

Interview with Doctor Stanley B. Prusiner

Interviewed by Doctor Douglas J. Lanska and Lauren E. Klaffke

for the American Academy of Neurology Oral History Project

**at the Boston Convention & Exhibition Center
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**Footnotes and Commentary by Douglas Lanska
Transcription editing by Douglas Lanska and Lauren Klaffke**

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| Stanley B. Prusiner, MD, FAAN | - SP |
| Douglas J. Lanska, MD, MS, MSPH, FAAN | - DL |
| Lauren E. Klaffke | - LK |

[Note: At DL's invitation, SP agreed to a private and public interview at the annual meeting of the American Academy of Neurology, which was held in Boston in 2017. As DL arranged before the interview, the initial portion of the private interview was led by LK, with the final portion led by DL. The later public interview the same day was conducted by DL.]

LK: This is Lauren Klaffke. It's April 27, 2017. I'm here today with Dr. Doug Lanska to interview Dr. Stanley Prusiner in Boston at the annual meeting for the American Academy of Neurology.

So, to get started, I wonder if you could tell me a little bit about your early life and education, growing up in Iowa and Ohio.

SP: There's not much to tell. It was a very uneventful time, at least from my point of view. I probably lived like most middle class people in a reasonable house. I had two wonderful parents.¹ My brother² and I recently reflected on our parents and what they gave us and did for us. That was a fantastic childhood when I look back on it. It was a childhood in which I didn't really get pushed. I wasn't being pushed by my parents so I

¹ Laurence and Miriam Prusiner

² Paul Prusiner

could get into Harvard or Yale. I did what I wanted to do. I had time to grow up. I had time to think. I had time to imagine. I didn't have my iPhone.

LK: Yes. [chuckles]

SP: I didn't have my iPad, and I didn't have my Mac. My world was what I imagined. That was great. It was good.

The only thing that was negative was when I was about six years old, my mother became quite ill. It turned out in the end that she had hyperlipoproteinemia and hypercholesterolemia. So she was chronically ill from this. These were the days before statins. Only when statins came along in the middle 1970s did she see real improvement in her life. She lived to be seventy-four after a heart attack at thirty-four.

LK: That's incredible.

SP: Yes.

LK: Especially at that time period.

SP: Right. Exactly. That colored my life, but there was nothing I could do about it.

LK: Was she on bed rest for that long period of time?

SP: The first heart attack she had—people called it pericarditis—she was in bed for, I don't know, three months or something like that. They had *no* understanding what was going on.

LK: In terms of your education, you were commenting that your parents didn't push you. I know you've talked a bit in the past about the fact that even if they didn't push you, they instilled within you a sense of confidence and support and that really helped you along in pushing forward with your career. I didn't know if you have any further comments on that.

SP: Well, I think there was a healthy mix of confidence and non-confidence. If you're too confident and you're too cocky, you don't really do anything. I found that, as I grew up, my self-esteem increased with success, but these were successes that I created. These weren't inherited successes. These weren't given to me. There wasn't anything for me to acquire from them, except a wonderful background and loving environment. That was all that I really should have had. A lot of inherited wealth, I think, becomes a drag on a lot of people. They don't understand how hard it is to achieve success in life, which is created by them and not by the external world. It's within them. To have that kind of opportunity, it's partly my parents and it's this incredible country we live in. I sound like [President Donald] Trump; I'm not trying to be Trump.

LK: [laughter]

SP: But it is an amazing country that we live in. We have these opportunities all the time. They're there. Young people are constantly availed of these opportunities.

LK: In terms of school, I know that you said that you weren't very interested in school in elementary, middle, high school years. I wondered, were particular subjects of interest to you or did you have hobbies that were more interesting to you? How did you like to spend your time?

SP: I don't really know how I spent my time.

LK: [chuckles]

SP: But it wasn't with marijuana.

LK: Okay. [laughter] For the record.

SP: Yes. Well, that's true.

I was a Boy Scout. I became an Eagle Scout. I became whatever they used to call it...this Explorer group after becoming a Boy Scout, later when you were older, whatever the highest rank was of that. I can't even remember. That was an area that I spent a lot of time in, because I enjoyed that.

I was on the swimming team for a while, but it became so incredibly boring, one lap after another, and I eventually found it uninteresting. I tried to play football, but I wasn't really big enough to play football, and I really didn't love being nasty to the guy on the other side of the line. I played center, and I quit that. I could see that my temperament was *not* that of wanting to kill the guy on the other side, and that's what you needed to be good. So that ended.

I don't really know what I did. I found chemistry interesting. I liked chemistry.

LK: Did you take that in high school?

SP: Yes.

There's actually a good story. The homeroom teacher taught advanced chemistry and he wouldn't let me take the advanced chemistry course. He said that I wasn't equipped to be able to do this. My parents went and lobbied him, and they got nowhere with him. So I ended up taking the regular chemistry course. Then, I ended tutoring all these kids, because none of them had a clue about what this all meant. They just couldn't do it. So I spent a lot of time tutoring half the class. In the end, it didn't matter. But I was pretty annoyed with this guy.

When I won the Nobel Prize [in Physiology and Medicine]—this was 1997—there wasn't really much in the way of easy access to the Internet, so I got all of these handwritten notes. I never did anything with them, because it just was impossible to do that. I remember the day it happened. I ended up with probably about a thousand phone calls. I said, "Okay, there's only one thing I can do with this and that's erase them."

LK: [laughter]

SP: What am I going to do with a thousand phone calls? I can't capture them—I guess I could have captured them, but I wasn't smart enough to do that.

One person—I think it was a woman—writes me and she says—Jake Skilkin, he was the Advanced Chemistry teacher— "I know Jake Skilkin is in heaven, and he's applauding you and he's really excited about you." I said [sic, wrote], "I've rarely written a note back to anybody. I've thought about this more than once, and I just want to make sure that you understand that *nobody* could have been *less* supportive of what I've done than Jake Skilkin. Jake Skilkin, wherever he is, cannot take any credit for *anything* I did."

LK: [laughter]

SP: And I was laughing, of course. I thought it was really fun. That's good for the oral history. I think it's in there.³

DL: This is the kind of stuff I'm talking about.

LK: In terms of chemistry, I know you commented that you liked to balance the equations.

SP: Yes.

LK: I was interested in...were you were drawn to math, as well, or was this really just chemistry focused?

SP: No, no. I like the math. I like quantitative everything. I like to think in numbers. I want numbers. I don't want vague concepts. I'm not a literary person. That's what literary people do. Some of them are absolutely incredible.

I was listening to this audiobook on Truman⁴ by David McCullough,⁵ who's really an extraordinary historian and writer. I don't understand how anybody can put together that

³ SB was referencing his memoir, *Madness and Memory* (2014), but that anecdote was not included.

See: Prusiner SB. *Madness and Memory: The Discovery of Prions—A New Biological Principle of Disease*. Yale University Press, 2014.

much information, where they can find it, where they can read it, how they can incorporate it. Then, they put it out for the public, and it's just fantastic. This book makes Truman come alive. The reader, the narrator, is really quite good. He's phenomenal.

LK: Yes, having that writing style that appeals to the public is a great skill.

SP: That's not me.

LK: [chuckles]

How did you come to apply to and go to the University of Pennsylvania? What drew you to that university?

SP: Ah, well, my mother was pushing for Washington and Lee [University]. She thought that was a good school. I applied there. Then, my aunt in Philadelphia wrote me a note, and she said, "You should come to Philadelphia and you should live with us," meaning her three sons. All of a sudden, that was a problem that got solved, because my parents didn't have any money, and there I was with room and board. That was terrific.

LK: Yes.

SP: So, then, I applied. I don't know how the hell I got in, but it was a lot easier then than it is now. So I got in. My father's cousin had sent me a note a few weeks earlier saying that he wanted to pay all of the tuition.

LK: Wow!

SP: So that was everything, then. It was a nice package. Only one thing wrong was that I just couldn't live with my aunt. I couldn't live with my aunt. I was there for two weeks, and I called up my parents, and I said, "I'm going to fail out of this place. It's not possible for me to go there like high school."

But the ride was extended. I had this old Buick that I had bought from a friend of my parents and it was really a lemon. It broke down on the Schuylkill Expressway.

LK: Oh, no.

⁴ American statesman Harry S. Truman (1884-1972), who became the 33rd President of the United States (1945-1953) upon the death of then-President Franklin Delano Roosevelt (1882-1945).

⁵ McCullough D. *Truman*. New York: Simon & Schuster, 1992.

SP: All of these cars are going by seventy miles an hour and this car breaks down after one week. I said, "This is not okay. I can't make it." They understood. They said, "Just do what you have to do."

So I then went and applied and got into the dormitory. I sold the car, and then I got a job.

LK: What were you doing?

SP: I joined this fraternity. I was running the kitchen for the fraternity. I knew how to do all this from the Boy Scout camp.

LK: Oh, oh, yes.

SP: This was a kitchen for 300 people. So this was trivial.

That was the beginning of all of this.

I stayed very friendly with my aunt, but this was a complicated woman. When she was nineteen, she developed polio. She only walked with these massive braces that she could swing her hips. She lived to be eighty. This was at nineteen that she developed polio. She was a lawyer and went to work every day on the train, on this commuter train. She, somehow, got up these god-awful stairs. She'd walk with her arms.

LK: Yes, yes.

SP: She was amazing.

LK: In terms of going to the University of Pennsylvania, was there much of a culture shock between going from growing up in Sioux City...?

SP: No, Des Moines. I would never have lived in Sioux City.

LK: Okay. Growing up in Des Moines and living in Philadelphia?

SP: Well, Des Moines was not my world. I left Des Moines when I was ten. For eight years, I'd been in Cincinnati. So Cincinnati was more like Philadelphia than Des Moines. So there was a transition that wasn't very hard. I never liked any kind of school. There wasn't any love of going to classes, but I didn't have anything else to do. I needed something to do. I really didn't want to be a grease monkey in a gasoline station. I didn't see anything that appealed to me out there. There wasn't some calling.

What you should know is that when I was in high school, I tried to delay going to college. I applied to the Boy Scouts. There was one position for one Boy Scout and that Boy Scout was going to be an aide to somebody. I don't know who it was. It was a military officer in Thule, Greenland. This is the end of the world. This is sort of this love of the Polar Regions; it hasn't disappeared. But I didn't get that [position]. I got rejected.

So I went to the University of Pennsylvania instead.

LK: [chuckles] What a different path....

SP: About seven years ago, I went to the Antarctica. This was part of a blue-ribbon committee of polar scientists and me—because I'm not a polar scientist. This committee was run by the National Research Council for the White House.⁶ What to do with all this money? I was the only non-polar scientist. We'd have these big meetings afterwards, and then all these polar scientists would come up to me and would say, "You know Stan, we're really happy you're here, because you're the only one who's not afraid to ask questions about things that we don't know anything about, but we're supposed to know everything about them."

SP and LK: [laughter]

SP: I've told this story a few times, because there I was standing at the South Pole saying, "My god, this is the most godforsaken place on the earth." And I wanted to be in Greenland for an entire winter? This would've destroyed my life *completely*. I was so lucky not to go to this place. So then, I just got done... I've just been back to the Antarctica; less than a month ago I came back.

LK: Oh, wow.

SP: I didn't go to the Antarctic continent. I went to South Georgia and the [South] Sandwich Islands.⁷

DL: Did you go to Prion Island?

SP: Well, the problem was I went to Prion Island, but I never *stepped* on Prion Island, because there was a cyclone.

DL: Really?

⁶ From 2010-2011, Prusiner was a member of the Committee on Future Science Opportunities in the Antarctic and Southern Ocean, National Research Council, National Academy of Sciences.

⁷ The South Sandwich Islands, an archipelago in the South Atlantic Ocean, were tentatively named "Sandwich Land" by British explorer Captain James Cook (1728-1779) in 1775. The South Sandwich Islands are part of the British overseas territory of South Georgia and the South Sandwich Islands (SGSSI). The South Sandwich Islands are distinguished from the Sandwich Islands, the name given by Cook to the Hawaiian Islands (in the Pacific Ocean) in 1778.

SP: We were going through this [storm] and the waves were just too damn big [for] these small Zodiac boats. This was a boat 500 feet long. So to get off that boat and get into the Zodiacs is a big deal when there are huge swells. We tried in the afternoon when the cyclone was just reappearing. We'd just come through this quiet time. We'd spent some time in South Georgia, but we weren't at the island at that point. We traveled down the island, but it was starting to get dark, and I really didn't want to do that. I said to these guys, "You know, this is important, but it's not important enough to lose somebody's life here."

So the next morning, I got up, and the captain said, "Well, we can do this." Then, this other guy who was the scientific director of the voyage, a bureaucrat, kept saying, "Well, we've got a schedule. We've got a schedule." Well that was so stupid, because in the end we had days and days of extra time.

DL: Is that right? Did you see...

SP: I saw it.

DL: Did you see a prion bird?

SP: Oh, yes, there's a million of those. I didn't realize that in order to take pictures of birds, ornithologists, birders, use gigantic lenses that look like penises. They're so long.

[chuckles]

SP: Or imagined!

[laughter]

SP: We saw one. After this I went on a safari. I'm trying to remember which animal. I think it was an elephant that had the most gigantic... It was so funny.

LK: [laughter]

SP: This guy, who was an ornithologist at the University of Cape Town, just sent me a whole stack of photos of prion birds.

DL: Good.

SP: I've got a huge collection now.

DL: Good, because I knew that was one of your agendas.

SP: The funny thing was that when we were waiting... We were on this area called Grytviken,⁸ which was the place where Shackleton⁹ was and got a ship to go rescue his crew.

DL: Exactly.

SP: There, we walked around, and I collected all of these samples that I wanted to take back because I wanted to make natural products libraries out of these. It's actually being done in Vancouver now. There was a whaling station and a museum. I walked inside there. There was this big sign that said, "There are twenty-two million prion birds in the Antarctic Region." It had a stuffed one. I said, "Well, if all this is for naught, I'll have a picture of a bird, and I'll have a picture of this sign saying there are twenty-two million of them, and I can't find *one*."

[laughter]

SP: This has all been pretty funny. Then, the guy who organized all of this said to me, "Stan, don't worry about it. This is something great to do. We'll go back."

DL: There you go.

SP: He knew I was having a great time.

DL: There's also a Prion Mountain in Turkey.

⁸ Grytviken is a settlement on the island of South Georgia. The settlement's name, meaning "Pot Bay" (Swedish), was coined in 1902 by the Swedish Antarctic Expedition and documented by Swedish surveyor Johan Gunnar Andersson (1874-1960), after the expedition found in that location some old English "try pots," large vats used to remove and render the oil from blubber. Grytviken was established as a whaling station in 1904 by Norwegian captain Carl Anton Larsen (1860-1924) for his *Compañía Argentina de Pesca* (Argentine Fishing Company).

⁹ Sir Ernest Shackleton (1874-1922) led three British expeditions to the Antarctic, the most notable of which was the Imperial Trans-Antarctic Expedition (1914-1917), an attempt to make the first land crossing of the Antarctic continent. Unfortunately, Shackleton's ship, the *Endurance*, became trapped in pack ice and was slowly crushed before the shore parties could be landed. Shackleton and the crew camped on the sea ice, but, when the ship disintegrated and finally sank beneath the ice, the party boarded the lifeboats to reach Elephant Island, an ice-covered, uninhabited mountainous island off the tip of the Antarctic Peninsula. Using one of the lifeboats, modified by the ship's carpenter, Shackleton and five others then made a daring 800-nautical-mile open-boat journey through heavy polar seas and force-9 winds to reach South Georgia. From there, Shackleton was eventually able to mount a rescue of the men waiting on Elephant Island and bring them home without loss of life.

[pause]

SP: Really?

DL: Yes.

SP: You've got to show this to me. I've found two more Prion Islands.

DL: There's a Prion Mountain near a city that's referred to in the Bible [Ephesus], and it's in Turkey.¹⁰

¹⁰ Mount Prion (sometimes misspelled Pion or Peion; now *Panayır Dağ*, Turkish for “fairy mountain”) is in the vicinity of the ancient Greek colonial city of Ephesus (with a portion of Mt. Prion incorporated within the walls of the city), three kilometers southwest of present-day Selçuk on the west coast of Turkey.

Ephesus was famed for the nearby Temple of Artemis (completed around 550 BC), one of the Seven Wonders of the Ancient World. Among many other monumental structures were the Library of Celsus (completed between circa 114–117 AD), and an amphitheater capable of holding 25,000 spectators. Ephesus was the birthplace of the pre-Socratic Greek philosopher Heraclitus (c. 535 - c. 475 BC), the so-called “weeping philosopher,” in contrast to the “laughing philosopher,” Democritus (c. 460 - c. 370 BC). Later, the Christian apostle Paul lived in Ephesus twice in the interval from 51-57 AD, and then afterwards wrote his Epistle to the Ephesians when he was in prison in Rome (c. 62 AD); for further details, see *Acts of the Apostles* 19:1, Paul's *First Epistle to the Corinthians* (written when Paul was in Ephesus), and Paul's *Epistle to the Ephesians*. Ephesus was destroyed by the Goths in 263, and although rebuilt, the city's importance as a commercial center declined as the harbor was slowly silted up by the Küçükmenderes (“Little Meander”) River and the coastline moved seaward—the ruins of Ephesus are now some 8 km (5.0 mi) inland. Ephesus was then partially destroyed by an earthquake in 614 AD.

A very detailed account of the ruins of Ephesus and Mount Prion was given by English antiquarian Richard Chandler (1738-1810), who traveled there in the 18th century on behalf of the Society of Dilettanti. The Society of Dilettanti had been founded in 1734 as a society of noblemen and scholars who promoted the study of classical antiquities. In 1764, the society commissioned Chandler to lead an expedition to Greece and Asia Minor, with a painter, William Pars, and an architect, Nicholas Revett. The expedition left London in 1764 and explored the antiquities of Ionia, including Ephesus, before being forced by an outbreak of plague to move to Athens in 1765. The results of their labors were *Ionian Antiquities* (1769), in two folios, and, later, Chandler's record of the tour, *Travels in Greece, or an Account of a Tour Made at the Expense of the Society Of*

SP: How high is it?

Dilettanti (1776). It is in the latter volume that Chandler describes Ephesus and Mount Prion.

See:

1. Anonymous. Ephesus. *The Friend: A Religious and Literary Journal* 1877;50(39):305-306.
2. Anthon C. Ephesus. In: *A Classical Dictionary: Containing an Account of the Principal Proper Names Mentioned in Ancient Authors, and Intended to Elucidate all the Important Points Connected With the Geography, History, Biography, Mythology, and Fine Arts of the Greeks and Romans. Together With An Account of Coins, Weights, and Measures, with Tabular Values of the Same.* New York: Harper & Brothers, 1848:474-477.
3. Chandler R, Revett N, Pars W. *Ionian Antiquities, Published with Permission of the Society of Dilettanti.* London: T. Spilsbury and W. Haskell, 1769.
4. Chandler R. *Travels in Asia Minor, and Greece: Or, An Account of a Tour Made at the Expense of the Society of Dilettanti.* Third edition. London: Joseph Booker and R. Priestley, 1817;1:137-150.
5. Chisholm H (Ed.). "Chandler, Richard". *Encyclopædia Britannica.* (11th ed.). Cambridge University Press. 1911;5:838.
6. Condor J. Ephesus. In: *The Modern Traveller. A Description, Geographical, Historical, and Topographical, of the Various Countries of the Globe. In Thirty Volumes.* London: James Duncan, 1830;3:123-146.
7. Cramer JA. *A Geographical and Historical Description of Asia Minor; With a Map. In Two Volumes.* Oxford: University Press, 1832;1:362-380.
8. Hobhouse JC. *A Journey Through Albania, and Other Provinces of Turkey in Europe and Asia, to Constantinople, During the Years 1809-1810.* London: James Cawthorne, 1813: 646-668.
9. Knight W. *Oriental Outlines; or, A Rambler's Recollections of a Tour in Turkey, Greece, & Tuscany.* London: Sampson Son, 1839:263-269.
10. Moustier A de. *Voyage de Constantinople a Éphèse, par l'intérieur de l'Asie Mineure, Bithynie, Phrygie, Lydie, Ionie, Par M. Le Comte A[uderic] de Moustier, 1862.* [Voyage from Constantinople to Ephesus through Asia Minor, Bithynia, Phrygia, Lydia, Ionia, by Count Auderic de Moustier, 1862.] *Le Tour du monde. Nouveau journal des voyages publié sous la direction de Edouard Charton et illustre par nos plus celebres artistes.* Paris: L. Hachette, 1864:2:269.
11. Ripley G, Dana CA (Eds.). *The American Cyclopædia: A Popular Dictionary of General Knowledge* 1879;6:677-679.
12. Murcia FJ. Grandeur for the goddess: the Temple of Wonder. *National Geographic History* 2017;3(5):30-39.

See images in Appendix 2.

DL: I don't think it's very high.¹¹

SP: Good.

DL: It was used to quarry marble, and it was named from the Greek word, which means "saw," because...

SP: Exactly! That's right, because the bird has got a saw-tooth beak.

DL: Right. Well, the mountain had a skyline topography that resembled a saw.

SP: This is great!

DL: Yes.

SP: That's got to be a trip soon, but that idiot, Erdoğan,¹² has got to leave before I go there.

DL: Yes, yes. It's going to make it complicated for a moment.

SP: Trump¹³ will fix it. I'll call him.

[laughter]

DL: I'll send you the information on Prion Mountain.

SP: How did you find that?

DL: I was actually trying to see how the development of the word *prion* [pronounced *pree-on*] changed over the course of time, so I've done a little study of my own on that. Then, I was looking at the stuff where it was referenced before you actually coined the term and tried to see what the references were to: some of them were to the bird; some of them were to the island that you tried to go to; and some of them were to Prion Mountain in Turkey.¹⁴

¹¹ The name notwithstanding, Mt. Prion is really only a large hill, with three peaks between 105 and 155 m above sea level, crowned with ancient fortifications.

