the way of facilities to work in. I was given a cinder block building out at the Patuxent Wildlife Research Center in Laurel, Maryland. I was told what we had to do was to inoculate chimpanzees, small non-human primates, and mice, all kind of animals. I arranged to get some chimpanzees; at that time they were costing \$150 or \$200 for a chimpanzee.

Rowland

Compared to what now?

Gibbs

Compared to about \$25,000 for one now. We started under very primitive conditions. The laboratory out at the Patuxent Wildlife Research Center, where I worked, had no bio-safety controls in it what so ever. For the mice that were inoculated, I had to arrange to remodel, in a very primitive fashion, the basement of a barn where they had milk cattle in that barn. The building for the primates was a cinder block building with an asphalt roof on it. It was not air-conditioned and it had a huge monster of a furnace that you couldn't rely on. Nevertheless, we went to work. I and two technicians; two very basic technicians. And they would come to me asking, 'Please, let's get this or get that'. I said, "Look, let's get some results first. If we get results first, then we don't have to ask for anything, they'll come to us and ask us to take this". That was the philosophy I worked under. I enjoyed the work very much. I did my arthropod borne virus work and one of the faculty of Johns Hopkins, Keerti Shah, who's still on the faculty at the School of Public Health, was using the space out in Patuxent lab too. Together we isolated for the first time a virus in India that caused a major outbreak of human disease called Chickungunya. These arthropod borne viruses have very famous names. It was a great life.

Then it was decided (Bob Marston was the Director of NIH at the time) by the political powers that we've got to get something up at Fort Detrick in Frederick, Maryland that's got positive findings. Here we're spending all this money on cancer and we have all these facilities, but we don't have any positive findings yet. The first thing they did was to pick on me, and say you're moving to Frederick, Maryland. I had redesigned one of the buildings up at Frederick, and I was not told as to how much I could spend, but I did a job. I designed the whole remodeling of the building to handle infectious diseases. Then I took off to go to New Guinea.

Rowland

Where was Carleton when you were out there?

Gibbs

When I was out at Patuxent? Most of the time he was out of the country. One time he was out for one full year.

Rowland

But you didn't have a lab on this campus.

Gibbs:

He had a lab, but not one that you could... It was in a small space, very small space. Then he moved into this building, upstairs on the fifth floor, things sort of mushroomed. Most of the time Carleton was circulating around the world. In fact, in one of the years, he just spent the entire year over in New Guinea, while I was out at Patuxent. Much of what was done; I was the one that originated the experiments to develop the data that we needed. Then Marston moved my lab up to Fort Detrick, but I refused to go up there, it was just too far for me to travel daily. And I was not about to move up there. So, I got space here. Don Tower gave me space here that Jake Brody used to be in. I, and my few technicians occupied this space, while Carleton had moved upstairs, and he had a much larger group of people. Subsequently, he moved up to Frederick, Maryland where he lived, and he would go into the research building up at Fort Detrick, in Frederick on a daily basis, when he was in the country. He seldom came down here while he was living up there. The excitement, for me, that made this program more interesting was that within two years of inoculation of Kuru into chimpanzees, we had a positive reaction in the chimpanzees. We actually flew Dr. Elizabeth Beck over from England as our neuropathology consultant. She was present when we sacrificed the first chimpanzee. And she took the brain back to England with her. When

she left she looked at me and she says, “Here is a Nobel Prize”. And I said, “Oh, yes, I’m sure of that”!

Rowland

Let me interrupt you for a second. You said a while ago that there was no specific test, so can I ask you about the 14-3-3 test?

Gibbs

Oh sure, sure. Several years ago in trying to develop diagnostic test, we picked up on some work done by Gajdusek, Asher and Harrington. They used 2D gel electrophoresis to examine spinal fluid in neurological diseases. In the spinal fluid of Creutzfeldt-Jakob disease patients, they recognized two protein spots on the gel, Spot 130/132, I don’t know really what the definition of 130/132 is. They published that and that was the end of the story.

Then I had a young boy from Johns Hopkins come to me, a Howard Hughes fellow for a year, and I asked him what he would like to work on. He said right off the bat he said he would like to know just what the protein 130/132 is. We started all over again working on the spinal fluid of both human patients and chimpanzees. We did identify the 130/132 proteins and then we were able to isolate those proteins from the gel and sequence them and found that they belonged to a family of proteins known as the 14-3-3 protein, which amongst other places was a protein that’s in the membranes of neurons. We proceeded than to develop a simplistic diagnostic test. We developed a one dimensional gel electrophoresis, and we began than to test hundreds of spinal fluids. Not only Creutzfeldt, but of kuru and other neurological diseases. In our hands, this simplified test gave us about a 96% sensitivity and specificity. If we detected this marker protein in spinal fluid, it would support a clinical diagnosis of Creutzfeldt-Jakob disease. It would not diagnose the disease,

but it would support the clinical diagnosis. We tested just a few of the new variant Creutzfeldt-Jakob cases from England and only one or two of those cases had detectable 14-3-3 protein.

Then again, we didn't get many of them. It has been a problem of getting material from our British colleagues to work on. Stan Prusiner had that problem, and we've had that problem from the very beginning. I was very disappointed when I went to the Central Veterinary Laboratory in Weybridge, England, and asked for brain tissue on the cattle; and they had not yet developed a brain bank for these cattle brains. That astounded me. Dr. Leona Bollis from Italy set up 6 different workshops on bovine spongiform encephalopathy. We invited the British; we invited people from all over the world to participate in these meetings. Five of the meetings were held in the United States, one was held in England. Still, we didn't get any kind of cooperation out of these people. By the time we did get some cooperation out of them, then the English had influenced our Department of Agriculture to require that you can't work on these agents without a bio-safety level 3 containment. It surprises me that we don't have a bio-safety level 3 containment on the NIH campus, except in the new facility that is dedicated to studying tuberculosis. To me, that is absolutely unimaginable.

Now, meanwhile, I'm presenting something to you, a little bit out of context here, because all this while we've had this building up at Fort Detrick, and we housed our chimpanzees and our monkeys and we did all of our experiments. Had all the mouse room, hamster room, rabbit room, all kind of stuff that what we wanted. It was just inconvenient, but we had people stationed up at the building at Fort Detrick. We were then ordered to get the chimpanzees out of there, so we had to take the chimpanzees down to Louisiana. And that's an interesting situation too. When we left

Patuxent Wildlife Research Center to come up to Frederick, Maryland, we had all these chimpanzees, a hundred and something. We took a part of those down to Louisiana right away. To do that, I couldn't get any help from the NIH to get me transportation for the chimpanzees. I went to the Department of Defense and asked them for help because this had been declared a national interest program. They made a military aircraft available to me. One of these was a C-57, the big cargo planes. We brought the chimpanzees in their cages from the Patuxent Wildlife Research Center to Andrews Airforce Base; where they sat out in the sun at the Presidential Ramp until the aircraft came from New Jersey down to pick them up. We loaded those chimps on the aircraft and took them down to Louisiana where I had a contract.

Now the interesting thing about all of this, outside of the fact that we accomplished something with the help from the military, was that shortly after we got those chimps down to Louisiana, a number of those chimps started showing clinical signs. They had been perfectly fine before they left Patuxent. I suspected that it was the stress of the transportation that induced the onset of clinical signs. That's stuck with me even more so now, when we inoculated recently 6 chimpanzees with Creutzfeldt-Jakob disease. Three different cases of Creutzfeldt-Jakob disease; two for each of the three cases. For the purpose of doing leucopheresis on those animals to look for infectivity in blood. They went through the leucopheresis procedure under anesthesia, of course. Shortly after undergoing leucopheresis, all six developed clinical signs of disease. As though this was stress induced. Then I looked at my records and saw that this fellow drove his car, had an automobile accident, suffered a head injury, was taken into the hospital and proceeded to go downhill and died; and he had a living will not to do anything for him, but he also had a donor's card in his pocket. And they were ready to take that donor tissue and the pathologist looked and said, "Hey,

this guy's got Creutzfeldt-Jakob disease"! Now, whether he had the automobile accident because of the symptoms developing or not, we'll never know.

But then there was the lady who stepped on the rake. And the rake handle came up and hit her violently in the head. Within a month she was showing signs of Creutzfeldt-Jakob disease and died with the disease. The questioning that came up in my mind, and I don't know how to resolve it yet: Is there a latent Creutzfeldt-Jakob disease? There must certainly be. Can it be precipitated by some kind of a severe stress? I think that's an interesting question and obviously the people that developed Creutzfeldt-Jakob disease, at least the sporadic Creutzfeldt-Jakob disease could have the makings of that disease for 35 years or so. But, what triggers them to show clinical signs?

I don't know how we're ever going to do that because one of the things that happened, now this gets into the more recent times of NIH; when Murray Goldstein retired from the NIH as Director of NINDS, that was the last time we had a, in my opinion, a proponent for this program. We had undergone a bad Board of Scientific Counselors review, when Zach Hall came here. It was told to me a number of times that Zach's job here was to do away with the intramural research, not just this laboratory, but NINDS. There was no question that Zach was going to be quite different from Murray Goldstein. At his first meeting with the Laboratory and Branch Chiefs, he summarily dismissed 13 people who had been recommended for tenure, and said, "No".