¹² Turkish President Recep Tayyip Erdoğan (1954-)

¹³ U.S. President Donald J. Trump (1946-)

¹⁴ There are also other terms derived from *prion* (Greek for saw): prionoderma, priodon, priodontes, prionidae, prionites, prionodon, prionops, prionotes, prionotheca, prionotus, prionurus, and prionus (Craig, 1858).

SP: Oh, that's really good.

DL: I'll share that with you.

SP: Yes, I've got to have that. Wow! Okay, that's terrific! All of these guys on the ship I got to be friendly with, really friendly with, I'll send that to them today or tomorrow.

DL: I'll get it to you.

SP: Yes, that's great! I love it!

LK: In your studies at Pennsylvania, were you focused on medicine the entire time you were there? Was that what you had decided to go into or when did that...?

SP: I guess it was now, probably the first or second year. My Jewish mother sends letters, little articles from *Reader's Digest*, about doctors and what they did or didn't do—mostly what they did. I used to throw these things away.

LK: But some of it stuck.

SP: Yes, yes. I wanted to have a profession. I needed something. I needed something to do. They didn't have any money. It dawned on me that I needed to have something to make a living. I couldn't just be anything. There were limits on what I could do. I could not go work in a park my whole life and have enough money to not have to worry about where my next meal was going to come from. So I actually was attracted for a long time, without any real knowledge of why... I thought being a cardiac surgeon would be a great thing to be, because that was the heyday of Michael DeBakey¹⁵ and Cooley.¹⁶

Craig J. *A New Universal Etymological, Technological, and Pronouncing Dictionary of the English Language, Embracing all the Terms Used in Science, Literature, and Art.* London: George Routledge & Co., 1858;2:57.

¹⁵ Lebanese-American cardiac surgeon, scientist, and innovator Michael Ellis DeBakey (1908-2008) had a long and distinguished medical career, continuing to practice until his death at age 99. Around 1931, while still a medical student at Tulane University, DeBakey developed the roller pump, which decades later became an essential component of the heart-lung machine that ultimately made open-heart surgery possible. DeBakey was one of the first surgeons to perform coronary artery bypass surgery. Throughout the 1950s DeBakey pioneered surgical treatments of aortic aneurysms. A pioneer in the development of an artificial heart, DeBakey was the first to use an external heart pump successfully in a patient. DeBakey was also the first to successfully perform carotid endarterectomy (1953), and later performed the first successful patch-graft angioplasty to counteract post-endarterectomy carotid stenosis (1958). Among his many awards and

LK: [And] Lillehei.¹⁷

SP: Yes, all of these guys. Some of the early work had been done on extracorporeal circulation and hypothermia at Jefferson Medical School. Nobody at the University of Pennsylvania thought Jefferson was worth thinking about, and they really turned down their noses at Jefferson. But, nevertheless, it was there. I thought about this a lot.

Then, what happened was... the key turning points were I now wanted to go to medical school and I was doing this research project. Well, that's not true. I wanted to go to medical school. I said to my aunt, "You know I.S. Ravdin,"¹⁸ who's a very famous surgeon. He operated on Eisenhower,¹⁹ on his colon, when Eisenhower was president. He

honors, DeBakey received the American Medical Association Distinguished Service Award (1959), the Albert Lasker Clinical Medical Research Award (1963), the Eleanor Roosevelt Humanities Award (1969), the Presidential Medal of Freedom with Distinction (1969), the Presidential National Medal of Science (1987), and a Congressional Gold Medal (2008). He also received more than 50 honorary degrees from universities around the world.

¹⁶ American heart and cardiothoracic surgeon Denton Arthur Cooley (1920-2016) worked on developing artificial heart valves throughout much of the 1960s (1962-1967), resulting in a marked drop in mortality for heart valve transplants. In 1968, he performed the first successful human heart transplant in the United States. In 1969, he became the first heart surgeon to implant an artificial heart in man (although the patient, Haskell Karp, survived for only 65 hours following the surgery).

¹⁷ American cardiothoracic surgeon Clarence Walton ("Walt") Lillehei (1918-1999) pioneered open-heart surgery, and developed numerous techniques and equipment for cardiothoracic surgery.

¹⁸ American general surgeon Isidor Schwaner ("Rav") Ravdin (1894-1972) is noted for introducing intravenous feeding to prevent malnutrition in surgical patients. Ravdin's many honors included Honorary Fellowship of the Royal College of Surgeons of England (1956), and Presidencies of the American Surgical Association (1958), the American Cancer Society (1963), and the American College of Surgeons (1960).

¹⁹ In June 1956, President Dwight David ("Ike") Eisenhower (1890-1969) developed an acute small bowel obstruction due to ileitis (regional enteritis). Ravdin was in Chicago, but was called emergently to the White House as a Civilian Consultant, and ultimately recommended surgery. On June 9, 1956, Ravdin and three other surgeons (Leonard D. Heaton, Brian Blades, and John H. Lyons) performed a successful small bowel bypass with ileotransverse colostomy in continuity, after which the President had an uneventful recovery.

This event was recounted by Jonathan E. Rhoads, Ravdin's former trainee at the University of Pennsylvania:

was the Vice President for Medical Affairs at the University of Pennsylvania. I said, “Can you get me a job through him so I can work this summer between my junior and senior

As is widely known, [Ravdin] was called upon to consult with the president’s physician, Dr. Howard McC[rum] Snyder [1881-1970], and the chief of surgery at Walter Reed Army Hospital, Dr. Leonard Heaton [1902-1983], when President Eisenhower came in with an intestinal obstruction. It was previously known, but not publicized, that Eisenhower had trouble with ileitis. Apparently, he had eaten a good deal of celery, of which he was fond, and with all this fiber the bowel had become obstructed. Rav was attending a meeting of the board of regents of the American College of Surgeons in Chicago when the call came requesting his assistance. One of the officers of the college called the airport and found out that an American Airlines plane was about to leave for Washington. He asked them to hold the plane and called the police to send a squad car. Rav left the meeting without any luggage and was hurried to the airport. When the traffic was stopped at a red light, the squad car would pass the vehicles waiting and cross the intersection to the empty side of the street beyond. About half way to the airport, the policeman who was driving it turned to Dr. Ravdin and said, “Don’t worry doctor, I haven’t lost a patient yet.” At the operation, [Ravdin] decided to bypass the area of chronic ileitis and relieve the obstruction and not to resect. This was, of course, criticized by surgeons around the country who perhaps felt that they could have handled the situation better. Again, his judgment was vindicated. The president was able to resume his duties shortly after he came out of anesthesia. The ileitis never again required an operation on the president. (Rhoads, 2000)

See also:

1. Heaton LD, Ravdin IS, Blades B, Whelan TJ. President Eisenhower’s operation for regional enteritis: a footnote to history. *Ann Surg* 1964;159(5):661-666.
2. Rhoads JE. My teacher and chief: I.S. Ravdin. *Surgery* 2000;127:584-585.
3. Rhoads JE, Miller LD. Festschrift for Dr. Isidor Schwaner Ravdin. Foreward. *Surgery*. 1964;56:606-608.
4. Wangensteen OH. Isidor Schwaner Ravdin—Versatile surgeon and nonpareil surgical statesman. *Surgery*. 1964;56:609-610.
5. Farber S. I. S. Ravdin—Civilian activities at the national level. *Surgery*. 1964;56:611-613.
6. North JP. The 20th General Hospital—I. S. Ravdin, Commanding General. *Surgery*. 1964;56:614-623.
7. Anonymous. Isadore S. Ravdin (1894-1972). *J R Coll Surg Edinb*. 1973;18(2):123.
8. Roberts B. Memoir of I. S. Ravdin 1894-1972. *Trans Stud Coll Physicians Phila*. 1974;41(3):237-241.
9. I.S. (Isadore Schwaner) Ravdin Papers: 1912-1972. University Archives and Records Center, University of Pennsylvania.
http://www.archives.upenn.edu/faids/upt/upt50/ravdin_is.html [Accessed 9-29-17].

years doing research?” I had never done anything... Despite being a chemistry major, I didn't do any research. There was nothing there. There were labs, but these weren't research labs. These were teaching labs.

LK: There was no requirement to do research as part of your...?

SP: Well, it's more than that. Research is about a process of going through a series of questions and deciding which ones are the best, modifying them, and then trying to answer them.

I worked with this man named Sidney Wolfson,²⁰ who taught me everything. He was remarkable. He spent so much time with me. He was really great. I really enjoyed doing this. I said, “This is unbelievable. Somebody can make a living at this?” But that was a little distant. It was fuzzy. As I did more and more of this, I decided that there was a problem that I'd rather work on that was more quantitative. He's a physiologist/surgeon and I was more interested in numbers and I was more interested in defined chemicals. He was interested in brain edema.²¹ The way you measure brain edema is you measure the

²⁰ Sidney K. Wolfson, M.D. (1931-).

Prusiner recounted Wolfson's strong positive influence on him in an interview in 2016:

Beginning in the summer before my senior year at Penn, I studied brain swelling in rats with Sidney Wolfson, and the experience persuaded me to stay on at Penn and enter the medical school there. Wolfson showed me how to read scientific papers and analyze data. He taught me statistics and how to formulate a scientific problem. He spent an immense amount of time helping me delve into the fascinating world of scientific research. (Shea, 2016)

See:

1. Shea J. The Nobelists return to campus. Penn Medicine Magazine 2016;Fall. <https://www.pennmedicine.org/news/publications-and-special-projects/penn-medicine-magazine/fall-2016/nobelists> [Accessed 9-29-17]
2. Resolution of Appreciation for Stanley B. Prusiner. Trustees of the University of Pennsylvania University Archives and Records Center, University of Pennsylvania, June 17, 2005. http://www.archives.upenn.edu/primdocs/upa/upa1_1/2000to09/20050617res.pdf [Accessed 9-29-17]

²¹ Prusiner wrote two papers with Wolfson, both of which concerned cerebral edema:

1. Prusiner SB, Moskovitz PA, Wolfson SK Jr. Relationship of acidemia to cerebral edema. Arch Surg. 1965;91(6):902-905.
2. Prusiner S, Wolfson SK Jr. Hypothermic protection against cerebral edema of ischemia. Arch Neurol. 1968;19(6):623-627.

water content of the brain. What you do is you dry down the brain. The problem is that as you dry the brain, the brain has less and less water, but there is no absolute. So it's always going down, and down, and down, and down; and then it drifts down and down. You're evaporating all of the water and you have a vacuum. You're pulling a vacuum. How long is this? It goes down like this, but now you're beyond ninety percent water—it's gone. So now you have this little fuzzy stuff, this powder. So that's going down, but where do you stop? This gets really fuzzy, and I don't like that kind of stuff. I wanted to know what was going on. I wanted something I could measure.

So I changed advisors, and I went to this man named Britton Chance, who is very well known.²² He was very welcoming. I told him what I wanted to do. I wanted to study brown fat metabolism, because I was interested in the fact that brown fat created heat for animals that were hibernating to wake up.

LK: Okay.

SP: Hamsters hibernate. So I didn't need to study bears. I then started this project with him, and that got to be terrific.²³ I got consumed by these little research projects, but I had to make sure that I got decent grades, because now all of this desire not to study and not to excel shifted completely. It went 180 degrees. So I stayed focused on my medical school studies. That was really worthwhile, because it opened all kinds of doors that weren't going to open otherwise.

LK: Yes. I just think that's an interesting arc in your life, not finding anything you're interested in but when that interest happened, it's like you're very focused on it. It very much comes out in your life story.

SP: It's fun. I was doing things that were fun. I'm still doing fun things. That's why I want to keep working. If I go to a store or someplace and they all say, "Are you retired?" All my contemporary friends get really annoyed when people say, "Are you retired? Are

²² Britton Chance, Ph.D. (1913-2010) was a physical chemist, who became the Eldridge Reeves Johnson University Professor Emeritus of Biochemistry and Biophysics, as well as Professor Emeritus of Physical Chemistry and Radiological Physics at the University of Pennsylvania School of Medicine. At the time that Prusiner worked with him, Chance was the E. R. Johnson Professor of Biophysics and Physical Biochemistry (later renamed as Biochemistry and Biophysics). Among his numerous awards, Chance won a gold medal in sailing at the 1952 Summer Olympics, received the National Medal of Science (1974), and received ten honorary degrees.

²³ Prusiner S, Williamson JR, Chance B, Paddle BM. Pyridine nucleotide changes during thermogenesis in brown fat tissue in vivo. *Arch. Biochem. Biophys.* 1968;123:368–377.

you retired?" I want to say, "What business is it of yours?" This is this age... What's the right word? Oh, boy.

LK: Not ageism.

SP: No, it's not ageism. They want the old people out of the way. They need to take over and run their show. It's time. As people live longer and some of them are quite vital, that's not okay with a lot of people. They want their parents out of the way, their parents' generation out of the way.

LK: When you were working with Dr. Wolfson and Dr. Chance, they were very receptive to your work and your presence there. Was that something common, or do you think that you were lucky in that, or a little bit of both?

SP: Oh, I was really lucky. I was exceptionally lucky. These were people that were so nice to me. They were so gentle, caring, nurturing.

LK: That kind of mentorship for undergraduates seems very... I don't know if it's unique, but it's definitely worth commenting on.

SP: It was unusual. Here was this guy who was greater than God in medicine, Ravdin, telling this guy who had just dropped out of the surgery program and now is sort of moving on to experimental surgery, physiology, "Why don't you take this guy on and see what this character looks like. Do me a favor." Then, it just happened. It was perfect.

LK: Did you ever consider shifting from medicine to a Ph.D. program in chemistry or quantitative science?

SP: Yes. I was only worried about Vietnam then. There was a guy who was sort of the opposite of Chance and Wolfson. He wanted me to work for him in the same department as Chance. He ran a physics department called the Johnson Foundation.²⁴ This guy, people really disliked him. There were notes on the blackboard, "What's mine is mine and what's yours is mine." Then, they would sign the guy's name. [laughter] We laugh about that. These are friends of mine who are still alive. We talk about those days. Anyway, he wanted me to get a Ph.D., because he thought this was the way to avoid the draft. When I sat down with Chance and talked to him about this, he said, "This is idiotic. Figure out another way to do this, because you don't need a Ph.D. and an M.D." He had two Ph.D.s himself.

²⁴ The Eldridge Reeves Johnson Foundation for Research in Medical Physics was founded in 1929 at the University of Pennsylvania School of Medicine in Philadelphia. Eldridge Reeves Johnson (1867-1945) was an American businessman and engineer who had perfected the disk-playing phonograph and later founded the Victor Talking Machine Company (1901), which ultimately became RCA Victor.

LK: Oh, my god. [chuckles]

SP: He said, “This is a waste of time. You don’t need to spend your time doing this. It’s just routine.” It was clear to me: I just needed one degree. An M.D. for me, I knew, was going to be much better. Eventually, it became clear to me that I wanted to be a scientist, but I didn’t want to live like a scientist. I wanted to live like a physician.

LK: [laughter] Okay. Got it.

SP: It became clear to me that there were not a lot of great options. After I did an internship, I went to the NIH [National Institutes for Health] for three years, while the war was really at its height, 500,000 people, or men, serving in Vietnam. I said to myself, “I’m going to go look at post doctoral experiences in the neurosciences,” because I decided that I really wanted to work on the brain. I thought the brain was the most interesting part of the human’s anatomy.

LK: Did that just evolve for you or did that come from a specific experience?

SP: I don’t know. I’d done this work that I was telling you about, about brain edema, with Wolfson. You go to medical school and if you’re not interested in the brain, then you don’t belong in medicine. Ask anybody here in this hall [at the annual meeting of the American Academy of Neurology].

DL: That’s kind of a biased group, though!

[laughter]

SP: The rest of it is really dull. Do you want to work in the gut? It takes nice looking food, it gets ground up, and then it ends up in the gut, and it turns into shit.

[laughter]

SP: How interesting is that? I have a lot of friends who do this for a living, but...

LK: I heard comments that neurology isn’t the most lucrative specialty.

SP: No.

LK: So your interest overrode the practical...

SP: Well, no. I’m just talking about the difference between being a Ph.D. scientist in physiology and being a neurologist. That’s a big difference in the academic world. I’m not talking about becoming exceedingly rich, because I’m doing cosmetic surgery or something like that, or laser treatments for people’s eyes. That’s *not* what I’m talking about. I’m just talking about where I didn’t want to end up like my parents where every

single month they had to look at their checkbook and decide that they couldn't do this or that, and they especially couldn't do it for their kids, my brother and myself. They just were so strapped. It seemed to me that if I'm spending my time, and I can do what I want to do, and I'm lucky to find this whole career about research, then I should try to do it in a setting where I would be a little better compensated. I didn't want to be sitting there like my parents were, always worrying about money. It's really a drag. But I wasn't interested in spending my time becoming a billionaire.

LK: Yes. I didn't mean to infer that.

SP: No, no. I'm just trying to clarify it, making sure it's clear.

LK: Yes.

We can also talk about Stockholm a little bit and your work with Lindberg.²⁵

SP: Yes, sure.

LK: I know you really enjoyed that experience. I didn't know if you wanted to comment on the impact that had on your research interests.

SP: That was kind of the culmination of all this doing research while I'm going to medical school. Again, that was an issue of money. I didn't have any resources from my parents to be able to take off a year and go to Stockholm or some other place and do more research before finishing my degree. I wasn't going to get any money from my father's cousin. He was paying the tuition, but that was it.

What happened was that I went to see the dean at the end of my second year of medical school. I said, "I really want to go and do research in the fall of my senior year." He said, "Well, if you do really well in medical school in the third year"—that's the clinical year; that's the key year—"then, yes, you can go and we'll give you credit." So that fit with my program in my head about what I was capable of putting together. So that's what I did. And when I went to see him at the end of the third year of medical school, I said,

²⁵ Swedish zoologist Olov Lindberg, Ph.D. (1914-2001) was a professor and prefect of the Wenner-Gren Institute at Stockholm University. He became a member of the Swedish Academy of Sciences in 1968.

Prusiner published two papers with Lindberg:

1. Prusiner SB, Eisenhardt RH, Rylander E, Lindberg O. The regulation of oxidative metabolism of isolated brown fat cells. *Biochem. Biophys. Res. Commun.* 1968;30:508-515.

2. Lindberg O, Prusiner SB, Cannon B, Ching TM, Eisenhardt RH. Metabolic control in isolated brown fat cells. *Lipids* 1970;5:204-209.

“Okay, Bill”— he was actually the Vice Dean for Student Affairs, I guess, named William Kennedy —“Do you think I’ve done well enough?” He looked and I had all these A’s. He said, “Well, you did this. It looks good, but I want to tell you that if you had one more A, I was going to tell you ‘No.’ You got a C in psychiatry.” I said, “Let me tell you why I got a C in psychiatry.” He said, “Well, okay, but it really doesn’t matter, because having a C in psychiatry makes it okay for you to go to Stockholm.”

LK: [laughter]

SP: I said, “Everyday I would come in and I would have to sit there and play psychiatrist to the psychiatry resident. All he wanted to do was tell me about his failed escapades with women. It really got boring.” I wasn’t interested in his personal life. It was irrelevant to me. That was kind of fun.

So that was a key time. I’m now in my fourth year of medical school, and I’m having a great time. Lindberg, who was the director of this big institute,²⁶ was so nice to me. He was just a gem in the sense that he would include me in all of these conversations. I brought some skills and techniques that I had worked out at Penn to Stockholm, so we worked together. We wrote all of these papers together. There were a couple other people who were there who were really wonderful. He was so happy, because his work had really been taken over by a young man, who was not so young at that point, named Lars Ernster, who came from Hungary.²⁷ There were a lot of World War II refugees that came from these Middle Eastern [sic, central European] countries and settled in Sweden, who were professionals. They really changed the rigor of Swedish science in many respects—not all, because there were a lot of smart Swedes, who also had done a lot of great research in the previous fifty years. This was an opportunity. I said to myself, “I really like doing this. I like these people. The people are really nice. The people are interesting. They’re really interesting to talk to. They’re not dull. They’re doing something that I think is great.” Each day, there’s a progression, *or* we sit still and we don’t know what to do, and we sit, and we wait, and we wait, and we wait, and we think constantly. We don’t run away from the hard problem.

This is what I’ve done my whole life—you just stay focused on what you want to try to accomplish, and if you’re smart enough, you’ll figure out a way around it. You probably

²⁶ The Wenner-Gren Institute for Experimental Biology, located in the Arrhenius Laboratories at Stockholm University, is focused on basic experimental research to address fundamental biological problems at the molecular level, and consequently incorporates researchers in cell biology, developmental biology, immunology, and physiology.

²⁷ Hungarian-born Swedish scientist Lars (László) Ernster, Ph.D. (1920-1998) was a professor of biochemistry at Stockholm University, a member of the Royal Swedish Academy of Sciences (1974), and a member of the Board of the Nobel Foundation (1977-1988).

won't go right through it. You won't get through that big pillar sitting back there. You have to go around it, and you'll get there.

DL: Reading your book,²⁸ and reading some other things, that focus that you've had is really a defining feature of your career. You've been able, as you indicate, to go around tremendous obstacles. You've pulled colleagues in, collaborators, to accomplish steps that you saw as necessary to achieving a goal. You built collaborations. You worked around problems. You did fifty-eight steps to accomplish something that seemed impossible to accomplish. But you always maintained that focus. It's quite a remarkable feature.

SP: Well, that's *exactly* what I've been doing now for twenty years.

DL: Yes.