Then the next thing that happened was that we had Story Landis as the Scientific Director. She decided that it was just too much to keep that building up at Fort Detrick. It was costing the institute too much money. She turned the building over to NCI, and in a sense, that stopped us

from doing any more animal work, except down in Louisiana. Then she didn't want us to do it down in Louisiana either because she felt that we should get rid of all the monkeys. We got rid of a good number of monkeys but, you can't get rid of chimpanzees, they're endowed for life. The work has become extremely difficult. We've tried to do some mouse work here on campus. We cannot do any work with the new variant Creutzfeldt-Jakob disease because we don't have biosafety level 3 facilities. We cannot do anymore work with the spongiform encephalopathy because we don't have biosafety level 3 facilities. You can still work with scrapie, but then that group has gotten so difficult. If an animal looks a little dehydrated, they report it and it has to be killed. If an animal is showing, what they call ataxia, "Oh , that's scrapie." Well, they don't know scrapie in small rodents. They don't know Creutzfeldt-Jakob disease in small rodents, and yet it's the Veterinary Division that has the ear of the scientific director, and it's practically impossible for us do to any animal work. We tried to make up for this in the fact that I have in the freezers a lot of infected animal tissues that I can work on. We certainly are still capable of working on new cases of Creutzfeldt that come in. Without doing transmission studies we can do the prion protein extraction. We can look at the glycosylation of protein and we can do the 14-3-3 test. Which, if I am not careful, they will stop me from doing that because that is not a research project, it's a service. And yet it's a needed service, to be perfectly frank with you. We keep pushing. Paul Brown has been pushing more on inactivation of scrapie by heat. I'm not quite sure I agree with Paul. He does some risky work. I mean he draws some risky conclusions.

Rowland

Let me go back to moving the animals from Frederick to Louisiana. Was that an issue of closing down an expensive facility? An animal rights issue? Or what was the motive?

Gibbs

The motive, first of all, for closing down Patuxent (It was the Patuxent Wildlife Research Center, which is a part of the Department of Interior). The people in the Department of Interior really didn't want us out there at their facility. That was one situation. Then the other situation is that Nixon declared Fort Detrick, in Frederick, Maryland, to be the nation's research center on cancer. He was going to conquer cancer in 5 years. Bob Marston, was the Director of NIH.

Rowland

NIH or NINDS?

Gibbs

No, NIH, Bob Marston was NIH. He directed that we pull out of Patuxent and go up to Frederick, because we had positive findings in our program; and that the Congress would like to see this. That's what got us up to Frederick, but at the same time, we could not take all of the chimpanzees that we had on hand, and we'd have to split them up and send some down to Louisiana, and ultimately we sent all the chimps down to Louisiana. That was nothing to do with any of these animal rights people.

One evening at a cocktail party associated with an international meeting on AIDS, someone said, "You see that man over there, he's Chairman of your Board of Scientific Counselors, and he's going to cut Gajdusek down below the knees. This guy's telling me this, you know? There are a lot of people who did not like Carleton Gajdusek, one thought he had for too many years, too much money, too much freedom, too much everything else. Even within the scientific community, forget anything else about the law, this was just within the scientific community. So, when we did have that bad session with the Board of Scientific Counselors, a lot of it was because of the

publicity Gajdusek had had about the wealth of his program, I'm convinced of that. He knew that they were going to cut him down and that's why he said, "Okay, I'm going to close this laboratory rather than have somebody else close it on me". That's my supposition, but I think it's a pretty true one, and a pretty sharp one.

Rowland

If you look at the positive side, in a sense, don't you think it's true that this program could not have developed in a private university? Maybe in the Rockefeller or ...

Gibbs

Absolutely. No, I don't even think Rockefeller would have done this. No, it had to be the federal government. The sheer impact of all the primates, the monkeys, the chimpanzees, the cost of travelling all over the world in support of this program, it's no question it was an expensive program.

Rowland

You were also involved in Guam, not yourself, so much, but the lab was.

Gibbs

Yes, we took over the Guam situation. First, Jake Brody, when he left here, then the Guam situation came to us and to Tom Chase, from a clinical point of view. We had already included ALS as a subject of research transmission to some form or another species of animal, trying to find out its etiology from the very beginning of this program. We had arrangements for collecting all the brains of people who died of ALS – PD - dementia on Guam. We supported the laboratory down there. Then that expanded from Guam to West New Guinea, where Carleton went into West New Guinea and found a high incidence of ALS in the natives in West New Guinea. We got

mileage out of studying ALS, but not the kind of a mileage that I would like to have seen. I would like to have seen a fuller explanation of the disease.

Rowland

Do you think it's strange that so many smart people worked so hard, spent so much money, and we're still don't understand what's happening?

Gibbs

Yes, I think it's very strange, very frankly. You sometimes wonder about the total commitment that everybody's been in this field, what percentage of those in the field committed themselves totally to the disease. I think a high percentage of them do, and some very bright people. It's just the disease that doesn't lend itself to an immediate understanding. You should know that better than most of us.

Rowland

Now, I want to ask you some personal questions. Not just your person, but personal, I want to preface my questions with saying, I'm not interested in blowing up battles and so on, but there have been some things around you. Just personal about you, what I've always wondered how you reacted to the fact that you were such an integral part of everything that Carleton achieved, and yet **he** got the Nobel Prize. I don't even know if you went to the ceremony.

Gibbs

I went to the ceremonies, because I knew if I didn't go I'd be severely criticized. I felt it for a while, but I felt equally as bad for Bill Hadlow. Had it not been for Bill pointing out the similarities between scrapie and kuru, we might have been years away from opening up a new field. I felt it, but then I have a funny attitude toward life, you know, so you get the Nobel Prize, okay, so what are you going to do with it when you die, huh? That tends to take away some of the

sting. I got a lot of nice letters from people expressing their thoughts in the matter when this all took place. I actually said, and I didn't mean this meanly in any sense of the word, but I felt that Carleton getting the Nobel Prize for this field was a bit early in the field. Yes, he recognized the importance of kuru, and it certainly turned out to be just that, when you think of what has evolved from these studies. But, it seems to me that he, we, all should have gone a little bit further before a prize was given in this field.

I was totally shocked when Stan got a prize, so you called it a prion, so what! In fact, I had a lady here working with me from Spain, we were looking for the nucleic acid in scrapie, and we wrote a paper, basically just described what we did and said we didn't find any nucleic acid. We did make a statement in the title of it and we did in the paper that scrapie for infectivity needed a protein. We knew that, and that's what we were pointing out. Carleton scratched that out completely. He didn't see it, and that's the same damn protein that proved to be the prion protein. There's been a lot of robbery in this field, but I've never made myself part of it. I think Stan is a very close friend of mine and while I didn't agree with the way he did certain things, I'm going to keep him as a friend. Paul and Carleton, not. I don't know what it is. There's a bad feeling between Carleton, Paul and Stan Prusiner.

Rowland

That came out in that book by Richard Rhodes.

Gibbs

Even Richard Rhodes, I think he exaggerated some stuff, but that's because he was a devotee of Carleton. I looked at it sort of philosophically and say well, it didn't, therefore why.

Rowland

How about one simple thing. I was impressed by the fact that you used the word prion disease as opposed to spongiform encephalopathy which is a lot harder to say.

Gibbs

We've gone through this whole rigmarole of what to call it. First of all, when Carleton insisted that it be called "cerebral amyloidosis" even before we called it "subacute spongiform encephalopathy", earlier than we called it "transmissible spongiform encephalopathy". Then Stan came along, with his prion protein. We all laughed because prion is the name of in the literature for a bird in the south arctic, you know. We thought this is kind of funny. I would not have chosen the word "prion", but that's all right too. And I have no objection to using the word prion, although I remember we went through the trouble of drawing up a table to Carleton. We say this, he says that, we say this, this is what it's called. It's one of those funny things. The relationship between Carleton and Stan Prusiner as to what this lab called it. I don't ever want to hear the word "prion" in this laboratory.

Rowland

I want to ask you something personal about me, but I think you haven't seen it yet. We just wrote a paper about amyotrophy and prion diseases.

Gibbs

Yes, I did see it, but I haven't studied it.

Rowland

Someday, you'll tell me about what you think about it.

Gibbs

Remember Andy Salazar wrote a paper

Rowland

Yes, but we thought that paper killed any concepts of a relationship between ALS and prions.

Gibbs

You know what I don't understand about this laboratory, because I get in the background because I'm not an MD. Carleton was very emphatic that there is a big difference between being an MD and being a Ph.D.

Rowland

Is that right?

Gibbs

Oh, yeah. The first 11 cases of Creutzfeldt-Jakob disease, in chimpanzees, everyone of those animals developed fasciculation.

Rowland

Is that right?