SP: I've been trying to develop drugs to stop Alzheimer's and Parkinson's. Now, when I started this, I thought, well, some of these big pharmaceutical companies—we're talking about big companies with gigantic loads and loads of people, huge staffs—I thought I'll be competing with all these people, but we'll see what happens. If they fail, this is an unbelievable mess, and that's exactly what we're faced with. It's in the literature now and in the newspapers. It's everyday. Why the hell has all this failed? We—meaning the American people—have put all of this money into Alzheimer's disease.²⁹

I don't know the number—I was going to look it up the other day, but I didn't do it—I was going to look up the number of papers with Alzheimer's disease in the title. You can do this in PubMed. My guess is it's 100,000 or 200,000.³⁰ It's just an enormous number of papers, and we're nowhere.

But I really think we're getting somewhere. We're moving in a very positive way, so I'm really excited. I'm really happy about this. I've got these groups of people. It's about marshaling all of the skills you need. This is a little more complicated than prions. You've got to kill the prion without killing the person. It's one failure after another. There's a drug that we've been studying. It's useful in mice. But Amgen killed the drug because it was putting fatal arrhythmias into the hearts of dogs.

²⁸ Prusiner SB. *Madness and Memory: The Discovery of Prions—A New Biological Principle of Disease*. Yale University Press, 2014.

²⁹ According to the Alzheimer's Association, the NIH spends \$480 million per year on Alzheimer's disease research. This is actually significantly less than cancer (\$6 billion), heart disease (\$4 billion), and HIV/AIDS (\$3 billion).

³⁰ There were 53,143 papers indexed in PubMed with "Alzheimer disease" or "Alzheimer's disease" in the title, and 104,488 papers with either of these in the title or abstract, as of the date of the oral history interview.

Then, there's another one that was just announced not long ago by Merck.³¹ Merck said, "Well, there's no efficacy." That's probably because, without stopping the tau protein from becoming a prion, it just tried to stop the A β peptide from becoming a prion. That's actually *lowering* the A β level. It doesn't work, because the tangles are being generated already. It's fascinating to me. I want to see this scourge stopped. It's horrible! I've listened to one story after another, because everybody wants to talk to me about their Alzheimer's disease.

So we got off the track. We were with Lindberg. It was so clear to me, at that point, that that's the way I should make a living. He's a really nice man. I really enjoyed being with him, and I enjoyed everyday going to work. I wasn't ever bored. I wasn't sitting around saying, "This is really boring." It wasn't like a bad book. I've learned not to continue with these bad books.

LK: [chuckles] They're not worth the time.

SP: Right. Exactly.

LK: I think there's a difference between boring and tedious. Your studies involve long periods of time doing...

SP: Yes, but that's not tedious.

LK: Because it's interesting?

SP: It's not boring.

LK: Yes.

³¹ Verubecestat (MK-8931), an inhibitor of beta-secretase 1 (also known as beta-site amyloid precursor protein cleaving enzyme 1, or BACE1), was developed as an experimental drug for the treatment of Alzheimer's disease. As of December 2016 development had progressed to phase 3 clinical trials. However, in February 2017 Merck halted its late-stage trial of verubecestat for mild-to-moderate Alzheimer's disease after the external Data Monitoring Committee concluded that it had "virtually no chance of finding a positive clinical effect."

See: "Merck announces EPOCH study of verubecestat for the treatment of people with mild to moderate Alzheimer's disease to stop for lack of efficacy" [Press release]. Merck. February 14, 2017.

<http://www.businesswire.com/news/home/20170214006278/en/Merck-Announces-EPOCH-Study-Verubecestat-Treatment-People> [Accessed 12-6-17]

SP: If it's boring, it becomes tedious. That's my view. You can parse the words the way you want.

LK: Ohay. [chuckles]

When you moved to the NIH, you worked with Earl Stadtman.³² You've mentioned that he was really influential in your scientific education.

SP: Yes.

LK: I read that his way of teaching, having his mentees do scientific research, was called the Stadtman way?

³² American biochemist Earl Reece Stadtman, Ph.D. (1919–2008) was Chief of the Laboratory of Biochemistry at the National Heart Institute, and was also a member of the National Academy of Sciences (1969). Stadtman received the National Medal of Science (1979) "for seminal contributions to understanding of the energy metabolism of anaerobic bacteria and for elucidation of major mechanisms whereby the rates of metabolic processes are finely matched to the requirements of the living cell."

According to Stadtman, "Very often in the course of scientific experimentation a totally unexpected observation is made that is either unrelated or only incidentally related to the problem under immediate investigation. When it captures the attention of an alert, inquisitive mind, this observation may open the door for an entirely new study that is often more fruitful than that of the original design"

See: *The Stadtman Way: A Tale of Two Biochemists at NIH*.

<https://history.nih.gov/exhibits/stadtman/index.htm> (An online exhibit produced by the Office of NIH History in collaboration with the Heart, Lung, and Blood Institute.) Accessed 12-6-17.

See also:

1. Prusiner S, Stadtman ER (eds.). *The Enzymes of Glutamine Metabolism*. New York: Academic Press, 1973.
2. Prusiner S, Davis JN, Stadtman ER. Regulation of glutaminase B in *Escherichia coli*. I. Purification, properties, and cold lability. *J. Biol. Chem.* 1976;251:3447-3456.
3. Prusiner S, Stadtman ER. Regulation of glutaminase B in *Escherichia coli*. II. Modulation of activity by carboxylate and borate ions. *J. Biol. Chem.* 1976;251:3457-3462.
4. Prusiner SB, Stadtman ER. Regulation of glutaminase B in *Escherichia coli*. III. Control by nucleotides and divalent cations. *J. Biol. Chem.* 1976;251: 3463-3469.
5. Requena JR, Groth D, Legname G, Stadtman ER, Prusiner SB, Levine RL. Copper-catalyzed oxidation of the recombinant SHa(29–231) prion protein. *Proc. Natl. Acad. Sci. U.S.A.* 2001;98:7170-7175.

SP: Oh, yes. This is an embellishment.

LK: Is it? [laughter]

I wondered if this research process, and what you learned in research there, how that influenced the way you did research going forward. I noticed that in looking at other people's studies around scrapie, you didn't agree with their methodology or didn't agree with the way they interpreted that data. I didn't know if the way that you viewed your work had its foundations in your work with Stadtman.

SP: It all comes out of Stadtman. This is true good luck. Here I am. I get trained in protein purification, in enzymology, protein characterization, always looking at the activity of the protein while I'm manipulating it physically—all of these things. And, then, having him be somebody—I wrote this down in the book [*Madness and Memory*] pretty carefully—who would discover something.

He made one really important discovery and that was about adenylation of the glutamine synthetase, so you end up with this nucleoside bound to glutamine synthetase.³³ This regulates nitrogen metabolism.

When he did that—he made that discovery—it was a discovery; it was new by definition. Nobody had done that. He wanted to know whether this was an artifact, because he really cared about being right and *not* being wrong. Because he understood that if you're

³³ Regulation of glutamine synthetase by mechanisms that involve covalent attachment of adenylyl groups only occurs in prokaryotes. In mammals, glutamine synthetases do not exist in adenylylated forms (Legrain et al, 1982).

See also:

1. Stadtman ER, Ginsburg A, Ciardi JE, Yeh J, Hennig SB, Shapiro BM. Multiple molecular forms of glutamine synthetase produced by enzyme catalyzed adenylation and deadenylylation reactions. *Adv Enzyme Regul.* 1970;8:99-118.
2. Mura U, Chock PB, Stadtman ER. Allosteric regulation of the state of adenylylation of glutamine synthetase in permeabilized cell preparations of *Escherichia coli*. Studies of monocyclic and bicyclic interconvertible enzyme cascades, in situ. *J Biol Chem* 1981;256:13022-13029.
3. Legrain C, Vissers S, DuBois E, Legrain M, Wiame J-M. Regulation of glutamine synthetase from *Saccharomyces cerevisiae* by repression, inactivation and proteolysis. *Eur J Biochem* 1982;123:611-616.
4. Stadtman ER. The story of glutamine synthetase regulation. *J Biol Chem* 2001;276(48): 44357-44364.
5. Kresge N, Simoni RD, Hill RL. Fatty Acid Synthesis and Glutamine Synthetase: the Work of Earl Stadtman. *J Biol Chem* 2005;280(26):e23-e25.

wrong, then it destroys your thinking, and it destroys all the people around you, because now you've lost your compass. The compass is to be right at any cost, or throw it all out and not publish it. You don't want to publish something that's wrong, because if you go down this road, and you keep going down this wrong road, and you keep apologizing for it, you will lose your scientific reputation. If you're doing something that's risky, like trying to develop drugs for Alzheimer's and Parkinson's disease, then you have an unbelievable mess, and you can't get out of it. It's just a quagmire, and then you sink and it's like quicksand. You have no way out. So I learned from him. I watched him. I watched what he did. I read his papers. I understood how much work he went to. If there were seven ways that he could find to ask whether the discovery he made was real or just bogus, he'd go and get whatever was needed in the way of reagents and tools to look at all seven possibilities.

Here he was looking at proteins. The scrapie agent turned out to be a protein. I needed to isolate the scrapie agent, so I knew what I was working on. He had this constant refrain that he would talk about: how dirty enzymes, meaning impure enzymes, meaning all these other proteins, gave dirty data. His push, his mantra, was "You've got to purify what you're looking at so that you don't have all of these artifacts."

So I had all the right training and I had the right skills to do this scrapie problem. It was like a primer. I had all this background in protein purification and it turned out that I was studying a protein, albeit a difficult assay system, but it was perfect[ly suited to me]. That's all luck. That's total luck. It has nothing to do with anything that I ordained. It's just that I got interested in this problem, because I was becoming a neurologist. I was interested in the clinical nervous system. If you can't be interested in the clinical nervous system, there's something wrong with you. A human has got the best nervous system to study, by far. There's nothing else close. So if you don't have an opportunity to study the human nervous system... The only people who can study it are neurologists. Shrinks have a little hope...

DL: [laughter]

SP: ...but not much. Not much. Vague and fuzzy.

DL: That's an oral history point right there.

SP: Yes, well, it's true. It's absolutely true.

So this is all just wonderful luck. I get interested in the brain. I see the kidney as repetitious, because it just spits out urine. I look at the liver and it just detoxifies mercury and other things, not doing a very good job sometimes. And say to myself, "The brain is where it's at."

When I was at the NIH—I had just come³⁴—that was the first meeting of the Society for Neuroscience. It was created then.³⁵ A whole bunch of people who were neuroscientists got together and created this society, which now is enormous. It dwarfs neurology. That just grew right in front of my eyes. I never went to one of the meetings.

LK: [chuckles]

SP: It was the funniest thing, because when I would go to these neurology—they're all alike—interviews, residency interviews, what do they do? They put you in their library and you sit in this library. If you stand there and you look at the titles of these books, you understand that you know nothing about the nervous system. If you're going to become a neurobiologist, a neuroscientist, you damn well better know a lot about the nervous system.

What's clear is that if you go and you study action potential[s] or something... I never liked electricity. There's two things I really dislike. I dislike electricity, because it's all about these little spikes, and they fire, and how many of these spikes fire, and when they fire, and where they go. I just don't relate to that, because I want numbers. I want chemical structures. So that's one side of it.

Then the other side is that if you study a phenomenon in cats, well, whatever you're studying is much more interesting when it's played out in a human, but you can't ever study a human unless you're a physician. You never can stand there and ponder what the hell is going on. You can never stand there and say, "You know..." This was a revelation that only neurologists have. They're the *only* people on earth, who when they work up a patient... He [i.e., DL] is going to relate to this completely. Now, you [as a neurologist] say to yourself, "I don't know the diagnosis. The only thing I can do is wait, and I'll see what comes out of all of this. Whether it's six months or three years, I've got to follow the patient. The disease will declare itself." That's unique to neurology. I thought—God! This is great! What a puzzle that this is acceptable! This is not acceptable when you have a hematologic problem, [or] when you have a urine problem. Between the nephrologists and the urologists, you've got to come to some conclusion about what's happening with the urine and [similarly] the hematologists and the oncologists have to work together and they figure it out [if there is a hematologic problem]. They don't sit around and say, "Well, I'm waiting to declare. We'll see what happens." They've got to come up with a diagnosis, but in neurology, we don't always get a diagnosis right away.

³⁴ From 1969 to 1972, Prusiner was a Research Associate in the Laboratory of Biochemistry (Section on Enzymes) at the National Heart and Lung Institute, National Institutes of Health, Bethesda, Maryland. In this capacity he was also appointed as a Lt. Commander in the U.S. Public Health Service.

³⁵ The Society for Neuroscience was founded in 1969.

Anyway, it all unfolded in a perfect way. I had the right training and background. I had the right nose. That's all I contributed. I just said, "I want to go do neurology. This is the place." So I would sit in these libraries and I would say, "I don't know what's in these libraries, in these books, because I don't have any training. I *need* to know this." I can get two things out of neurology at the same time: I can get the normal nervous system, and I can get the *abnormal* nervous system. I can know about *both*. If I go and study neuroanatomy or functional neuroanatomy, I'll only know about the normal nervous system. If I spend my time on rats, and I want to do electrical recordings—which I really dislike—then what am I going to learn? I'm going to learn about the normal nervous system in the rats before some experiment is carried out on the rat, and I'm going to gain something, but I'm not going to have any sense of what the diseases are.

I'd already spent four years in medical school. Then, I'd spent a year being an intern—which was really the most horrible experience I ever had, because I was on for thirty-six hours every other night, and then I was off for twelve hours, or eight hours usually. I didn't like that. That was really unpleasant. Everybody said, "We know you're throwing your black bag over the railing of the Golden Gate Bridge when you finish."

[laughter]

SP: I never did. I still have this thing, but I haven't taken it off of this really high shelf in my office for *years*.

[short interchange regarding interview logistics, and pending switch to interview directed by DL]

LK: Moving to your residency at UCSF [University of California, San Francisco] and talking a little bit about luck, you had the patient with Creutzfeldt-Jakob [disease], which was critical to shaping your interest in prion work. When you set out to explore that problem in terms of funding, one of the issues people were raising with you was that you didn't have the experience in that area.

SP: Yes.

LK: What strikes me about the way you were able to fund [your research] going forward—it happened at several critical moments—is that you found private philanthropy to support your research. I wondered if you had any commentary on I guess the way that typical funding structures are looking for particular attributes of the people they fund versus private philanthropy. Do you think private philanthropy is more willing to invest in a project that to the insider seems unlikely, but the outsider sees the opportunity in it? Is there an insider/outsider perspective on that, I suppose?

SP: Oh. There is nothing I can say that's not going to get me in trouble.

LK: [laughter] I can also change the question.

SP: Edit it?

LK: Yes—or ask a different question if you don't want to answer it.

SP: I don't want to get into this, because it gets really complicated.

LK: Okay.

SP: There's no one answer to the whole thing. It's about relationships with people and about getting to know them, being able to talk to them in ways they can understand what you're trying to do. You just have to talk to them in a way that they can understand. Then you have to let the cards fall, because most of the time it's not going to work, but occasionally you're going to meet somebody who really wants to do something about what you want to work on and help you, and it's fantastic. The United States is... There's no other place on the planet where this work could have been done. It could not have been done in Europe.

LK: Because there wasn't the private funding to do something risky?

SP: Yes—well, and the fact that the NIH, already in the 1970s, was huge compared to anything on the rest of the planet. Biomedical research was growing. There was a lot of excitement, and there weren't so many people trained. It's the U.S. It's where these incredible opportunities were made possible by this incredible country we live in. We're so lucky. There's nowhere else this could have been done. They tried in Britain, but they never really got very far.

LK: Right, right.

DL: Why do you think that was?

SP: There are several possibilities, right?

DL: I have some, too, yes.

SP: One is that they're so damn stupid in Britain. These are the same people that voted in Brexit,³⁶ but then we have Trump...

SP and LK: [chuckles]

SP: ...so that's one possibility.

³⁶ Brexit is the popular term for the prospective withdrawal of the United Kingdom (UK) from the European Union (EU). In a referendum on June 23, 2016, the UK electorate voted to leave the EU.

The second one is that the Queen always inhibited the research. [chuckles] I don't know if that's true.

SP and LK: [chuckles]

SP: The third one is that they just had a lot of difficulty. Each investigator had his or her own prejudice. These prejudices, they really didn't know... None of these people were equipped with what I was equipped with, which was that sense of, "Okay, I've got to purify this substance and figure out what it is, because all these theories, or all these hypotheses, mean nothing unless I systematically go about this." Not one of these people did that. They didn't have a clue how to do it. They didn't know how to think about it. I don't know... There are a lot of very biased people. The social structure of a country like Britain with all of these lords, these peerages, these hereditary peers, or just the public peers, they've tried to break this down, but it's still rampant. All these people with these hereditary peerages have this money that's been in their pockets for centuries. Of course, their whole world is preserving their estates so they can pass it on. It's all pretty crazy.

DL: What do you think about the issue of being stuck in a paradigm that forces a certain viewpoint and puts blinders on things, and then the other issue of using a bio-assay system that has such a long incubation period that you can't get an experiment done in a week or a month. It will take years to get one experiment done. Don't you think those were factors that contributed to the slow progress of scrapie research?

SP: Yes. Oh, absolutely! There's no question. They thought about incubation times, which is where I flipped the problem over, but they didn't *use* them. They wanted to use these titrations. There was something about the slowness and the excuse of having all this slowness that some of these people thought made them very special.

DL: Right. Perhaps, reading documents on both sides, they had this framework, and then this young fellow comes along with a different framework threatening their whole schema. I think some of the reactions that were produced kind of threatened people trying to protect their own turf.³⁷

³⁷ In his Nobel Lecture in 1997, Prusiner wrote, "The discovery of prions and their eventual acceptance by the scientific community of scholars represents a triumph of the scientific process over prejudice" (Prusiner, 1997, 1998).

See:

1. Prusiner SB. Prions. Nobel Lecture, December 8, 1997. In: Jörnvall H (ed.). *Nobel Lectures, Physiology or Medicine 1996-2000*. Singapore: World Scientific Publishing Co., 2003:74-129.

SP: Absolutely! I couldn't agree with you more. I think you are absolutely right. They did not want the world to change. If the problem was solved, they wanted everybody to cross the finish line simultaneously. This was a very important issue for them. In the beginning, I didn't really care about the finish line. I just wanted to study a problem and be absorbed by it. But after it became pretty clear that what I was thinking had been played out over and over and over again, because I did all of this very careful science and I tried to overthrow my results and show that I had misinterpreted the results and I couldn't do that. Then I started to get a little annoyed about the idea that we were all going to cross the finish line at the same time, when I'd done the work and they hadn't done any of it, or they had done so little of it that this was becoming ridiculous.

I never wrote that down [in my memoir, *Madness and Memory* (2014)], because it's pretty horrible to say all these things. You can do what you want with it.

SP and LK: [chuckles]

DL: Well I think those are important issues that really have to be discussed.

SP: Yes, they are. They are. Yes, they are important issues. They're very important issues. I do say that. I put in a whole chapter in this book [*Madness and Memory* (2014)] about Charles Weissmann,³⁸ because Charles Weissmann was my friend and I felt violated by him. I felt that what he did to me was not out of friendship. He's since written me letters saying, "You know, Stan, one thing I regret is what I did with you." I can't answer that. There's no way to answer that. There's nothing that I can say that is gentle or reasonable. I can't sit down and apologize for *me* recognizing what he's doing to me. That chapter got edited and re-edited. The bile got removed by non-professional editors, and then editors, and then lawyers. [chuckles]

DL: Is that right?

https://www.nobelprize.org/nobel_prizes/medicine/laureates/1997/prusiner-lecture.pdf
[Accessed May 10, 2017]

2. Prusiner SB. Prions. Nobel Lecture. Proc Natl Acad Sci USA 1998;95:13363-83.

³⁸Charles Weissmann, M.D., Ph.D. (1931-) is a Hungarian-born Swiss molecular biologist, who is known for the first cloning and expression of interferon. Weissmann was director of the Institute for Molecular Biology in Zurich, President of the Roche Research Foundation, and co-founder of Biogen, a biotech company in Geneva.

See:

Prusiner SB. What's in a shape? In: *Madness and Memory: The Discovery of Prions—A New Biological Principle of Disease*. Yale University Press, 2014:170-183.

SP: Yes.

DL: Interesting.

SP: A lot of people weighed in on that chapter. The proof that we did it about right is that he didn't sue us. He's sued people in the past. He's a very sophisticated businessman.

DL: Those issues, those contentious issues, difficult as they are, I think probably come with something that's very novel, where the stakes are very high.

SP: Yes, I agree with you. I think that's absolutely right.

This has been so new and the breadth of this discovery keeps growing. This keeps getting played out over and over again where people start to see: "Oh, my god! *This* is prions? More of this *crap* from Stan Prusiner. We've had enough of him already." It's clear that Alzheimer's and Parkinson's disease are prion diseases and that the conformations of these proteins are changing, that [an] altered conformation is increasing. The [abnormal conformation of the] protein becomes stable and it causes neuro-degeneration as it accumulates. They are *so* resistant to this; it's unbelievable! They did *not* want this to happen and they're trying to prevent it by not calling it a prion. They describe everything about it.

I can give you this, if you remind me, in June... I have now two books that I will send you [i.e., to DL]. It's a thousand pages. The first is about 300 pages [sic]. It's called *Prion Biology*.³⁹ The second one is called *Prion Diseases*⁴⁰ and it's 600 pages. It's published by Cold Spring Harbor Press. So it *will* be published.

DL: Good!

SP: This is sixty chapters by lots of people.

DL: I look forward to it.

SP: There's two introductions. This topic is played out now in more detail.

³⁹ Prusiner SB (Ed.). *Prion Biology*. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press, 2017. 456 pages.

⁴⁰ Prusiner SB (Ed.). *Prion Diseases* (Cold Spring Harbor Perspectives in Medicine). Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press, 2017. 677 pages

DL: I've thought about this whole problem within the kind of Kuhnian framework of scientific revolutions. If you read Thomas Kuhn,⁴¹ when people are working in the

⁴¹ American physicist, historian, and philosopher of science Thomas Samuel Kuhn (1922-1996) was noted particularly for his landmark book, *The Structure of Scientific Revolutions* (1962, with subsequent editions in 1970, 1996, and 2012). In this work, Kuhn challenged the prevailing view that science progresses “by the accumulation of individual discoveries and inventions,” and instead argued for an episodic or fits-and-starts model in which periods of conceptual continuity (i.e., “normal science”) were interrupted by irregular periods of revolutionary science (i.e., “revolutions”) that “necessitated the [scientific] community’s rejection of one time-honored scientific theory in favor of another incompatible with it” (Kuhn 1970, p. 2). Kuhn believed that normal science was generally a “mopping-up operation” or enterprise that simply attempts “to force nature into the preformed and relatively inflexible box that the paradigm supplies” (Kuhn 1970, p. 24). Kuhn’s concepts of scientific progress in general thus had parallels with evolutionary theories promoting punctuated equilibrium over gradualism, and geological theories that favored catastrophism over uniformitarianism (gradualism). Work within an existing “paradigm”—an accepted scientific model or framework—is “sufficiently unprecedented to attract an enduring group of adherents away from competing modes of scientific activity” and is “sufficiently open-ended to leave all sorts of problems for the refined group of practitioners to resolve” (Kuhn 1970, p. 10). Paradigms gain status and are considered successful if they are better able to solve pressing scientific problems than their competitors (Kuhn 1970, p. 23). Inconsistencies and anomalies are frequently ignored or attributed to experimental error, and less commonly are considered as puzzles to be solved within the existing paradigm. When scientists are finally confronted by anomalies that cannot be dismissed, “They will devise numerous articulations and ad hoc modifications of their theory in order to eliminate any apparent conflict” (Kuhn 1970, p. 78). When “persistent failure to solve a noteworthy puzzle has given rise to a crisis,” paradigm testing can begin, but “only after the sense of crisis has evoked an alternate candidate for paradigm” (Kuhn 1970, p. 145). If the rival paradigm successfully competes for the allegiance of the scientific community, there is a “paradigm shift” and a period of “normal science” resumes within the new paradigm.

Prusiner too has referenced Kuhn’s ideas, as he did in his biographical essay after winning the Nobel Prize in Physiology or Medicine in 1997: “While it is quite reasonable for scientists to be skeptical of new ideas that do not fit within the accepted realm of scientific knowledge, the best science often emerges from situations where results carefully obtained do not fit within the accepted paradigms.” Prusiner again used Kuhnian concepts to describe his own work in his memoir, *Madness and Memory* (2014): “our discoveries would create a new paradigm of the human prion diseases that represented a major leap forward” (Prusiner 2014, p. 153). Prusiner had been introduced to Kuhn’s book, *The Structure of Scientific Revolutions*, by one his post docs, David Bolton, Ph.D., around 1981 (Prusiner, 2014, p. 100).

standard paradigm of a time, and then a new paradigm is thrust into that group of scientists doing what he calls “normal science,” their reaction is bitter. It becomes louder and louder and is often vituperative, you know, very vocal, very personal at times.

SP: Yes.

DL: And what’s interesting to me is that the skeptics, they don’t go away by changing their minds. They go away by dying.⁴²

See:

1. Kuhn TS. *The Structure of Scientific Revolutions*. Second edition. Chicago: University of Chicago Press, 1970.
2. Kuhn TS. Second thoughts on paradigms. In: *The Essential Tension: Selected Studies in Scientific Tradition and Change*. Chicago: University of Chicago Press, 1977:293-319.
3. Hoyningen-Huene P. *Reconstructing Scientific Revolutions: Thomas S. Kuhn’s Philosophy of Science*. Translated by Alexander T. Levine with a forward by Thomas S. Kuhn. Chicago: University of Chicago Press, 1993.
4. Margolis H. *Paradigms and Barriers: How Habits of Mind Govern Scientific Beliefs*. Chicago: University of Chicago Press, 1993.
5. Prusiner SB. Stanley B. Prusiner – Biographical. http://www.nobelprize.org/nobel_prizes/medicine/laureates/1997/prusiner-bio.html [Accessed 11-24-16, and 12-21-17]
From: Prusiner SB. Stanley B. Prusiner – Biographical. In: Frängsmyr T (Ed). *Les Prix Nobel en 1997. The Nobel Prizes 1997*. Stockholm: Nobel Foundation, 1998.
6. Prusiner SB. *Madness and Memory: The Discovery of Prions—A New Biological Principle of Disease*. Yale University Press, 2014.

⁴² As Kuhn wrote:

When in the development of a ... science, an individual or group first produces a synthesis able to attract most of the next generation’s practitioners, the older schools gradually disappear. In part their disappearance is caused by their members’ conversion to the new paradigm. But there are always some men who cling to one or another of the older views, and they are simply read out of the profession, which thereafter ignores their work. (Kuhn, 1970, pp. 18-19)

Worse,

No part of the aim of normal science is to call forth new sorts of phenomena; indeed those that will not fit the box are often not seen at all. Nor do scientists normally aim to invent new theories, and they are often intolerant of those invented by others. (Kuhn, 1970, p. 25)

SP: Yes, that's Max Planck.⁴³

See:

1. Kuhn TS. *The Structure of Scientific Revolutions*. Second edition. Chicago: University of Chicago Press, 1970:18-19, 25.
- 2, Barber B. Resistance by scientists to scientific discovery. *Science* 1961;134:596-602.

⁴³ Max Karl Ernst Ludwig Planck, Ph.D., F.R.S. (1858-1947) was a German theoretical physicist, who is regarded as the father of quantum theory, and who was awarded the Nobel Prize in Physics in 1918 for "his discovery of energy quanta." As Plank wrote in his autobiography: "A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it." This idea has been dubbed "Planck's principle."

Kuhn accepted Plank's principle as true, at least for many cases in which there is a clear paradigm shift, and cited British naturalist Charles Darwin (1809-1882), who wrote at the end of his *Origin of Species* (1859) a prescient version of this principle:

Although I am fully convinced of the truth of the views given in this volume..., I by no means expect to convince experienced naturalists whose minds are stocked with a multitude of facts all viewed, during a long course of years, from a point of view directly opposite to mine. ... [B]ut I look with confidence to the future,—to young and rising naturalists, who will be able to view both sides of the question with impartiality. (Darwin, 1859, p. 481)

Kuhn also mentioned other examples (albeit without any elaboration), including British natural philosopher Joseph Priestly, F.R.S. (1733-1804). From 1773-1786, Priestly's life was dominated by scientific investigations which culminated in his discovery of several "airs" (gases), including "nitrous air" (nitric oxide), "dephlogisticated nitrous air" (nitrous oxide), "alkaline air" (ammonia), "vitriolic acid air" (sulphur dioxide), and most famously what Priestley dubbed "dephlogisticated air" (oxygen); however, Priestley's rigid defense of his phlogiston theory and his rejection of the chemical revolution led by Antoine Lavoisier (1743-1794) eventually left Priestly isolated within the scientific community.

Lavoisier had predicted resistance to his ideas in the same sense as had Darwin. In his *Reflections on Phlogiston* he concluded:

I do not expect my ideas to be adopted all at once. The human mind gets creased into a way of seeing things. Those who have envisaged nature according to a certain point of view during much of their career, rise only with difficulty to new ideas. It is the passage of time, therefore, which much confirm or destroy the opinions I have

presented. Meanwhile, I observe with great satisfaction that the young people are beginning to study the science without prejudice, and also the mathematicians and physicists, who come to chemical truths with a fresh mind—all these no longer believe in phlogiston... (Lavoisier, quoted in Gillispie, 1960)

Notably, Lavoisier suggested it was only the older chemists who had worked in a prior chemical paradigm were particularly resistant to his new paradigm, whereas those working outside the prior chemical paradigm (e.g., mathematicians and physicists), *of whatever age*, were not similarly resistant.

The validity of Plank's principle has nevertheless been challenged, although these challenges to Plank's principle really either did not assess the restricted domain of true scientific revolutions or considered only the age of all scientists (rather than, say, their degree of entrenchment to a paradigm, by prior productivity and demonstrated leadership within the paradigm or some similar metric) (Blackmore, 1978; Hull et al, 1978; Diamond Jr., 1980; Azoulay et al, 2015/2016). Plank's principle addresses opponents to a new idea as unwilling to change, and those opponents eventually having to pass out of the picture by aging and then dying, but this has sometimes been interpreted simplistically and incorrectly as "older scientists are less willing to accept new ideas than young individuals." The latter idea (ignoring for the moment its correctness) apparently fit more with the beliefs of English biologist Thomas Henry Huxley (1825-1895), "Darwin's bulldog," who "had long declared that that men of science ought to be strangled [at sixty], lest age should harden them against the reception of new truths, and make them into clogs upon progress, the worse, in proportion to the influence they had deservedly won."

If this older-scientists-are-more-resistant-to-new-ideas reformulation is nevertheless considered, then age explains only a small part of the variation in acceptance, as might be expected (Hull et al, 1978). It is by no means a universal circumstance that older scientists are unwilling to accept new theories or ideas that are contrary to ones they previously held and championed; however, scientists of whatever age who have demonstrated a strong commitment to one paradigm by their leadership or involvement in that paradigm probably are more resistant to a revolutionary change—they have a greater degree of investment. This is really just a form of commitment bias (a tendency to be consistent with what we have already done or said in the past, particularly if this is public). In fact, as is well documented in the psychological literature on decision-making, people frequently *escalate* their commitment to threatened or failing endeavors (e.g., Molden and Hui, 2010).

See:

1. Plank M. *Scientific Autobiography and Other Papers*. Translated by Frank Gaynor. New York: Philosophical Library, 1949:33-34.

DL: Yes, well, exactly.

LK: [chuckles]

DL: These things play out time and again and I think if you walk through the prion story, it has that flavor to me.

SP: Yes. It's more than the flavor. *It is* the story.

DL: I think so.

SP: Yes, it's the same thing. It's over and over again.

DL: There are still some rather vocal skeptics that have plagued you throughout much of your career.⁴⁴

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2. Kuhn TS. *The Structure of Scientific Revolutions*. Second edition. Chicago: University of Chicago Press, 1970:151.
 3. Darwin C. *On the Origin of Species by Means of Natural Selection, or the Preservation of Favoured Races in the Struggle for Life*. London: John Murray, 1859:481.
 4. Lavoisier AL. In: Gillispie C (Ed.). *The Edge of Objectivity*. Princeton, NJ: Princeton University Press, 1960:232.
 5. Huxley L (Ed.). *Life and Letters of Thomas Henry Huxley*, Volume 2. New York and London: D. Appleton and Co., 1913: 117.
 6. Fitzgerald J. Does science advance one funeral at a time? National Bureau of Economic Research. NBER Digest OnLine, 2016(March). <http://www.nber.org/digest/mar16/w21788.html> [Accessed 12-9-17]
 7. Azoulay P, Fons-Rosen C, Graff Zivin JS. Does science advance one funeral at a time? NBER Working Paper No. 21788. National Bureau of Economic Research, December 2015, revised October 2016. <http://www.nber.org/papers/w21788.pdf> [Accessed 12-9-17]
 8. Blackmore JT. Is Planck's 'principle' true? *Br J Phil Sci* 1978;29(4):347-349.
 9. Hull DL, Tessner PD, Diamond AM. Plank's principle: Do younger scientists accept new scientific ideas with greater alacrity than older scientists? *Science* 1978;202:717-723.
 10. Diamond AM Jr. Age and the acceptance of cliometrics. *J Econ Hist* 1980;40(4):838-841.
 10. Molden DC, Hui CM. Promoting de-escalation of commitment: a regulatory-focus perspective on sunk costs. *Psychol Sci* 2010;22(1):8-12.

⁴⁴ As Prusiner wrote in his biographical essay following being awarded the Nobel Prize,

SP: Yes, yes.

DL: I don't see their opinions changing, because they keep writing the same kinds of things.

At times the press became involved since the media provided the naysayers with a means to vent their frustration at not being able to find the cherished nucleic acid that they were so sure must exist. Since the press was usually unable to understand the scientific arguments and they are usually keen to write about any controversy, the personal attacks of the naysayers at times became very vicious. While such scorn caused Sandy considerable distress, she and my two daughters, Helen and Leah, provided a loving and warm respite from the torrent of criticism that the prion hypothesis engendered. (Prusiner, 1997)

See:

1. Prusiner SB. Stanley B. Prusiner – Biographical. http://www.nobelprize.org/nobel_prizes/medicine/laureates/1997/prusiner-bio.html [Accessed 11-24-16, and 12-21-17]
From: Prusiner SB. Stanley B. Prusiner – Biographical. In: Frängsmyr T (Ed). *Les Prix Nobel en 1997. The Nobel Prizes 1997*. Stockholm: Nobel Foundation, 1998.
2. Corbyn Z. Stanley Prusiner: “A Nobel prize doesn't wipe skepticism away”: The neurologist whose discovery of the agent that causes CJD reveals why his finding was greeted with disbelief. *The Guardian*, May 24, 2014. <https://www.theguardian.com/science/2014/may/25/stanley-prusiner-neurologist-nobel-doesnt-wipe-scepticism-away> Accessed 1-4-17.
3. Liu PA. *Creating Controversy: Science Writers, Corporate Funders, and Non-expert Scientists in the Debate over Prions (1982-1997)* [Thesis]. Toronto: University of Toronto, 2011.
4. Kimberline RH. The scrapie agent: prions or virinos? *Nature* 1982;297:107.
5. Taubes G. The name of the game is fame: but is it science? *Discover* 1986;7(12):28-52.
6. Manuelidis L, Sklaviadis T, Manuelidis EE. Evidence suggesting that PrP is not the infectious agent in Creutzfeldt-Jakob disease. *EMBO J*. 1987 Feb;6(2):341-7.
7. Manuelidis L. A 25nm virion is the likely cause of transmissible spongiform encephalopathies. *J Cell Biochem*. 2007;100(4):897-915.
8. Manuelidis L. The force of prions. *Lancet* 2000;355:2083.
9. Couzin-Frankel J. The prion heretic [re: Laura Manuelidis]. *Science* 2011;332(6033):1024-1027.
10. Reeves C. An orthodox heresy: scientific rhetoric and the science of prions. *Science Communication* 2002;24:98.
11. Green E. Scraping the barrel of research. *The Independent*, April 26, 1997. <http://www.independent.co.uk/arts-entertainment/scraping-the-barrel-of-research-1269701.html> Accessed 1-4-17.

SP: Right. Yes.

DL: My guess is it's going to be the same story.

SP: I was sitting having lunch one day with Bob Gallo, the AIDS guy.⁴⁵ I said, "Bob...

⁴⁵ American biomedical researcher Robert Charles ("Bob") Gallo (1931-) is best known for his role in the discovery of the human immunodeficiency virus (HIV), and for his role in the development of the HIV blood test. Gallo received the Albert Lasker Award for basic biomedical research in 1982 for "his pioneering studies that led to the discovery of the first human RNA tumor virus [a retrovirus] and its association with certain leukemias and lymphomas." Gallo was awarded a second Lasker Award in 1986 for "determining that the retrovirus now known as HIV-1 is the cause of Acquired Immune Deficiency Syndrome (AIDS)."

While the laboratory of Luc Antoine Montagnier (1932-) at the Pasteur Institute was the first to isolate HIV in 1983, Gallo's group first demonstrated that this virus is the cause of AIDs (in 1984) and had also provided much of the fundamental science that made this discovery possible [including isolation of a T-cell growth factor (interleukin-2) and a technique for growing T cells in the laboratory]. The dispute between Gallo and Montagnier remained acrimonious until 1987, when, upon the intercession of French President François Mitterrand (1916-1996) and American President Ronald Reagan (1911-2004), Gallo and Montagnier finally agreed to share credit for the discovery of HIV, and the French and US governments agreed to split the proceeds from the patent for the HIV test. The controversy was rekindled and further complicated in 1990,

Unfortunately, in 1990, Gallo's scientific reputation was tainted by allegations that he had misappropriated a viral sample of what was later named human immunodeficiency virus from Montagnier's laboratory. This resulted in an investigation by the National Institutes of Health and Gallo was later in large measure cleared of these charges, although it was demonstrated that Gallo's virus had in fact come from Montagnier's lab (Chang et al, 1993).

Gallo and Montagnier later collaborated in writing a history of these events, presumably to lay out their complementary roles in the discovery of HIV and in the discovery that HIV causes AIDS in anticipation of a later shared Nobel Prize (Gallo and Montagnier, 2003). However, when a Nobel Prize was awarded for the discovery of HIV in 2008, Gallo was excluded. Gallo was gracious in accepting the news, but nevertheless acknowledged worrying "that it may give people the notion that I might have done something wrong" (Cohen and Enserink, 2008, p. 174). Montagnier noted that, "It was important to prove that HIV was the cause of AIDS, and Gallo had a very important role

DL: Nobel laureate himself [sic].

SP: No.

DL: No?

SP: Nooo. He didn't receive the Nobel Prize. They gave it to Montagnier,⁴⁶ meaning the Swedes, and two assistants [sic]. They excluded him [i.e., Gallo]. I talked to them recently, meaning the Nobel committee, about what they did. I excoriated them...

DL: Is that right?

SP: ...in a very gentle way.

Anyway, what he said to me was, "You know, I think the only time this is going to stop is just what's going to happen with AIDS. When there's a therapy and the disease is now going down, and down, and down, and the therapy is focused on HIV, then people who talk about mycobacteria and other things will disappear." And that's exactly what's happened.

I think that's what's going to happen with prions. The final death to these people is going to be therapies. But we don't have one prion disease therapy in humans. We've tried to do this in CJD [Creutzfeldt-Jakob disease] and we had good results in mice and in

in that. I'm very sorry for Robert Gallo [that he was not recognized with a Nobel Prize]" (Cohen and Enserink, 2008, p. 174).

See:

1. Chang S-Y, Bowman BH, Weiss JB, Garcia RE, White TJ. The origin of HIV-1 isolate HTLV-III_B. *Nature* 1993;363(6428):466-469.
2. Cohen J. HHS: Gallo guilty of misconduct. *Science* 1993;259:168-170.
3. Gallo R, Montagnier L. The discovery of HIV as the cause of AIDS. *N Engl J Med* 2003;349:2283-2285.
4. Cohen J, Enserink M. HIV, HPV researchers honored, but one scientist is left out. *Science* 2008;322:174-175.

⁴⁶ French virologist Luc Antoine Montagnier (1932-) was a joint recipient, with French virologist Françoise Barré-Sinoussi (1947-) and German virologist Harald zur Hausen (1936-), of the 2008 Nobel Prize in Physiology or Medicine. Half of the prize was awarded jointly to Montagnier and Barré-Sinoussi, who worked together at the Pasteur Institute, "for their discovery of human immunodeficiency virus." The other half of the prize was awarded to Hausen "for his discovery of human papilloma viruses causing cervical cancer."

transgenic mice that are expressing deer [prions]. This is chronic wasting disease. We published all of this. But we don't have a drug for CJD, and that's because, for fifty years, people have been trying to make cultured cells that produce the *human* PrP prion, Creutzfeldt-Jakob disease prions, and nobody has achieved that. Even though we have these wonderful animal models, we don't have the cultured cell. Without that, we can't do medium throughput screening, so we can find a drug that works in mice that are producing human prions or human-mouse prions. That would go to the FDA [Food and Drug Administration]. It would be approved like that. But we don't have the drug. So we constantly are looking. I have one young woman who spent eight years with me. She's got another year to go but this has gone nowhere. She started in Edinburgh. She worked there for five years. It's really a hard problem. But it's really important to say, "No, I haven't been able to do that. This is an unsolved piece." It's here and you don't sit there and say, "Well, I have something that might work. Let's just try to go to the FDA and give it to people." If you have anything at all that looks slightly okay in CJD patients they will approve it like that, because people all die in three or four months. That's really stupid, but this goes on all the time.

DL: Yes, for lots of diseases.

SP: Yes. Yes.

Why don't we conclude with you [i.e., LK], so I can take a break...?

LK: Okay, sure. So one last question?

SP: Yes, sure.

LK: In terms of you stepping outside of the normal science of the time, looking outside of the viral cause, looking outside of the genetic basis, a couple of things stood out to me, like what kind of set you apart from that traditional way of thinking: being kind of young at the time, and also the fact that you had a bit of a different background than a lot of the people who are already doing the research. I didn't know if you had any comments on what about your background helped you to think about the problem differently.

SP: Right. So, number one, I never trained in virology. That was a huge leg up. That's the first thing. Second, I never trained with any of the scrapie-ologists from Gajdusek,⁴⁷

⁴⁷ American pediatrician and medical researcher Daniel Carleton Gajdusek, M.D. (1923-2008) was a co-recipient of the Nobel Prize in Physiology or Medicine in 1976 for "discoveries concerning new mechanisms for the origin and dissemination of infectious diseases," particularly in regard to his work on kuru.

See:

to Dickinson⁴⁸ to Hunter⁴⁹ to Kimberlin,⁵⁰ all these people. I never had any lab experience with them.

DL: Do you think Gajdusek was a “scrapie-ologist,” really?

SP: He’s a nut.

DL: But was he a “scrapie-ologist”?

SP: Yes.

DL: Really?

SP: Well, they studied scrapie as well as kuru and CJD in the labs at the NIH.

DL: Okay. He wasn’t like Dickinson, though, with the big sheep experiments and things.

SP: Well, no. He was worse because they transmitted all these diseases. They inoculated apes and monkeys.

DL: Right. That they did.