Gibbs

Uh-huh. Only it never came out in the paper. They even developed some evidence of liver malfunctioning, but it never came out in the paper. I wouldn't be at all surprised if you looked at some of these chimps long enough and hard enough, even clinically, you might see some amyotrophy in these animals. Fortunately, in a good number of cases we did record all of this on film.

Rowland

Part of the problem was that that paper had such a tremendous negative impact, and then other things happened. Everybody got interested in the relationship to dementia. That's all that people

are interested in now. Then the pathologists got nervous about hacking up spinal columns to, so they stopped taking out spinal cords.

Gibbs

Yeah, but a lot of these pathologists and neurosurgeons are scared to death and I think it is immorally and unethical.

Rowland

Yes, well that's because nothing so bad has really happened. I want to ask you another question, about the current status of NINDS and the intramural program. You said that somebody was trying to kill the intramural program. Do you think the intramural program now is valuable? Forget your own laboratory; do you think there should be an intramural program?

Gibbs

I think there should be an intramural program because I think that certain studies can only be done by the government.

Rowland

Okay, what now, besides yours, what would you say now.

Gibbs

I would say a lot of stuff on the MRIs, super-duper MRIs. Yes, you could do this outside and it is being done; supported by NINDS right across the street at Suburban Hospital. But there are other areas of neuroendocrinology and neuroimmunology that can be done on the outside, but can it be done with the same freedom and with the resources that are available on the inside? I think there's great need for both intramural and extramural support, and I've never objected to the extramural getting the lion's share of support.

I don't know why, but I think, first of all I know this, Varmus had no love for Carleton Gajdusek. He expressed outwardly in a meeting his distaste for Carleton. Varmus brought Zach Hall here. Zach was a nice guy. He and I had a nice relationship. He actually wrote me a note before he left and all that sort of thing. I had heard from people that went up to Woods Hole for the summer and stuff like that and have these cocktail parties. Zach very clearly stated that the intramural program at NINDS did not deserve support. She's made so many changes, Story Landis. They don't look at NINDS as we looked at it. They look at it as you don't have laboratory and branch chiefs' meetings anymore. You have faculty meetings. They're trying to change this intramural program into a university. The biggest difference is when I came here and when I was working under Murray and Don and other NINDS Directors, there was an excitement in the air. There was a feeling of accomplishment taking place. I don't get that same feeling anymore.

Rowland

Do you think it's harder to recruit good young people?

Gibbs

It may very well be. You get Carleton going around telling people, "If I were a young person, I would never come to the NIH". I don't know what effect that has on people that hear it. I don't know, I'm not so sure I know what the overall plan is for intramural research. I know what Gerry's doing for extramural. I know how disease-orientated he is. I think it's exciting to talk about Parkinson's disease and see where we're going to go with it. I think that there are a number of exciting areas and I think those kind of things deserve to be done on a combined intramural/extramural collaborative program type of thing. Whether you can ever bring in again the bright people into NIH and steal them away from academia, that's another question. Academia is getting so much support right now, and they have all the opportunities in the world. You can't

express. Some of these people come in and get under the rubric of salary, of what the Government offers; when people have kids who have to go to college and things of this sort.

Rowland

There was a time when NIH salaries were higher than university salaries.

Gibbs

That's right, but no more. The other thing is that I think a lot of the talent is in academic medicine right now. Guys and girls that are on the faculty at a university, and have a deep interest in research, that have a lot of smarts to do research. I see more and more collaboration between intramural people and extramural people. Which I think is a great way to go. I was always very happy to be involved because at Laurel, Patuxent Wildlife Research Center is half way between here and Baltimore. When Dick Johnson and Guy McKhann and that crowd were in charge at Hopkins, that's when I started in Hopkins, and I've been on that damn faculty from the time they showed up at Hopkins. That was a great feeling, to be involved over there. But, clinically and with the medical school and giving lectures and so forth. We did a lot of research work together; and I still look forward to doing that kind of stuff with them. Certain things we can do that they can't do. So, yes, I think there should be an intramural program, yes, I think that it should be tied tightly into academia outside of NIH. I don't think NIH should develop into a degree-giving facility like has been talked about. I think greater need needs to be recognized on a part ... I don't know what Mark Hallett is doing, I don't know what he's going to do, but it seems to me I don't hear much about the clinical side of neurology.

Rowland

He's stepping down. They're looking for a new Clinical Director. Listen, I've beaten on you for a long time.

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Dr. Joseph Gibbs

Gibbs

That's all right, I don't mind.

Rowland

I have to come back sometime and you tell me whether we're wild about amyotrophy in spongiform prion disease. How does that sound for a compromise? Thanks a lot.