SP: That’s even worse than the sheep—I don’t know if worse is a bad thing. It’s not terrible what they did. What they did at the time was all they could do. They could only look so far.

DL: That’s true.

Asher DM, Oldstone MBA. D. Carleton Gajdusek: 1923-2008. A biographical memoir. Washington, D.C.: National Academy of Sciences, 2013.

<http://www.nasonline.org/publications/biographical-memoirs/memoir-pdfs/gajdusek-d-carleton.pdf> [Accessed 9-29-17]

⁴⁸ British veterinary geneticist Alan G. Dickinson, Ph.D. (1930-2017) worked for the AFRC (Agricultural and Food Research Council) and MRC (Medical Research Council) Neuropathogenesis Unit, Edinburgh, United Kingdom. He found that a host gene affected susceptibility to scrapie, and that scrapie came in distinct strains with different incubation times, clinical symptoms, and patterns of brain damage.

⁴⁹ Nora Hunter, Ph.D., earned her Ph.D. in plant disease, but now works as a genetics researcher at the Neuropathogenesis Unit, Institute for Animal Health, Edinburgh, UK.

⁵⁰ Richard H. Kimberlin, O.B.E. (Order of the British Empire), Ph.D., a former director of the Neuropathogenesis Unit, Edinburgh, United Kingdom, and the former head of the Scrapie and Related Diseases Advisory Service (SARDAS), Edinburgh, UK.

SP: There was a wall there. They couldn't see out that door. They didn't have a clue.

DL: They were still working with the virus framework so ...

SP: Yes, absolutely.

DL: ... they struggled with this "slow virus" concept, which was actually a Swedish [sic] veterinarian...

SP: Right, Sigurdsson⁵¹...Icelandic.

DL: ...Sigurdsson in 1954, or something, who came up with that concept.⁵² There are, in fact, sheep slow viruses.⁵³

⁵¹ Icelandic veterinarian Björn Sigurðsson (1913–1959) was the first director of the Institute for Experimental Pathology, University of Iceland, Keldu, Iceland.

⁵² In 1954, Sigurdsson proposed the concept of "slow" viral infections, using the example of Rida, a chronic encephalitis of sheep. These "slow infections" were characterized by:

- (1) A very long initial period of latency lasting from several months to several years.
- (2) A rather protracted course after clinical signs have appeared usually ending in serious disease or death.
- (3) Limitation of the infection to a single host species and anatomical lesions in only a single organ or tissue system. (Sigurdsson, 1954, pp. 351-352)

Sigurdsson recognized these criteria as preliminary and particularly the latter criterion as possibly too restrictive, as he wrote: "These last statements may have to be modified as knowledge increases" (Sigurdsson, 1954, pp. 351-352). This concept of a "slow virus" infection was applied later to prion diseases, most prominently by Gajdusek and colleagues at the U.S. National Institutes of Health.

See also:

1. Sigurdsson B. Rida, a chronic encephalitis of sheep: With general remarks on infections which develop slowly and some of their special characteristics. *Br Veterinary J* 1954;110:341-354.
2. Pálsson PA. Dr. Björn Sigurdsson (1913-1959). A memorial tribute. *Ann N Y Acad Sci.* 1994;724:1-5.
3. Ingvarsson S. In memoriam Björn Sigurdsson born 100 years ago (editorial). *Icelandic Agricultural Sciences* 2013;26:2.

⁵³ Maedi-visna is a "slow virus" infection of sheep, which is invariably fatal. It affects multiple organs, but primarily the brain and lungs. The responsible agent, visna virus (also known as visna-maedi virus, maedi-visna virus, and ovine lentivirus) from the genus *Lentivirus* and subfamily *Orthoretrovirinae*, is a retrovirus. The disease of sheep

SP: Yes, there are. Exactly.

DL: So Gajdusek tried to plug everything into that framework and couldn't get out of it, really.⁵⁴

SP: Right. Then, he would just throw out terms. One day, he calls me up, and he says, "Can we meet at the airport?" I said, "Sure." So I drove down there. There he was. We were talking about what causes scrapie. He said, "It's a calcium ion." I said, "Carleton, there's no chance of that, but it doesn't really matter what you say. Just because you say it doesn't mean that it's real." He said, "Well, that's just not true. Whatever I think it is, that's what it is." I said, "Well, that's not science. That's just kind of babble." He'd get all annoyed. I said, "But, Carleton, it's true. People who are scientists do not change their mind every minute. They investigate. There is *no* evidence that calcium ions are the cause of scrapie. Not one experiment shows that to be true." That was typical.

So now where were...?

LK: Virology and not working with "scrapie-ologists."

caused by this retrovirus is known as visna when it produces encephalitis (as was commonly observed in Icelandic sheep), and maedi when it causes interstitial pneumonia or pneumonitis.

⁵⁴ See for example:

1. Gajdusek C, Gibbs CJ, Alpers M. Slow-acting virus implicated in kuru. *JAMA*. 1967;199(7):34.
2. Gajdusek DC. Slow-virus infections of the nervous system. *N Engl J Med*. 1967;276(7):392-400.
3. Gajdusek DC, Gibbs CJ Jr. Slow, latent and temperate virus infections of the central nervous system. *Res Publ Assoc Res Nerv Ment Dis*. 1968;44:254-80.
4. Gajdusek DC. Slow virus diseases of the central nervous system. *Am J Clin Pathol*. 1971;56(3):320-32.
5. Gajdusek DC. Spongiform virus encephalopathies. *J Clin Pathol Suppl (R Coll Pathol)*. 1972;6:78-83.
6. Gajdusek DC. Kuru and Creutzfeldt-Jakob disease. Experimental models of noninflammatory degenerative slow virus disease of the central nervous system. *Ann Clin Res*. 1973;5(5):254-61.
7. Gajdusek DC. Slow infections with unconventional viruses. *Harvey Lect*. 1978;72:283-353.
8. Gibbs CJ Jr, Gajdusek DC. Virus-induced subacute slow infections of the brain associated with a cerebellar-type ataxia. *Adv Neurol*. 1978;21:359-72.

SP: Right. So this was hugely important: (a) I wasn't a virologist, and (b) I wasn't a scrapie-ologist. Those were *huge* advantages that I had. I was trying to view this problem objectively. This was an unknown. When you're a chemistry student, there are whole classes that go for a year on unknowns. This is called analytical chemistry. You purify whatever substance you're interested in. You take it down to the most pure point, and then you try to determine the structure of it. Well, that's what I was trying to do, but it turned out that I couldn't do it quite the same way.

Arthur Kornberg,⁵⁵ who was a very famous biochemist, said to me, "Stan, you know, you just take this all the way down. You'll see whether there are any nucleotides, and, if there

⁵⁵ American biochemist Arthur Kornberg (1918-2007) won the Nobel Prize in Physiology or Medicine in 1959, together with Spanish-American physician and biochemist Severo Ochoa (1905-1993), "for their discovery of the mechanisms in the biological synthesis of ribonucleic acid and deoxyribonucleic acid." While working in Ochoa's laboratory from 1946 to 1947, Kornberg learned techniques of enzyme purification that he later applied to his work on how DNA is built up from nucleotides. In 1956, Kornberg isolated the first DNA polymerizing enzyme (DNA polymerase I) in the intestinal bacterium *E. coli*, and subsequently established that this enzyme catalyzes the production of new DNA strands, and showed how a single strand of DNA forms new strands of nucleotides. This elucidated important underlying functional aspects of the double helix structure of DNA that had been proposed by Francis Crick and James Watson. Kornberg wrote several monographs and memoirs, and even a book of children's verse—*Germ Stories* (2007)—in the style of Dr. Seuss (Theodore Geisel; 1904-1991). Kornberg was awarded the National Medal of Science in 1979.

The Germ Parade [From A. Kornberg. *Germ Stories*, 2007]

Hurry, hurry to the parade
Of the strangest creatures ever made.
No legs, no fins, no mouth, nor eyes,
Little beasties of the tiniest size.
Far too small for the eye to see—
"Just how small is this menagerie?"
Imagine, Zac, if you can,
A tiny dot, a grain of sand.
Break each grain into tinier ones still—
Into a thousand, if you will.
Into each minigrain (big enough),
Thousands of germs you can stuff,
With lots of room for every germ
To swim and tumble, turn and squirm...

are, then you'll know what they are." So then it was three or four years later, and I said, "Arthur, you know, this was not a good idea that you had." The problem is that when you start analyzing the water, the water has nucleotides, and they're all over. So that reductionism doesn't really work.

Nevertheless, this problem was made for me. I had all this protein chemistry experience. I had this fabulous mentor, Earl Stadtman, who, when he wanted to prove something, he did it seven ways, backwards, sideways, upside down. This was exactly what I needed, and all this protein chemistry that I learned at the NIH, instead of going into these tunnels in Vietnam, that was *huge*. That's what I needed! If this problem had turned out to be some..., I don't know, some very strange nucleic acid that had properties of proteins, I would have never got there, probably. Maybe I would have figured it out, but maybe I wouldn't have figured it out. I didn't have to do much of anything except take everything I learned at the NIH during this Vietnam period and do it again with scrapie. That's a simplified view. It's not exactly quite that simple, but there were many parallels to what I'm saying.

LK: It's interesting that you say it was a benefit to you in the thinking, but, in terms of like funding and having credibility among your peers, it worked against you.

SP: That's right.

LK: It also strikes me that there's so much discussion about interdisciplinary [collaborations] in research and medicine, which is what you brought to the table, but at the same time it worked against you.

SP: Yes.

LK: That's an interesting struggle.

SP: Yes. I think that's what happens.

See:

1. Kornberg A. *DNA Synthesis*. San Francisco: W. H. Freeman & Co., Ltd., 1974.
2. Kornberg A. *DNA Replication*. San Francisco: W. H. Freeman & Co., Ltd., 1982.
3. Kornberg A. *Genetic Chemistry and the Future of Medicine*. San Diego, CA : San Diego State University Press, 1988
4. Kornberg A. *For the Love of Enzymes: The Odyssey of a Biochemist*. Harvard University Press, Cambridge, MA, 1989.
5. Kornberg A. *The Golden Helix: Inside Biotech Ventures*. Sausalito, CA: University Science Books, 1995.
6. Kornberg A. *Germ Stories*. Sausalito, CA: University Science Books, 2007.

I put in the book⁵⁶ that introduction...the name of that guy, Sasson.⁵⁷ There were all these CCD [charge-coupled device] cameras that had been developed, and he was told by his boss to turn this into a photographic camera, meaning a digital camera, and make something like that from the CCD technology. It wasn't such a huge thing to do this, but he created this revolution, and he killed Kodak, because these people were so damn stupid. One CEO after another couldn't visualize what life would be like without photographic paper, without little slides in cardboard borders sitting in tray after tray after tray. He changed it all, but it was the Japanese that took it over and made a fortune off of it, and Kodak became a relic.

⁵⁶ Prusiner SB. *Madness and Memory: The Discovery of Prions—A New Biological Principle of Disease*. Yale University Press, 2014:ix-x.

⁵⁷ American electrical engineer Steven J. Sasson (1950-) is the inventor of the digital camera. Sasson began working for Eastman Kodak in 1973, and just two years later, at age 24, invented digital photography, including a mechanism to digitize and store the transient impulses from a charge coupled device (CCD) and a mechanism to play back the images on a television screen. According to Sasson, the executives at Kodak “were convinced that no one would ever want to look at their pictures on a television set.” The first digital camera was patented in 1978, but Sasson was not allowed to talk about it or demonstrate his device publicly. In 1989, Sasson and colleague Robert Hills created the first modern digital single-lens reflex camera, called the Ecam, but Kodak refused to sell the camera because it would erode the company’s film sales. According to Sasson, “Kodak didn’t really embrace any of it. That camera never saw the light of day.” When digital photography was nevertheless developed by other companies, the original patent earned billions for Kodak until it expired in the United States in 2007. Kodak did eventually market digital cameras, but by then the company was in serious financial trouble and was no longer a leader in photography: Eastman Kodak filed for bankruptcy in 2012. Kodak stopped making digital cameras, pocket video cameras, and digital picture frames; sold its photographic film, commercial scanners, and kiosk operations; and sold many of its patents. In 2013, the company emerged from bankruptcy after shedding its large legacy liabilities and selling off several businesses.

In 2009, President Barack Obama (1961-) awarded Sasson the National Medal of Technology and Innovation. The prototype digital camera Sasson invented in 1975 is now on display at the Smithsonian’s National Museum of American History.

See:

1. Estin J. Kodak’s first digital moment. *The New York Times*, August 12, 2015. https://lens.blogs.nytimes.com/2015/08/12/kodaks-first-digital-moment/?_r=0# Accessed 12-9-17.
2. De la Merced MJ. Eastman Kodak files for bankruptcy. *The New York Times*, January 19, 2012. <https://dealbook.nytimes.com/2012/01/19/eastman-kodak-files-for-bankruptcy/> Accessed 12-9-17.

LK: It's ten forty-five. We'll take a break and reconvene.

SP: Okay. Thank you for doing this.

[break in the interview]

DL: There are a few things I'd like to kind of cover as part of inclusiveness in this discussion. I think you must be the living neurologist with the most clinical experience with kuru of anyone. I think collectively you saw fifteen patients with kuru.

SP: Yes. But Michael Alpers⁵⁸ is alive. He's not a neurologist, but he's seen a lot of cases. He was alive when Gajdusek and Gibbs⁵⁹ were.

⁵⁸ Australian medical researcher Michael Philip Alpers, A.O., F.R.S. is the John Curtin distinguished Professor of International Health, at Curtin University, an Australian public research university based in Bentley and Perth, Western Australia. After graduating from medical school in 1961 Alpers became a medical officer for the Australian administration, and was stationed in Papua New Guinea. He developed a strong relationship with the Fore people, and subsequently met D. Carleton Gajdusek in 1962. Gajdusek and Alpers planned to collect autopsy specimens from kuru victims for transmission experiments to primates. Despite administrative opposition, Alpers managed to conduct limited autopsies of kuru victims in the villages, assisted by local people, including family members of the deceased. The insulated brain specimens of the kuru victims were transported by chartered aircraft the following morning and eventually flown to Gajdusek at the U.S. National Institutes of Health in Bethesda. In 1964, Alpers joined Gajdusek at the NIH where they spent the next 4 years conducting transmission experiments in chimpanzees. By 1966 they had demonstrated that kuru could be transmitted to chimpanzees by intracerebral inoculation. This resulted in the landmark papers in *Nature* in 1966 and in *Science* in 1967 with Gajdusek and C. Joseph ("Joe") Gibbs (1924-2001). Subsequent papers from this group demonstrated the transmission of Creutzfeldt-Jakob disease to chimpanzees in 1968 and 1969. Alpers' and Gajdusek's work in Papua New Guinea was the subject of a documentary film, *Kuru: The Science and the Sorcery* (2010).

See:

1. Gajdusek DC, Gibbs CJ, Alpers M. Experimental transmission of a Kuru-like syndrome to chimpanzees. *Nature*. 1966;209(5025):794-796.
2. Gajdusek DC, Gibbs CJ Jr, Alpers M. Transmission and passage of experimental "kuru" to chimpanzees. *Science*. 1967;155(3759):212-214.
3. Gibbs CJ Jr, Gajdusek DC, Asher DM, Alpers MP, Beck E, Daniel PM, Matthews WB. Creutzfeldt-Jakob disease (spongiform encephalopathy): transmission to the chimpanzee. *Science*. 1968;161(3839):388-389.

DL: Right, and he was part of the original paper [in 1966 demonstrating transmission of kuru to chimpanzees].

SP: Yes. And he did all the fieldwork. He's alive, so you can't pin that on me.

SP and LK: [laughter]

DL: Well, as a *neurologist*, I think it's fair.

SP: Yes, okay. There's another guy who's done a little bit named John Collins. I don't know how many patients he ever saw.

DL: Okay. At least when Zigas⁶⁰ and Gajdusek reported patients with kuru originally, in their clinical description, they misinterpreted the tremor as a manifestation of

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4. Beck E, Daniel PM, Matthews WB, Stevens DL, Alpers MP, Asher DM, Gajdusek DC, Gibbs CJ Jr. Creutzfeldt-Jakob disease. The neuropathology of a transmission experiment. *Brain*. 1969;92(4):699-716.
 2. Spark C. Michael Alpers (FRS), Kuru, and Papua New Guinea: The combined allure of problem, people, and place. *Health and History*. 2012;14(2):26-45.
 3. Chandler J. The man who linked kuru to cannibalism. *Cosmos* 2016
<https://cosmosmagazine.com/biology/solving-the-mystery-of-laughing-disease> Accessed 12-9-17.

Alpers subsequently authored two papers with Prusiner, one also including Gajdusek that reported kuru with extremely long incubation periods:

- 1: Prusiner SB, Cochran SP, Alpers MP. Transmission of scrapie in hamsters. *J Infect Dis*. 1985;152(5):971-978.
- 2: Prusiner SB, Gajdusek C, Alpers MP. Kuru with incubation periods exceeding two decades. *Ann Neurol*. 1982;12(1):1-9.

⁵⁹ Microbiologist Clarence Joseph ("Joe") Gibbs, Jr., Ph.D. (1924-2001) was chief of NINDS's Laboratory of Central Nervous System Studies.

See:

1. Johnson RT. Clarence Joseph Gibbs, Jr, 1924-2001. *Ann Neurol* 2001;50(4):556.
2. Garnett SE. Pioneering NINDS scientist Joe Gibbs dies. *NIH Record* 2001;8(6).
https://nihrecord.nih.gov/newsletters/03_20_2001/obits.htm Accessed 12-11-17.

⁶⁰ Estonian-born physician Vincent ("Vin"), M.D. (1920-1983) moved to Australia in 1948, and became an Australian medical officer, who was stationed in Papua New Guinea during the 1950s. Zigas was one of the first Western medical officials to note the uniqueness of *kuru* (meaning "to shiver") and begin to investigate it.

When Gajdusek arrived in Papua New Guinea in 1957, he barraged Zigas with questions concerning kuru. Zigas introduced Gajdusek to the Fore people (pronounced “*For-ay*”), and the two planned the initial investigations of the disorder.

The inconsistency of the original description of kuru by Gajdusek and Zigas is clear in their 1957 report in the *New England Journal of Medicine*: “Both involuntary tremor and ataxia increase, the tremors assuming a character typical of paralysis agitans, with exaggeration during voluntary motor activity or fatigue, subsidence during rest and disappearance during sleep.” As they report, the tremor is evident with action and subsides at rest, exactly the opposite of a parkinsonian tremor.

Although Zigas was an important contributor to the early studies of kuru, Gajdusek chose later to denigrate his involvement. In the foreword to Zigas’ posthumously published and certainly idiosyncratic memoir, *Laughing Death: The Untold Story of Kuru* (1990), Gajdusek wrote:

I disagree with Vin on many of the ‘facts’ and many of his judgments—we always did! ... I cannot quibble with historical fiction—Vin has taken the liberties of imaginative creative writing and projects his ‘truths’ with the ambiguities of poetry. ... My uncertain verdict is that he has written the most remarkable work in existence of abstract expressionistic ironical parody, his own style of biography. (Gajdusek, in Zigas, 1990)

See:

1. Gajdusek DC, Zigas V. Degenerative disease of the central nervous system in New Guinea; the endemic occurrence of kuru in the native population. *N Engl J Med*. 1957;257(20):974-978.
2. Zigas V, Gajdusek DC. Kuru: clinical study of a new syndrome resembling paralysis agitans in natives of the Eastern Highlands of Australian New Guinea. *Med J Aust*. 1957;44(21):745-754.
3. Gajdusek DC, Zigas V. Untersuchungen über die Pathogenese von Kuru; eine klinische, pathologische und epidemiologische Untersuchung einer chronischen, progressiven, degenerativen und unter den Eingeborenen der Eastern Highlands von Neu Guinea epidemische Ausmasse erreichenden Erkrankung des Zentralnervensystems. [Studies on the pathogenesis of kuru; a clinical, pathological and epidemiological study of a chronic, progressive, degenerative disease of the central nervous system achieving epidemic proportions among the natives of the Eastern Highlands of New Guinea]. *Klin Wochenschr*. 1958;36(10):445-459.
4. Gajdusek DC, Zigas V. Kuru; clinical, pathological and epidemiological study of an acute progressive degenerative disease of the central nervous system among natives of the Eastern Highlands of New Guinea. *Am J Med*. 1959;26(3):442-469.
5. Klatzo I, Gajdusek DC, Zigas V. Pathology of kuru. *Lab Invest*. 1959;8(4):799-847.

Parkinsonism. It wasn't until the New Zealand neurologist Richard Hornabrook⁶¹ saw the patients that he correctly interpreted the intention tremor as a manifestation of cerebellar dysfunction.

6. Wilson K, Zigas V, Gajdusek DC. New tremor syndromes occurring sporadically in natives of the Wabag-Laiagam-Kundep region of the Western Highlands of Australian New Guinea. *Lancet*. 1959;2(7105):699-702.
7. Gajdusek DC, Zigas V. Studies on kuru. I. The ethnologic setting of kuru. *Am J Trop Med Hyg*. 1961;10:80-91.
8. Curtain CC, Gajdusek DC, Zigas V. Studies on kuru. II. Serum proteins in natives from the kuru region of New Guinea. *Am J Trop Med Hyg*. 1961;10:92-109.
9. Gajdusek DC, Zigas V, Baker J. Studies on kuru. III. Patterns of kuru incidence: demographic and geographic epidemiological analysis. *Am J Trop Med Hyg*. 1961;10:599-627.
10. Neumann MA, Gajdusek DC, Zigas V. neuropathologic findings in exotic neurologic disorders among natives of the highlands of New Guinea. *J Neuropathol Exp Neurol*. 1964;23:486-507.
11. Zigas V. Kuru in New Guinea: discovery and epidemiology. *Am J Trop Med Hyg*. 1970;19(1):130-132.
12. Zigas V, Van Delden J, Rodrigue R. New Guinea: studies relating the medical and behavioral sciences. II. Kuru: a study of attitudes toward pain, disease and death among the Fore people. *Soc Sci Med*. 1972;6(6):689-695.
13. Zigas V. Kuru: a critical review. *Med J Aust*. 1975;2(12):483-486.
14. Zigas V. *Auscultation of Two Worlds*. New York: Vantage Press, 1978.
15. Zigas V. *Laughing Death*. Clifton, NJ: The Humana Press, 1990.

⁶¹ New Zealand neurologist Richard W. ("Dick") Hornabrook, M.D. (1925-2012) was the first neurologist to examine patients with kuru, and was among the first to recognize the evidence of cerebellar involvement based on the clinical features, which he presented in a classic paper in *Brain* in 1968, based on the study of 214 cases.

Hornabrook's neurological training was at the National Hospital for Nervous Diseases, Queen Square, London (1955-1959) and he was subsequently an Associate Professor of Neurology at Cornell University and Assistant Director of Neurosurgical and Neurological Services at Bellevue Hospital in New York. Hornabrook later became the Neurologist-in-charge of the Kuru Research Centre in New Guinea from 1964 to 1965, and subsequently was the Director of the Institute of Medical Research in New Guinea from 1968 to 1975.

In Hornabrook's paper in *Brain* in 1968, he acknowledged that as early as 1958-1959 Donald A. Simpson, Harry Lander (1928-1998), and Professor (later Sir) Hugh Norrie Robson (1917-1977) of the Department of Medicine at the University of Adelaide had suggested, based on observations in 27 cases, that many of the neurological features of kuru were consistent with a disorder of the cerebellum. Simpson had in fact just

completed his training in neurosurgery in 1958 before visiting New Guinea from 1958 to 1959 as a member of the University of Adelaide group investigating kuru. Consequently, Simpson was well versed in clinical neuroscience, so it is perhaps not surprising that his assessment of the clinical features of kuru was fundamentally correct, whereas those of Gajdusek and Zigas were erroneous. Unfortunately, the paper by Simpson and colleagues was overlooked as it was published in an obscure journal, the *Australasian Annals of Medicine*.

In his paper in *Brain*, Hornabrook noted various signs of cerebellar disease in patients with kuru:

The only abnormality found early in a case of kuru was usually disorder to [sic, of] heel-to-toe walking. ... The patients behaved as if they were attempting to walk on a tight-rope; the arms were held out from the side and it was obviously a conscious effort to maintain balance. ... The finger-to-nose test revealed a fine wavering at the termination of the movement, which later developed into a conspicuous intention tremor. An intention tremor also appeared in the course of the heel-to-shin test. The ability to carry out rapid repetitive movements of the hands or feet [i.e., dydiadokokinesis] was not usually disturbed until late in the course of the illness. Hypotonia was often present in advanced cases. (Hornabrook, 1968, p. 62)

By 1969, in a letter to *Lancet*, Hornabrook and Field noted:

In kuru all observers are [now] agreed that the earliest symptoms and signs are referable to cerebellar dysfunction. There is good experimental evidence that both postural (static) and ataxic ("intention") tremor can result from cerebellar lesions. Nevertheless, full-blown lesions certainly occur in the basal ganglia in kuru, but do not fully manifest themselves, clinically. It is suggested that the neural deficit, which would ordinarily express itself in parkinsonian signs, is unable to do so when cerebellar function (especially of the anterior vermal area) is eliminated. If signs of striatal rigidity and tremor are encountered these may result from retention of enough cerebellar activity for signs of parkinsonism to come through. The signs in early kuru are entirely cerebellar, and whether or not basal ganglion defects are added to the picture depends upon whether morphological changes extend to this area before or after cerebellar functioning is profoundly interfered with. (Hornabrook and Field, 1969, p. 576)

See:

1. Hornabrook RW. Kuru. *Proc Aust Assoc Neurol*. 1968;5(2):317-319.
2. Hornabrook RW. Kuru—a subacute cerebellar degeneration. The natural history and clinical features. *Brain*. 1968;91(1):53-74.
3. Hornabrook RW, Field EJ. Clinical and pathological findings in kuru. *Lancet*. 1969;1(7594):576.

SP: Right. Yes.

DL: So what was your experience with kuru?

SP: Well, this has all been really well described at that point because Hornabrook and Richard Johnson had done a lot together,⁶² but it was mainly Hornabrook. Hornabrook was a good neurologist. I don't know that he was an outstanding neurologist, but he was a good neurologist. He could go through all these signs, and he understood what was what. So there were no mysteries for me to solve when I went and looked at the patients. Yes, it was new, because I had never seen patients with this kind of disease, but it was very clear to me that this was within the bounds of what had been clinically described as kuru by Hornabrook. I don't want to take any credit. [laughter]

DL: Oh, it wasn't credit, but I'm just saying in terms of people who one could talk to about having seen patients [with kuru]... It's not a matter of who described it. It's a matter of what neurologist could one talk to who has this walking experience with these patients that you can't find anymore.

SP: Right. Exactly. That's true. You're right.

DL: How did you make the arrangements to go see the patients with kuru?

SP: What happened was that I wrote Gajdusek. This was right after the Nobel Prize that he received in 1976. I wrote him a note, and I said, "I'd really like to go to see patients with kuru," because I had some money from Howard Hughes [Medical Institute], and I could convince them that they should pay for this trip. He didn't answer. Dick Johnson said to me, "Listen, get hold of Michael Alpers, and he'll arrange everything." So that's

4. Hornabrook RW, Moir DJ. Kuru: epidemiological trends. *Lancet*. 1970;2(7684):1175-1179.

5. Beasley A. Richard Hornabrook's first impressions of kuru and Okapa. *Philos Trans R Soc Lond B Biol Sci*. 2008;363(1510):3626-3627.

6. Simpson DA, Lander H, Robson HN. Observations on kuru: II. Clinical features. *Australas Ann Med*. 1959;8(1):8-15.

7. Simpson DA. The Adelaide Kuru Team in 1957-1959. *Phil Trans R Soc B* 2008;363:3665.

⁶² Neurologist and neurovirologist Richard T. Johnson, M.D. (1931-2015)

See:

1. Prusiner SB. *Madness and Memory: The Discovery of Prions—A New Biological Principle of Disease*. Yale University Press, 2014: 58-59, 93-94.

what I did. Then, Michael Alpers wrote me a note a couple days before I was ready to leave and said, “I can’t be there.” I thought now I’m not going to have anybody to help me. I’m just going to wander around in the bush.

DL: [laughter] Papua New Guinea, yes.

SP: This doesn’t make much sense. I got very nervous. He said, “I have to go to China, but don’t worry, it will all be taken care of by my wife.” I didn’t get much more security out of that.

Then, some of my friends used to say to me, “You know, Stan, what you should really do is just go rent a room somewhere along the Pacific Coast in an area that’s not very populated, and then you come back in a few weeks, and you say that you went and did all this.”

DL and LK: [chuckles]

SP: I said, “Nah, I can’t do that. I’ve got to go do this. I’ve got to see all this. It’s too important to me. It’s what I’m doing everyday.”

So, I flew there. I eventually arrived in Goroka, this little town in the Highlands of New Guinea. There, with Michael’s wife [were] two or three of her kids. I met them. They took me to their home. They were so nice to me. After a few days, I got on this big four-wheel-drive long-bed pickup truck and with another couple of pickup trucks, like a little caravan, we drove and we drove for several hours.

DL: Up and up and up, probably.

SP: It was more up and down.

DL: Okay.

SP: Then, we stopped, got out, and we started to walk. We walked up this mountain and walked along this flat trail. Eventually, we come to a clearing, and there’s a big space and there are huts, where people are living. And who pops out of this hut? Gajdusek. I think I wrote all that down.

DL: You wrote that part.⁶³

⁶³ Prusiner SB. Dr. America and the trembling cannibals. In: *Madness and Memory: The Discovery of Prions—A New Biological Principle of Disease*. Yale University Press, 2014:50-64.

SP: I just couldn't believe my eyes. He was taking care of his domain, his world. He didn't want it invaded unless it was on his terms. So, that's the beginning. It was very nice. I had to spend about three days with him, nonstop. I think I described that in the evenings, he would just go. He would never let a word out from me. I had one sentence. I could try to direct him in some direction that I wanted to hear him talk about. But that was it.

DL: He was just nonstop?

SP: Yes. He could go for three of four hours without ever a question from me.

DL: Wow.

SP: The only time he would shut up was because I would get up from the table and I would climb up this loft, and I would go to the left, and he would go to the right. He would keep talking, and I eventually would fall asleep with his talking. I don't know whether he kept talking or whether he stopped talking.

DL and LK: [chuckles]

SP: I don't have a clue. It was an adventure.

DL: Fair enough. Now, you wrote that your initial interest in this group of disorders was from a clinical case of CJD.⁶⁴

SP: Right.

DL: But then, when you became aware of Tikvah Alper's work,⁶⁵ you shifted from human prion diseases to scrapie.

⁶⁴ Prusiner SB. Beginning of an odyssey. In: *Madness and Memory: The Discovery of Prions—A New Biological Principle of Disease*. Yale University Press, 2014:16-25.

⁶⁵ South African-born radiation biologist Tikvah Alper, M.A. (Physics) (1909-1995) used radiation to estimate the size of the scrapie agent. In 1966, while working at the Medical Research Council Experimental Research Unit at Hammersmith Hospital in London, she published a provocative and controversial paper concerning the small size of the scrapie agent, calculating the size from radiation inactivation data. As she and her colleagues noted in 1966,

If ... the target for radiation damage to this agent is a nucleic acid moiety, its [would be at most] about 800 bases. ... [T]he evidence that no inactivation results from exposure to a huge dose of ultraviolet light, of wavelength specifically absorbed by nucleic acids, suggest that the agent may be able to increase in quantity without itself containing nucleic acid. This possibility is supported by the data from electron

SP: Right.

DL: Why was her work so pivotal for you?

SP: It wasn't her work. It was the work inspired by Hadlow and Carl Eklund, who, when they were visiting England when Hadlow was on a sabbatical, came to produce this really seminal paper.⁶⁶

irradiations, since these yield a target size[,] which is implausibly small as a nucleic acid. (Alper et al, 1966, p. 283)

See:

1. Alper T, Haig DA, Clarke MC. The exceptionally small size of the scrapie agent. *Biochem Biophys Res Comm* 1966;222(3):278-284.
2. Alper T, Cramp WA, Haig DA, Clarke MC. Does the agent of scrapie replicate without nucleic acid? *Nature* 1967;214:764-766.
2. Hornsley S. Tikvah Alper (1909-1995). *Int J Rad Biol* 1995;68:105-106.
3. Hornsley S, Denekamp J. Tikvah Alper: an indomitable spirit. *Int J Rad Biol* 1997;71:631-642.

⁶⁶ Veterinary pathologist William John ("Bill") Hadlow (1921-2015) began the prion disease research program at Rocky Mountain Laboratories (RML) in Hamilton, Montana. Hadlow had been recruited to RML in 1952 by Carl M. Eklund. Hadlow spent his entire career at RML except for the period from 1958-1961 which he spent in the United Kingdom on a U.S. Department of Agriculture assignment. Upon Hadlow's return to RML in 1961, Eklund encouraged him to begin a prion disease research program at RML.

In 1959, while at the Agricultural Research Council Field Station in Compton, England, Hadlow published his now famous letter to the editor of *Lancet* in which he suggested that the similarities between scrapie and kuru were "too impressive to be ignored":

Onset of each disorder is insidious, and occurs in the absence of antecedent illness. The course is afebrile, and almost invariably is relentlessly progressive. Both diseases usually end fatally within three to six months after onset... [S]uch signs as ataxia, which becomes progressively more severe, tremors, and changes in behavior are features of both diseases. ... Lastly, the neuropathological changes, though essentially non-specific, are remarkably similar in the two diseases. Widespread neuronal degeneration ... Astrocytic gliosis... Inflammatory changes of the extent and severity usually associated with an active encephalitis process are not observed. Large single or multilocular "soap-bubble" vacuoles in the cytoplasm of nerve-cells have long been regarded as a characteristic finding in scrapie; this extremely unusual change, apparently seldom seen in human neuropathological material, also occurs in

kuru, and first aroused my curiosity about the possible similarity of the two diseases. (Hadlow, 1959, p. 290)

Hadlow then outlined the experiment that would later win Gajdusek a Nobel Prize:

Despite the lack of indications suggesting that scrapie is an infectious disease, the disorder can be induced experimentally in the sheep and in the closely related goat ... inoculated intracerebrally or subcutaneously with suspensions of brain tissue ... from scrapie-infected sheep. ... [S]uch experimental induction of a progressive neurodegenerative disorder of the central nervous system would seem to provide a valuable clue to the eventual understanding of the broadly similar and equally perplexing human neurological disorder represented in kuru. Thus, it might be profitable, in view of veterinary experience with scrapie, to examine the possibility of the experimental induction of kuru in a laboratory primate... (Hadlow, 1959, p. 290)

See:

1. Hadlow WJ Scrapie and kuru. *Lancet* 1959;2:289-290.
2. Hadlow WJ. The scrapie-kuru connection: recollections of how it came about. In: Prusiner SB, Collinge J, Powell J, Anderton B (Eds.). *Prion Diseases of Humans and Animals*. London: Ellis Horwood, 1992:40-46.
3. Hadlow WJ. Neuropathology and the scrapie-kuru connection. *Brain Pathol* 1995;5:27-31.
4. Hadlow WJ. Reflections on the transmissible spongiform encephalopathies. *Vet Pathol* 1999;36:523-529.
5. Hadlow WJ. Kuru likened to scrapie: the story remembered. *Phil Trans R Soc B* 2008;363(1510):3644.
6. Hadlow W, Ponte M. Dr. William Hadlow Interview. Office of NIH History: Oral History Program. August 31, 2004.
<https://history.nih.gov/archives/downloads/hadloworalhistory.pdf> Accessed 9-30-17
7. Anonymous. NIAID's Hadlow mourned. *NIH Record* 2015;67(6):1.
https://nihrecord.nih.gov/newsletters/2015/07_31_2015/milestones.htm Accessed 9-30-17
8. Pekoc K. Obituary: William J. Hadlow. *Veterinary Pathology* 2015;52(5):985.
9. Prusiner SB. Hadlow and transmission of kuru to chimps. In: *Madness and Memory: The Discovery of Prions—A New Biological Principle of Disease*. Yale University Press, 2014:52-54.

Prusiner collaborated with Hadlow and Eklund in a series of articles and books published between 1977 and 1980:

1. Prusiner SB, Hadlow WJ, Eklund CM, Race RE. Sedimentation properties of the scrapie agent. *Proc Natl Acad Sci USA* 1977;74:4656-4660.

DL: The letter.

SP: The letter about kuru—that it should be transmitted into apes and monkeys.

DL: Right. That was like 1959, I think.

SP: Yes. His collaborator, Carl Eklund, who is a little bit older, who's an arborvirologist and had done zillions of experiments with mice, said to Richard Chandler, who was working at Compton, England, where Hunter was and Kimberlin eventually came, "You ought to try to transmit scrapie from sheep into mice and see what the hell happens." So by 1960, that was the first set of experiments—I think it was published in the *Lancet*⁶⁷—showing that you could do experiments with mice, transmit the disease from sheep into mice, and then it could go into mice, into mice, into mice. You could also do titrations, end point titrations, where you dilute the samples tenfold repeatedly. Then, you can calculate the titer. So this was all virology replayed out. That was the only assay. The only method of measurement was [the] mouse.

DL: Going back to her [i.e., Tikvah Alper's] work... I think you wrote, also, that that helped you set a bound on the size of the scrapie agent.⁶⁸

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2. Prusiner SB, Garfin DE, Cochran SP, Baringer JR, Hadlow WJ, Eklund CM, Race RE. Evidence for hydrophobic domains on the surface of the scrapie agent. *Trans Am Neurol Assoc* 1978;103:62-64.
 3. Prusiner SB, Hadlow WJ, Eklund CM, Race RE, Cochran SP. Sedimentation characteristics of the scrapie agent from murine spleen and brain. *Biochemistry* 1978;17:4987-4992.
 4. Prusiner SB, Hadlow WJ (Eds.). *Slow Transmissible Diseases of the Nervous System, Vol. 1, Clinical, Epidemiological, Genetic, and Pathological Aspects of the Spongiform Encephalopathies*. New York: Academic Press, 1979.
 5. Prusiner SB, Hadlow W J (Eds.). *Slow Transmissible Diseases of the Nervous System, Vol. 2, Pathogenesis, Immunology, Virology, and Molecular Biology of the Spongiform Encephalopathies*. New York: Academic Press, 1979.
 6. Prusiner SB, Garfin DE, Cochran SP, McKinley MP, Groth DF, Hadlow WJ, Race RE, Eklund CM. Experimental scrapie in the mouse: electrophoretic and sedimentation properties of the partially purified agent. *J Neurochem* 1980;35:574-582.
 7. Hadlow WJ, Prusiner SB, Kennedy RC, Race RE. Brain tissue from persons dying of Creutzfeldt-Jakob disease causes scrapie-like encephalopathy in goats. *Ann Neurol* 1980;8:628-631.

⁶⁷ Chandler RL. Encephalopathy in mice produced by inoculation with scrapie brain material. *Lancet*. 1961;1(7191):1378-1379.

⁶⁸ As Prusiner wrote in a review article on prions in *Scientific American* in 1984, just two years after his landmark paper in *Science*:

SP: Yes...well...but most people didn't believe the work she did.

DL: Oh, that's true, yes.

The question of the prion's size also bears on the nucleic acid issue. Individual prions seem to be very small. Therefore the amount of nucleic acid a prion could encapsulate is probably quite limited. The target-size studies done by Alper and her colleagues suggested the infectious scrapie particle might have a molecular weight of between 60,000 and 150,000. The remarkable heterogeneity of prions has made it difficult to determine the size of the smallest infectious particle by more direct methods. After attempting to break up aggregates of prions with detergents and other chemicals, we have investigated the size of the particles by sucrose-gradient centrifugation, by timing their passage through a chromatographic column and by passing them through a membrane filter with pores of a known size. All the studies have given results consistent with a molecular weight of between 50,000 and 100,000, but each method has potential pitfalls. Because of the many sources of uncertainty, the most that can be said for now is that the smallest infectious form of the prion may be 100 times smaller than the smallest viruses.

If the prion has a molecular weight of 50,000, its diameter would be about five nanometers, or five billionths of a meter. If it is constructed like a conventional virus, it might take the form of an approximately spherical shell of protein surrounding a core of nucleic acid. The shell could not be less than about a nanometer thick, which would leave room in the core for no more than about 12 nucleotides. Limits on the size of any prion nucleic acid can also be derived from other measurements. The prion's resistance to inactivation by ultraviolet radiation is consistent with a nucleic acid made up of from 12 to 50 nucleotides; our experiments with psoralens would not have detected a nucleic acid with fewer than 40 nucleotides.

The failure to detect a nucleic acid in prions cannot be taken as proof that it does not exist. It could still be concealed in some way by a surrounding structure or could be present in quantities too small to be detected. Nevertheless, it seems reasonable to suggest that if the prion has any nucleic acid at all, it is likely to be less than 50 nucleotides long. In the standard genetic code three nucleotides are needed to specify each amino acid, and so the putative prion "genome" could not encode a protein with more than about a dozen amino acids. It should be noted that the molecular weight of PrP implies it has roughly 250 amino acids. (Prusiner, 1984, pp. 56, 58)

See: Prusiner SB. Prions. *Sci Am* 1984;251(4):50-59.

SP: I always factored that in. She was really a difficult woman.⁶⁹ You couldn't really have a conversation with her about all the data and then try to come to some set of conclusions that might be reasonable. She had her ideas, and they were set in stone. What she did was very interesting, but then it never went anywhere. It was clear what she didn't know how to do was to purify the substances she was irradiating. That's what she needed to do to take it to the next step.

DL: But when you did your first centrifugation experiments, you were trying to characterize that agent, purify it, isolate it, and those experiments helped you... First, it surprised you, I think, to find that there was a range of sizes of these agents.

SP: Yes, yes. You got it.

DL: Some were as big as bacteria and some were smaller than the smallest known virus. Using the size of the smallest one set a bound on how many potential nucleotides might be in the infective agent if, in fact, there were any nucleotides at all.

SP: Right. That's all true.

So what you had to do was to try to think about what all the possibilities to explain this data? I kept coming back to one, which was: the infectious agent was very small and the bigger infectivity particles were made up of aggregates of the smallest. It wasn't the other way around. You didn't have some that were big and some that were small. They were all

⁶⁹ Even her supporters acknowledged that her aggressive approach to scientific debate could be off-putting. For example, as noted by Hornsley and Denekamp (1997),

Tikvah is remembered by most people for her forceful discussion style, which could be quite alarming to anyone the first time it was encountered. She could not tolerate superficial or sloppy discussions, was always unwilling to ignore uncomfortable facts that did not fit the generally accepted theory, and would always push for a real understanding of the truth of whatever topic was being discussed. Unfortunately everyone did not always have the same view of what 'the truth' was, and she had extremely ascerbic interactions with some scientists, creating life-long rifts between them. Confrontational scientific interactions were not meant to be personal attacks and she was surprised if some people saw them that way. She genuinely believed that scientific debate and personal feelings could be disconnected, and was surprised and disappointed if others were hurt or angered by her remarks. (Hornsley and Denekamp, 1997, p. 631)

See: Hornsley S, Denekamp J. Tikvah Alper: an indomitable spirit. *Int J Rad Biol* 1997;71:631-642.

small, but the aggregates behaved like they were large. That's a supposition that I kept going on. It's the only logical one.

DL: Yes, yes, Occam's razor.

SP: Right.

DL: Fair enough.

Now, when you were starting your career at UCSF [the University of California at San Francisco], you had a fair number of difficulties trying to do the logistics of building a lab, getting enough animals, doing your clinical work.

SP: Right.

That led to some kind of tense times, I think. Bob Fishman⁷⁰ sent you a letter at one point, setting some lines in the sand almost, about whether tenure was even going to be possible. So this was not a simple thing that you accomplished. The logistics of this, just even reading about it...

SP: Great in retrospect. [hearty laughter]

⁷⁰ Robert A. ("Bob") Fishman (1924-2012) was the chairman of Neurology at the University of California at San Francisco for 26 years, and subsequently (starting a year after his retirement in 1992) he became the Editor-in-Chief of *Annals of Neurology*. Fishman was widely regarded for his monograph, *Cerebrospinal Fluid in Diseases of the Nervous System* (1980, 1994). Fishman's playful quips and aphorisms were referred to as "Fishmanisms" by colleagues, and these included Fishman's characterization of a 2-year-old child as a "psychotic dwarf who has a good prognosis."

See:

1. Hauser SL, Rowland LP. Robert A. Fishman, MD (1924-2012). *Neurology* 2012;80:1918-1919.
2. Hauser SL. In memoriam: Robert A. Fishman, MD (1924-2012). *JAMA Neurol* 2013;70:523-524.
3. Talan J. Robert A. Fishman, MD, Chair of "Modern Neurology," dies. *Neurology Today* 2013;13(3):4-5.
4. Newman L. Robert A Fishman: eminent neurologist, author and editor, and creator of "Fishmanisms." *BMJ* 2013;346: f1897.
5. Fishman RA. *Cerebrospinal fluid in diseases of the nervous system*. Philadelphia: W.B. Saunders, 1980 and 1994.

DL: Exactly. It looks almost superhuman to have been able to push and have that focus, despite the pressures of working in a clinical department. That is not an easy business. Can you elaborate on some of that part of your career?

SP: Well, I had a few people who really helped me and really kept pushing me. One was Curtis Morris, who I wrote down in there.⁷¹ He's a nephrologist. I got to know him when he was an attending, and I was an intern a few years earlier. Before I went to the NIH, I did my internship in San Francisco. He would always push me, "Keep going, Stan. You've got support. Just keep pushing." He helped me a lot. He was speaking to the dean; I was speaking to the dean. I didn't sit around waiting for Fishman to be my only port of entry into the administration of the system. That would have been deadly, because he was having such a hard time with this. It wasn't that he was a bad person at all. He was trying to be a responsible administrator.

DL: Right.

SP: He didn't want to have somebody whose research had washed out completely, a person who didn't want to see patients. Fishman was going to have to see all these patients to pay my salary, because I was now tenured professor.

DL: Kind of a dead weight financially for the department.

SP: Right, exactly. For the department, it was irresponsible if that had happened. He was really in a bind.

I got a lot of support. The biggest piece of private support came from R.J. Reynolds, the tobacco people, but it flowed through three extraordinarily accomplished people. One was Fred Seitz,⁷² who had been president of Rockefeller [University] and Mac McCarty,⁷³ who had been vice president of Rockefeller, but also was the person... It was

⁷¹Prusiner SB. *Madness and Memory: The Discovery of Prions—A New Biological Principle of Disease*. Yale University Press, 2014:75.

⁷² American physicist and pioneer of solid-state physics Frederick ("Fred") Seitz (1911-2008) was president of Rockefeller University (1968-1978), and president of the United States National Academy of Sciences (1962-1969). Seitz's awards included the National Medal of Science (1973), NASA's Distinguished Public Service Award, and more than 30 honorary degrees.

⁷³ American geneticist Maclyn ("Mac") McCarty, M.D. (1911-2005) was best known for his part in the discovery that DNA, rather than protein, constituted the chemical nature of the gene. This work was conducted with colleagues Colin Munro MacLeod, M.D. (1909-1972) and Oswald Theodore Avery Jr., M.D. (1877-1955).

See:

McCarty, MacLeod, and Avery who demonstrated for the first time that the genetic substance of life was DNA and not protein.⁷⁴ This was in 1944. Then, there was one more. This guy was the director of NIH during the 1960s and now his name is escaping me. I'm sorry I can't remember it.⁷⁵

Bruce Miller⁷⁶ and I have these discussions all the time about problems with remembering names. [chuckles] He always makes me feel a little better. He has the same problems.

Anyway, the three of them gave me \$350,000 a year. That was a *lot* of money then. The cachet of the three of them was really the pressure on Julie Krevans⁷⁷ to take over and not have me thrown out...with that kind of support and validation from three very illustrious, highly respected people in science. That was my good luck. That was really good fortune.

DL: But it wasn't simply accomplished either. It took a fair amount of—fair amount is even too light—it took dogged determination to even accomplish getting that kind of support, didn't it?

SP: That support came because Krevans told a few senior people that he needed some proposals to take to these three guys in New York. He talked about them as New York people. He never told me who they were in the beginning. Rudi Schmid⁷⁸, who was a

1, Gotschlich EC. *Maclyn McCarty : June 9, 1911-January 2, 2005*. Biographical memoirs of the National Academy of Sciences. Washington, D.C.: National Academy of Sciences, 2014.

2. Gotschlich EC, Fischetti VA. The career of Maclyn McCarty. *J Exp Med*. 2005;201(11):1699-707.

3. McCarty M. *The Transforming Principle: Discovering That Genes Are Made Of DNA*. New York: Norton. 1986

⁷⁴ Avery OT, MacLeod CM, McCarty M. Studies on the chemical nature of the substance inducing transformation of pneumococcal types. Inductions of transformation by a desoxyribonucleic acid fraction isolated from pneumococcus type III. *J Exp Med* 1944;79:137-158.

⁷⁵ American nephrologist James A. Shannon, M.D. (1904-1994) was the director of National Institutes of Health from 1955-1968.

⁷⁶ Behavioral neurologist Bruce L. Miller, M.D., UCSF Medical Center

⁷⁷ Hematologist Julius R. ("Julie") Krevans, M.D. (1924-2015) was Dean of the School of Medicine at UCSF from 1971 to 1982.

⁷⁸ Swiss-born American hepatologist Rudi Schmid, M.D., Ph.D. (1922-2007) was the dean of UCSF School of Medicine from 1983-1989.

very well known hepatologist/gastroenterologist had said to Krevans, “I’ll ask Stan for a proposal,” but then he never did. He forgot. Then, two days before it was due, he called me up, and he said, “Stan, there are these people”—and he reiterated what was going on—“and the dean needs to take this proposal to New York. You should write it up.” I said, “Oh! Okay.” I wrote it up. I sent it to him. He changed a few words and gave it to the dean, Julie Krevans. It was now in the hands of Fred Seitz, Mac MacCarty, and the former NIH director. God! What’s his name? I can see his face. It’s in the book.⁷⁹ Anyway, they say they’re interested in my proposal. Krevans took three or four proposals. They chose mine and then they came out and did the site visit. We were walking across the street to lunch and Seitz took me aside, took me by the arm, and he said, “We’re going to give you a lot of money.” [hearty laughter] Then, when I got the money, I said, “How ‘bout some more?”

SP, DL, LK: [hearty laughter]

SP: I’ve never had enough money to do all this.

DL: You did a tremendous amount. That’s for sure.

I want to cover here, and in the discussion later, I want you to at least talk about how you came up with the term *prion*.

SP: Okay. I’m happy to recite this. I thought I did a great job in the book, by the way.⁸⁰ [hearty laughter]

DL: Yes, and I enjoyed reading that.

SP: The problem was it was 1980. The data is coming fast now, because we have this hamster bioassay. I take the most purified fractions, and I try to kill off the infectivity in these different ways. This seems like the good idea to do. Then, I came to realize that there were these people who I was competing with and they were claiming that that these were viroids and viruses. I said, “What I can’t do is, I can’t get to the end. I can’t just keep working and working and working, and then declare victory out at the end, and now I do an analysis by mass spectrometry or some other technique, and I know what’s going

See: Ockner RK. *Rudi Schmid: May 2, 1922-October 20, 2007*. Biographical memoirs of the National Academy of Sciences. Washington, D.C.: National Academy of Sciences, 2013.

⁷⁹ Prusiner SB. *Madness and Memory: The Discovery of Prions—A New Biological Principle of Disease*. Yale University Press, 2014:75.

⁸⁰ Prusiner SB. *Madness and Memory: The Discovery of Prions—A New Biological Principle of Disease*. Yale University Press, 2014:86-91.

on. I *need*, along the way, to kill off the scrapie agent as I get more and more pure preparations. I've *got* to stay on top of this." That was pretty good insight. I'm not sure how I quite arrived at that. So that's what I was doing. At each step of purification, I was trying to destroy the infectivity. As I got greater and greater purity, I could see that there was evidence for a protein. It was clear. There wasn't any issue, and there was no nucleic acid. Now, a negative is always hard to establish, but I became quite confident, because I did these experiments over and over again. I did them in different ways. Some people would come to me and say, "Why don't you try this or that?" and I would always try it. Sometimes it was ambiguous and sometimes it was clear.

I was with a friend of mine who was a professor at Harvard. He was a friend because of my aunt, the one I couldn't stay with in Philadelphia. My aunt and his wife⁸¹ had been friends since age three, if you can believe this. She [Dr. Prusiner's aunt] lived to be eighty and then died of Alzheimer's disease. The wife lived a little longer. This was Frank Westheimer.⁸² Then he lived longer than that. He lived into his nineties.

He was in his fifties or sixties when he came to UCSF. It was an honorary professorship in the pharmacy school. So he spent a week. He came to see me and talked. I went over everything I was doing. He looked, and he said, "Stan, this is really fantastic. You've discovered something really new, and you need to give it a name, and you need to give it a *good* name. You need to think about this name for a long time. A lot of work needs to go into this. Because, if you give it a crappy name, someone else will come along and give it another name, and they will end up with the lion's share of the credit, but you will have done the work, and that's not a good idea. This is what you've done with your life, and you need to make sure that you don't screw it up. So you need to spend a lot of time on this." That was about...in the fall of 1980.

Then, 1981 came and my friend, Curtis Morris, the nephrologist, said, "Stan, you should write all of this up and publish it in *Science* as an article. I said, "Fine." I called Philip Abelson,⁸³ who was the editor of *Science*. I spent two hours on the phone telling him

⁸¹ Jeanne Westheimer

⁸² American chemist Frank Henry Westheimer, Ph.D. (1912-2007) was the Morris Loeb Professor of Chemistry Emeritus at Harvard University. Among his honors were the U.S. National Academy Award in Chemical Sciences (1980), the U.S. National Medal of Science (1986), and the Priestley Medal (the highest honor of the American Chemical Society) in 1988.

See: Ault A. Frank Westheimer's early demonstration of enzymatic specificity. *J Chem Educ* 2008;85(9):124.

⁸³ American physicist Philip Hauge Abelson (1913-2004) was the editor of *Science* from 1962-1984. Abelson was the co-discoverer, with Edwin Mattison McMillan (1907-1991), of neptunium on June 8, 1940. Subsequently, McMillan and Glenn Theodore

what I had done. He said, “That sounds good.” I said, “Yes, but there’s a lot of people who don’t like what I’ve done, and you have to be careful about that.” He said, “I know how to do that. I’ve refereed a lot of papers where I had that kind of problem.” So I wrote it all up. I sent it to him. By the summer of 1981, I had the reviews back, and it was clear they wanted to publish the paper, but I needed to make a few changes. And I gave it to them.

The whole fall of 1981, this woman, Eleanor Butts, who was a senior editor at *Science*, was sure that she had to be the gatekeeper—that if she dragged her feet long enough with this paper, someone would prove that what I was saying was wrong, and then they wouldn’t have to publish something which was *wrong*. This was a big paper. I kept pushing her, but I got tired of listening to this crap from her, because it was just one grammatical construction after another. Should it be this way or that way? It just became so obvious. I was scared to do anything else. I was scared that she was going to have an excuse to deep-six my paper. I was sure that was going to happen.

Then, it all escaped my hands, because in the winter, there was going to be an annual day [at UCSF] called Founders Day. A man named Frank Sooy⁸⁴ was the chancellor and he wanted to do a big splash. David Perlman⁸⁵ was the [*San Francisco Chronicle*] science writer. He still is. He’s ninety-five now. It’s unbelievable. He’s writing every day.

Seaborg (1912-1999) were jointly awarded the Nobel Prize in Chemistry in 1951 “for their discoveries in the chemistry of the transuranium elements,” but Abelson’s contribution was overlooked.

See:

Schudel M. Philip H. Abelson, 91, editor of *Science*, noted researcher in many fields. *Boston Globe*, August 9, 2004.

http://archive.boston.com/news/globe/obituaries/articles/2004/08/09/philip_h_abelson_91_editor_of_science_noted_researcher_in_many_fields/?page=1 Accessed 12-11-17.

⁸⁴ Otolaryngologist Francis A. (“Frank”) Sooy (1915-1986) was Chancellor at UCSF from 1972-1982.

⁸⁵ David Perlman (1918-), award-winning *Science* Editor of the *San Francisco Chronicle*, began his career there as a copy boy in 1940. Perlman felt his official title of *Science* Editor was too fancy, and considered himself just a “regular reporter.” When he retired on August 4, 2017, he was the oldest full-time reporter in the United States. He continues as *Science* Editor Emeritus for the *San Francisco Chronicle*.

See:

1. Miller C. At 98, legendary science writer David Perlman takes ‘early retirement.’ <https://ww2.kqed.org/science/2017/07/21/at-98-legendary-science-writer-david-perlman-takes-early-retirement/> Accessed 12-11-17.

LK: Every day? Wow.

SP: Or every other day. He writes all the time and I see him periodically. I take him to lunch.

Anyway, he came to see me. He had been sniffing around figuring out something was going on. He always wanted the paper. I said, “You can’t have the paper until it’s going to be published.” I knew he would love the paper, because it had a word in it that wasn’t there. So, he went to the chancellor, Frank Sooy, who wanted him to write a big long article about UCSF for Founders Day. He said, “I’ll do that, but you’ll have to give me Stan’s paper.” So he got that paper, because I wasn’t going to say “No” to Frank Sooy. He had helped me *enormously*. It’s all written out there.⁸⁶ He gave me all this space for animals, about the size of this room.⁸⁷

DL: Wow.

SP: Perlman loved all of this, you know. He called me up the day before and he said, “Stan, I want to check a few things. Tomorrow is going to be a big day.”

[chuckles] He had taken this picture of me. I had a lot of hair. It was dark, so he used white out. He decided to give me a haircut.

SP and LK: [chuckles]

SP: I don’t know why, but he didn’t like that. He had short hair. He still has short hair.

LK: Did he think it would go to your credibility? It’s kind of like an Einstein look, though.

SP: I don’t know.

LK: [laughter]

SP: There was still a lot there.

2. Rubenstein S. David Perlman, Chronicle science editor, caps distinguished career. August 11, 2017. <http://www.sfgate.com/bayarea/article/David-Perlman-Chronicle-science-editor-caps-11761249.php> Accessed 12-11-17.

⁸⁶ Prusiner SB. *Madness and Memory: The Discovery of Prions—A New Biological Principle of Disease*. Yale University Press, 2014:79-80, 91-92.

⁸⁷ The interview was conducted in a large meeting room, more than 50 feet by 50 feet (2500 ft²).

Anyway, that's when it all started. This was February [1982]. Now, the scientific community wanted the paper and Eleanor Butts was in deep shit, because there was no way that she was going to stop this any longer. So, in April, the paper⁸⁸ was published.

DL: Please tell us, though, about how you came up with the term.

SP: Oh, yes. So after Frank Sooy... I was still focused on the chronology for you.

[chuckles]

SP: It's 1981, and it's the spring of 1981, and I need to finish this paper. The only thing holding it up is the word, and I'm trying to figure out a word.

So I go through Latin dictionaries, because I knew—I still know—a lot of Latin. I'm not a scholar in it; that's for sure. I don't know any Greek. I don't really know how to come up with a word. I want a word like exon. I thought that's a great word. Where do I find somebody who can do that? I kept thinking of somebody at Berkeley [who] can help me, but then I didn't even know who to talk to. I thought this is going to be just frivolous to go to Berkeley and try to find some professor of words who will help me.

Then, I said, "Okay, I've got to come up with some rational approach to a word, just taking a bunch of letters, and where are these letters going to come from? Well, they're going to come from words that have something to do ... [with the responsible agent]." So I wrote out [the words] protein, infectious, and agent. I started with that. I got *piaf* out of that, because I wanted *protein*, and I wanted *infectious*, and then I wanted *agent*.

DL: You just kind of threw on an extra "f" for fun?

SP: For infectious.

DL: *Protein, infectious, agent...pia*. You added an "f."

SP: So you just underline the "f" in *infectious*, right? That's where the letters all come from.

DL: Okay.

SP: I always liked Edith Piaf.⁸⁹ Now, "Sparrow" is announcing all of this, right? [laughter]

⁸⁸ Prusiner SB. Novel proteinaceous infectious particles cause scrapie. *Science* 1982;216:136-144.

I then sent it to a friend of mine named Sidney Udenfriend,⁹⁰ who was running the Roche Institute in Molecular Biology. This was a *fabulous* place that was created by Roche to do basic science that would create drugs. Eventually, they shut it all down, because they never got one drug out of spending hundreds of millions of dollars over twenty years. He reads the paper, and he says, “Stan, this is an *American* discovery, not a French discovery.”

DL and LK: [chuckles]

SP: “You don’t need a French word. You need another word. Go find another word.” So that was the end of *piaf*. Short. You need something short. You need to have two vowels. Great words are words like virus. That’s a fabulous word. And quark [pronounced *kwork*] is a great word. Those are words that I think are just A+.

So I then throw out *agent*, because I don’t need *agent*. That’s totally non-specific, and I’m left with *protein* and *infectious*. Whenever I would go to a lecture, I would write out infectious across the top and protein on the side, or vice versa. Then, I’d just pick letters randomly. I didn’t get anywhere until one day. I’d probably stumbled across the same word ten times and never picking it out: p-r-i-o-n. I read it, and I say, “This is prion” [pronounced *pree-on*]. I could have pronounced it *pry-on*, but I pronounced it *pree-on*. Then, I said, “I’m going to write p-r-e-e-o-n as the pronunciation in parentheses.”

I leave this defunct faculty club that was now a sandwich shop across the street, and I walk upstairs. I look in my *Webster’s Unabridged Dictionary*, because there are no computers. I find a bird with a saw-tooth beak.

DL: A whalebird.

SP: Right. And I said, “Well, you know, this really doesn’t matter. Lots of words have more than one meaning. There’ll be two pronunciations. If I’m right, this will be the number-one definition, and the bird will continue to live on in oblivion...”

⁸⁹ French cabaret singer and songwriter Édith Piaf (1915-1963; nee Édith Giovanna Gassion), also known as “The Little Sparrow.” Piaf’s signature song was “*La Vie en rose*” (1946), which was also the title of the Academy-award-winning (2007) French musical film about the life of the singer. She adopted her stage name, Piaf, from her nickname, which is French slang for sparrow.

⁹⁰ American biochemist and pharmacologist Sidney Udenfriend (1918-2001) was the founding director of the Roche Institute of Molecular Biology.

See: Weissbach H, Witkop B. Sidney Udenfriend: April 5, 1918-December 29, 1999. *Biographical Memoirs* 2003;83:270-298.

DL: [chuckles]

SP: ...because no one is interested in prions [*pry-ons*]. I've never heard of a prion [*pry-on*]. It's a petrel that lives in the south, the Southern Ocean [Antarctic Ocean].

DL: Yes.

SP: It's not worth worrying about the bird. I said, "There'll be a little crap from some of my competitors who will say, '*That's a bird.*'" But I said, "It doesn't matter." So that's where it came from. It had all the right...it had *ion*, so it looked like it was something highly basic. An ion really gets right down to the essence. And it was short. It had two syllables. It was going to be okay.

DL: You wrote in your book, though, that one of the reviewers of your paper...

SP: Oh, yes.

DL: ...objected, that the name had unfortunate echoes of the author's name, *Prusiner ions*.⁹¹

SP: Yes. That was pretty clever. That was Paul Brown.⁹²

DL and LK: [chuckles]

SP: He worked with Gajdusek.

DL: Yes.

SP: I concluded that. I'm not certain that's Paul Brown, but I was pretty clear in my head that it was Paul Brown, because there was so much vitriol in the rest of the review.

DL: Is that right? Yes, wow.

⁹¹ Prusiner SB. *Madness and Memory: The Discovery of Prions—A New Biological Principle of Disease*. Yale University Press, 2014:90-91.

⁹² Paul Brown, M.D., was a longtime colleague and collaborator of Carleton Gajdusek at the National Institutes of Health. In 1962, when Brown was seeking a way "to circumvent the draft," he sought a position at the NIH, where Gajdusek hired him as a Public Health Services Officer to work in Gajdusek's lab, the Laboratory of Central Nervous System Studies. Brown retired from the NIH in 2004.

See: Ponte M. Dr. Paul Brown Interview. Office of NIH History Oral History Program February 20, 2004. <https://history.nih.gov/archives/downloads/paulbrown.pdf> [Accessed 12-11-17]

SP: Yes.

DL: Now, of course, *proteinaceous infectious* gets you *proin* rather than *prion*...

SP: Right, which is like loin.

DL: ...which has kind of a funny sound to it, of course, no matter how you pronounce it. So you made another, little flexible change in that, just to give it a more catchy flavor, I think. Is that fair?

SP: Yes. *Proin* is not a good word.

DL: But *proteinaceous infectious* as an acronym would get you that, right?

SP: Yes.

[brief discussion of interview logistics]

DL: A lot of people didn't like the term.

SP: Yes.

DL: There was a lot of backlash. Why do you think there was so much animosity to that term?

SP: If you read what other people have said, they didn't like it, because essentially I took over the field by putting my imprimatur on the field prematurely, because I didn't have enough information to come up with a word, and that really what I should have done was called it a *Gibbs*, or a *Gajdusek*, or a *Gajdusek and a Gibbs*, or a *Gibbs and a Gajdusek*, or something like that, or a *Dickinson*. Of course, this was nonsense from my point of view. I did exactly what Frank Westheimer told me to do.

DL: Yes.

SP: The result was exactly what Westheimer wanted to have happen, which was to get a good word and *not* have somebody else take over. They had a *lot* of time. I was the new guy on the block. But they never could figure out anything about what was truly going on. They didn't have a way of doing something, or they weren't clever enough, or they weren't sufficient showmen to figure out where all of this was going to go. But Westheimer saw it and called it completely.

DL: I think they were stuck in one little framework.

SP: Yes.

DL: And they struggled to keep fiddling with “unconventional virus” [or] “slow virus.”

SP: They had their own words. That’s true.

DL: Yes.

SP: But they were really dumb. “Unconventional virus” is as dumb as it gets.

DL: [chuckles]

SP: There’s that great quote that’s in the book from that guy Iain Pattison,⁹³ in which he says that “entering my fourth decade with scrapie...,” and he goes through the whole thing, and he says, “for is not a cottage an unconventional castle?”

DL: I think that is a great quote, actually.

LK: Yes.

DL: Now, when you got *the call* that you had won the Nobel Prize [on October 6, 1997], can you tell us your reaction to that call? Tell us about the call first.

SP: First of all, my ex-wife,⁹⁴ who was my wife at that time, she got the call. She was in San Francisco, and I was in Bethesda at an FDA meeting. I was staying in this really awful dump, a Holiday Inn. She got the call, then she told them where I am [was]. Then,

⁹³ Scrapie researcher Iain H. Pattison, of the British Agricultural Research Council’s Compton Research Institute.

As Pattison wrote in his memoir (1988),

The fourth decade of my association with scrapie ended in 1978, with the causal agent still obscure, and virologists as adamant as ever that theirs was the only worthwhile point of view. To explain findings that did not fit with a virus hypothesis, they rechristened the causal agent an ‘unconventional virus.’ Use of this ingenious cover-up made ‘virus’ meaningless—for is not a cottage an unconventional castle! (Pattison, 1988)

See:

1. Pattison IH. Fifty years with scrapie: a personal reminiscence. *Vet Rec* 1988;123:661-666.
2. Prusiner SB. *Madness and Memory: The Discovery of Prions—A New Biological Principle of Disease*. Yale University Press, 2014:30.

⁹⁴ Sandy Turk Prusiner

the guy woke me up. I knew him. I had met him. [He was] named Nils Ringertz.⁹⁵ He's now dead. He said, "Do you remember me?" I said, "Yes! We had dinner together six months earlier." He said, "Well, we've decided that we're going to give you the entire Prize." That was really a surprise to me. I thought surely they were going to have some other people. And, you know...I was shocked, because I knew people were nominating me for three or four years before that.

I had had a discussion with Hilary Koprowski⁹⁶ about all of this. He was really pushing for me. I said, "Maybe this just isn't going to happen." He said, "Well, it will happen eventually, but it could take another twenty years. It's going to have to go through its paces if this doesn't happen." I said, "Fine." Whatever it is, I can't control it. This is not *me*. I'm not running this process. These people in Sweden are doing this. They're the ones that decide all of this. Not me. You had this feeling all the time that people would

⁹⁵ Cell geneticist Nils Ringertz (1932-2002) was professor and chairman of the Department of Cell and Molecular Biology at Karolinska Institutet in Solna, Sweden (within the Stockholm urban area). From 1987 to 1997 he was Editor-in-Chief of *Experimental Cell Research*. From 1993 to 1999 Ringertz served as the secretary of the Nobel Committee for Physiology or Medicine, as well as a member of the Nobel Foundation's Board of Directors.

⁹⁶ Polish virologist and immunologist Hilary Koprowski (1916-2013). While at Lederle Laboratories, Koprowski created the first effective polio vaccine, based on an orally administered attenuated poliovirus. Koprowski developed his polio vaccine by attenuating the virus in brain cells of a cotton rat, *Sigmodon hispidus*. He administered the vaccine to himself in 1948 and two years later in a pilot trial he administered the vaccine to 20 children at Letchworth Village, a home for disabled persons in Rockland County, New York. Seventeen of the children developed antibodies to poliovirus (the other three apparently already had antibodies) and none developed complications. Although the vaccine was used overseas, it was never approved in the United States. Subsequently, in 1952, John Enders (1897-1985), Frederick Weller (1915-2008), and Thomas Robbins (1916-2003)—who shared the 1954 Nobel Prize in Physiology or Medicine "for their discovery of the ability of poliomyelitis viruses to grow in cultures of various types of tissue"—demonstrated that tissue-culture passage of a strain of virulent type I poliovirus produced marked attenuation of its paralytogenic activity in primates, a finding that boosted further efforts to develop an attenuated poliovirus vaccine. Albert Sabin's (1906-1993) early work with attenuated-live-virus polio vaccine began with attenuated poliovirus that Sabin had received from Koprowski. As noted by American virologist John Rodman Paul (1893-1971) in his monograph, *A History of Poliomyelitis* (1971), Koprowski "was later to lament the fact that the [live, attenuated] vaccine against poliomyelitis, which he had 'discovered,' should later bear the name of the Sabin vaccine."

See: Paul JR. *A History of Poliomyelitis*. New Haven and London: Yale University Press, 1971:442-443.

kind of say, “What’s wrong with you? Why didn’t you get the Nobel Prize? Some day, you’re going to get a Nobel Prize.”

It was really nice, but it wasn’t as though I was jumping up and down. It was just really nice that this had happened. I thought this is great.

People would ask me all the time, “How does it feel?” I would say, “You know, I recommend this.”

DL and LK: [laughter]

SP: It’s a nice thing to have happen to you.

DL: “Yeah, everybody, I recommend it!” [laughter]

SP: I sat there, and I was sort of stunned. I was really stunned about the whole thing, about getting the Prize alone.

Then I turned on CNN, and there was nothing about this Nobel Prize or any Nobel Prize at that moment. It’s now two o’clock in the morning, something like that, or maybe it’s four o’clock. I don’t remember. It’s written down.⁹⁷ The time goes on and on, and I’m not finding anything, and I think this is a hoax, because I knew this had happened.⁹⁸ It’s not

⁹⁷ Prusiner wrote in his memoir that the call from Ringertz came at 5:05 A.M. EDT (Prusiner, 2014, p. 218).

See: Prusiner SB. Stockholm. In: *Madness and Memory: The Discovery of Prions—A New Biological Principle of Disease*. Yale University Press, 2014:213-231.

⁹⁸ As Wall Street Journal reporter Ben Cohen wrote in 2015,

[M]any Nobel laureates start their celebrations in the same way. They assume it’s a prank call. The organizations that oversee the awards, including the Royal Swedish Academy of Sciences, are actually used to dealing with disbelief. They even have unofficial protocols for assuring the newly named laureates that they are not, in fact, at the center of an elaborate hoax. First a calming Swedish voice says hello. But an accent would be easy to fake. Then he says that you have won the Nobel Prize. But that could be a lie, too. Then he might insist it isn’t a prank. But of course he would say that. For some winners, only when he passes the phone to members of the committee whom they know personally does the achievement finally sink in. (Cohen, 2015)

Indeed, the list of Nobel laureates who suspected the call from the Nobel Committee was a prank call is quite long, and includes (in year order of their awards):

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- Richard P. Feynman (1918-1988), Physics 1965
 - William F Sharpe (1934-), Economics 1990
 - James A. Mirrlees (1936-), Economics 1992
 - Stanley B. Prusiner (1942-), Physiology or Medicine 1997
 - Alan J. Heeger (1936-), Chemistry 2000
 - George F. Smoot (1945-), Physics 2006
 - Martin L. Chalfie (1947-), Chemistry 2008
 - Venkatraman Ramakrishnan (1952-), Chemistry 2009
 - Brian P. Schmidt (1967-), Physics 2011
 - Stefan W. Hell (1962-), Chemistry 2014
 - Angus S. Deacon (1945-), Economics 2015
 - William C. Campbell (1930-), Physiology or Medicine 2015
 - Kazuo Ishiguro (1954-), Literature 2017
 - Beatrice Fihn (1982-), for the International Campaign to Abolish Nuclear Weapons (ICAN), Peace 2017
 - Jeffrey C. Hall (1945-), Physiology or Medicine 2017

Some examples of responses of scientists to calls from the Nobel Committee are as follows:

- American physicist Richard P. Feynman (Physics 1965) recounted, “I thought it was some student calling as a prank. I wasn’t too polite. But after the third call I was convinced. I hope the guys who called will accept my apologies.” (Hendrickson et al, 1965)
- American economist William F. Sharpe (Economics 1990) recalled, “and then, of course, your second thought is it's a hoax, one of your friends or colleagues... After we'd finished the chat we turned on CNN and within about five minutes the first announcement came across, and it had many inaccuracies... but nonetheless there was enough there that we were pretty sure that it was real.” (Griehsel, 2004b)
- Scottish economist James A. Mirrlees (Economics 1996) remembered, “I politely suggested that I’d need some proof.”
- American astrophysicist and cosmologist George F. Smoot (Physics 2006) recounted, “So they called and at first I thought I'd better be careful, this could be a hoax or something like that. But the guy sounded really serious and the next guy had a Swedish accent, so you know... I think I'd better take him really seriously. And so finally somebody I knew got on the phone, so I thought this was either a really elaborate hoax or this is the real thing, and I was kind of believing it, but I thought I better get on the web and check.”
- Australian physicist Brian P. Schmidt (Physics 2011) recalled, “I’m thinking, ‘Jeez my graduate students are getting pretty good with the accent this year.’”

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- It wasn't until the caller passed the phone to members of the Chemistry Committee that American physiologist Brian K. Kobilka (Chemistry 2012) believed the call was not a prank: "Then I really knew it was real. You know, I don't think any of my friends, first of all, would be able to put together such an elaborate hoax."
 - British-American economist Sir Angus S. Deacon (Economics 2015) recalled, "And then they were very keen to make sure that I did not think it was a prank. I don't know whether this is common. I've never had a prank phone call telling me that. And, of course, as soon as they said that, I thought, 'Oh, my god, maybe it *is* a prank.'" (Dubner, 2015)
 - American biologist and parasitologist William C. Campbell (Physiology or Medicine 2015) replied, "You must be kidding." He later recounted, "The first thing I did after that was to ask for a way to verify that this could be genuine, because it just seemed impossible." (Cohen 2015)
 - British novelist Kazuo Ishiguro (Literature 2017) said, "I thought it was a hoax in this time of fake news and everything. ... I didn't believe it for a long time. Then next my publisher phoned, and finally when the BBC phoned I thought it might be true." (Ishiguro, 2017)
 - Swedish jurist Beatrice Fihn, the Director of ICAN (Peace 2017) said, "I was worried that it was a prank. ... You are just so nervous that maybe it's not real." In a separate interview she said, "[I]t wasn't until the actual broadcast, when [the announcer] spoke the name ICAN, that we really understood that it was real." (Fihn, 2017)
 - American geneticist and chronobiologist Jeffrey C. Hall (Physiology or Medicine 2017) replied, "Is this a prank?" "I didn't really believe it," he later said. The caller responded, "No, it's not a prank," but Hall wasn't convinced until the Nobel Prize Assembly posted the official announcement later that morning. (Koch and Hall, 2017; McCrea, 2017; Ritter and Heintz, 2017)

In some cases the first call the scientist actually received was from a reporter, but typically the reactions were similar to those engendered by the calls from Stockholm:

- In response to a call from a reporter at CBS New York, Swiss-American biochemist Edmund H. Fischer (Physiology or Medicine 1992) said, "I don't believe you... What are you saying?" (Chu, Fischer, et al, 2016).
- When a reporter called and asked American physicist Steven Chu (Physics 1997), "How does it feel to win a Nobel Prize, Chu responded suspiciously, "Is this real?" The caller said, "Oh yes, it's actually on the Web." Chu countered disapprovingly, "You believe everything you hear on the Web?" (Chu, Fischer, et al, 2016).

While Prusiner believed that prank calls have occurred falsely notifying scientists that they have won a Nobel Prize, I found no clear evidence of this. The idea has certainly been discussed by scientists though, as noted by Wall Street Journal reporter Ben Cohen:

Whether or not a prankster has ever pulled off a successful Nobel Prize caper is uncertain. But there are at least some laureates who think the con could work. Dr. [Venkatraman] Ramakrishnan [Chemistry 2009], for one, said the idea has popped up in conversations with friends who love practical jokes. There are some scientists, he said, who almost actively campaign for the honor. That only makes them easier targets. “We often thought it would be great fun to have some Swedish postdoc call them up and say you’ve won the Nobel Prize,” he said. “But we’d never do it.” (Cohen, 2015)

See:

1. Hendrickson T, Galley S, Lamb F. Richard P. Feynman: Nobel prizewinner. *Engineering and Science* 1965;29(2):10-13.
2. Leachman S. A Nobel life: In new book, UCSB physicist and Nobel Prize winner Alan Heeger reflects on a life in science. *The UC Santa Barbara Current*, December 22, 2015. <http://www.news.ucsb.edu/2015/016239/nobel-life> [Accessed 12-15-17]
3. Cohen B. Is your refrigerator running? No, really, you won a Nobel prize: Persuading laureates they’re winners can be a tough call; ‘It’s not a prank.’ *Wall Street Journal*, October 7, 2015. <https://www.wsj.com/articles/is-your-refrigerator-running-no-really-you-won-a-nobel-prize-1444266470> [Accessed 12-15-17]
4. Taylor R. Australian Nobel winner thought prize call was a prank. *Reuters*, October 4, 2011. <https://in.reuters.com/article/idINIndia-59711220111005> [Accessed 12-15-17]
5. Kobilka B. 2012 Chemistry winner let Nobel call go to voice mail. *Morning Edition, Wisconsin Public Radio*, October 9, 2015. <https://www.npr.org/2015/10/09/447098680/2012-chemistry-winner-let-nobel-call-go-to-voicemail> [Accessed 12-15-17]
6. Annicchiarico F, Weinstock SY. Harvard professor and alum win Nobel prize in economic sciences: Alvin E. Roth shares prize with Harvard alum Lloyd S. Shapley '44. *Crimson*, October 15, 2012. <http://www.thecrimson.com/article/2012/10/15/economics-nobel-roth-harvard/> [Accessed 12-15-17]
7. Dubner SJ. How to win a Nobel prize: a new *Freakonomics* radio episode. October 15, 2015. <http://freakonomics.com/podcast/how-to-win-a-nobel-prize-a-new-freakonomics-radio-episode/> [Accessed 12-15-17]
8. [Hell S]. Chemistry laureate thought Nobel call was a 'hoax.' *Agence France-Presse*, October 8, 2014. <https://www.ndtv.com/world-news/chemistry-laureate-thought-nobel-call-was-a-hoax-676620> [Accessed 12-15-17]
9. Stilwell V, Ito A, Moss D. ‘This is not a prank:’ How Angus Deaton found out about Nobel Prize win. *Sydney Morning Herald*, October 16, 2015 .

<http://www.smh.com.au/business/the-economy/this-is-not-a-prank-how-angus-deaton-found-out-about-nobel-prize-win-20151015-gkahs9.html> [Accessed 12-15-17]

10. Nobel-winning economist worried prize phone call was prank: The British-born winner of the Nobel Economics Prize joked Monday that he worried the telephone call from Sweden alerting him of the award might have been a prank.

Agence France-Presse, October 13, 2015

<http://profit.ndtv.com/news/people/article-nobel-winning-economist-worried-prize-phone-call-was-prank-1231574> [Accessed 12-15-17]

11. Edwards J. 'You have 45 minutes warning': This is what happens when they call you at 6 a.m. to say you've won the Nobel Prize. Business Insider, February 4, 2017.

<http://www.businessinsider.com/what-happens-when-you-win-the-nobel-prize-2017-2>

12. Ishiguro K. Nobel winner Ishiguro's reaction: 'It was a hoax': The newest winner of the Nobel Prize for Literature, Kazuo Ishiguro, tells media that he didn't know he'd won until journalists started looking for him. The Washington Post, October 5, 2017.

https://www.washingtonpost.com/video/world/nobel-winner-ishiguros-reaction-it-was-a-hoax/2017/10/05/15dd1fc2-a9f7-11e7-9a98-07140d2eed02_video.html?utm_term=.928ea03f189a [Accessed 12-15-17]

13. Lewis M. Nobel Peace Prize awarded to anti-nuclear campaign group. Associated Press, October 6, 2017.

<https://www.bostonglobe.com/news/world/2017/10/06/international-campaign-abolish-nuclear-weapons-wins-nobel-peace-prize/zIXd3sPdrdbDvtQfi5G6hN/story.html> [Accessed 12-15-17]

14. Perrigo B. How the world is reacting to ICAN winning the Nobel peace prize. Time, October 6, 2017. <http://time.com/4972021/nobel-peace-prize-2017-ican-reacts/>

[Accessed 12-15-17]

15. Fihn B. Peace Prize winners thought Nobel call 'was a prank.' NBC News, October 6, 2017. <https://www.youtube.com/watch?v=dnh-fTK3zMM> [Accessed 12-15-17]

16. Wright R. The Nobel Peace Prize goes to anti- bomb idealists. The New Yorker. October 6, 2017. <https://www.newyorker.com/news/news-desk/the-nobel-peace-prize-goes-to-grassroots-anti-bomb-group> [Accessed 12-15-17]

17. Ritter M, Heintz J. Biological clock discoveries by 3 Americans earn Nobel prize. Associated Press, October 2, 2017.

<https://www.apnews.com/23246a2d670b460481305d4f9702b900> [Accessed 12-15-17]

18. McCrea N. Once ridiculed researcher and retired Cambridge resident wins Nobel Prize. Piscataquis Observer, October 4, 2017.

<https://observer-me.com/2017/10/04/once-ridiculed-researcher-and-retired-cambridge-resident-wins-nobel-prize/> [Accessed 12-15-17]

19. Koch M, Hall J. A Nobel pursuit may not run like clockwork. Cell 2017;171:1246-1251.

20. Sleep studies win Mainer Nobel Prize. Associated Press, October 3, 2017.

<http://www.wcsh6.com/news/local/sleep-studies-win-mainer-nobel-prize/480302154> [Accessed 12-15-17]

the first time some reporter called up and convinced somebody that they had been given the Nobel Prize. Now, the reporter was right, and the reporter became famous for predicting all of this, and what happens in the future, and the reporter would have unending access to the scientific community. But, this was not a joke. This was real. But I said, “I screwed up,” because I should have said to Nils Ringertz, “I don’t want to recite to you where I met you. I want you to recite to me where you met me, so I know it’s you.””

LK: [chuckles]

21. Chu, Fischer, et al. iBiologie. When Stockholm called. September 28, 2016. <https://www.youtube.com/watch?v=Giq-CJ8cxuo> [Accessed 12-24-17]
22. Griehsel M. Interview transcript. Transcript from an interview with Professor William Sharpe at the 1st Meeting of Laureates in Economic Sciences in Lindau, Germany, September 1-4, 2004. https://www.nobelprize.org/nobel_prizes/economic-sciences/laureates/1990/sharpe-interview-transcript.html [Accessed 12-24-17]
23. Griehsel M. Interview transcript. Transcript from an interview with Professor James A. Mirrlees at the 1st Meeting of Laureates in Economic Sciences in Lindau, Germany, September 1-4, 2004. https://www.nobelprize.org/nobel_prizes/economic-sciences/laureates/1996/mirrlees-interview-transcript.html [Accessed 12-24-17]
24. Whipple T. What it’s like to notify a Nobel Prize winner: “We tell assistants this is a very important call. A. Very. Important. Call.” Reader’s Digest <https://www.rd.com/culture/what-its-like-notify-nobel-prize-winner/> [Accessed 12-24-17]
25. Whipple T. Nobel calling. They are among the most coveted prizes in the world. But how do the winners hear the good news? The Economist, September/October 2013. <https://www.1843magazine.com/content/ideas/anonymous/nobel-calling> [Accessed 12-24-17]
26. Smoot G. US scientists react to news of Nobel Prize win. Associated Press, July 23, 2015. <https://www.youtube.com/watch?v=dSZmGfYAd9Y> [Accessed 12-25-17]
27. Fihn B. I can director: I thought Nobel peace prize win was a prank. Guardian News, October 6, 2017. https://www.youtube.com/watch?time_continue=16&v=csmqDwChaSE [Accessed 12-26-17]

SP: I didn't do that. I kinda said, "Well, alright."

Then, seven o'clock in the morning comes, and there's nothing more on the TV. I turn on the radio. That I found a radio was amazing. The radio was on, and then there it's all laid out, and I said [expressing relief], "Oh, okay."

Then, I thought, well, there's some assholes downstairs, who are at this same FDA meeting on kuru and prions. What are they going to say?

SP and LK: [chuckles]

SP: I said, "Fuck 'em!"

SP and LK: [laughter]

SP: It doesn't matter what they say. I got dressed, and I went downstairs. Most of them were clapping, and they were really excited. It doesn't happen that you're at a meeting when somebody wins a Nobel Prize.

DL: Not often.

SP: But a few of these people were really upset. You could see it in their faces. Then, they'd say, "*Congratulations*" [said with a sarcastic tone].

LK: [chuckles]

DL: Who do you think was in contention to be a co-recipient?

SP: I think... I don't know. I don't know. I've never seen the documentation, so I don't know.

DL: It's not common anymore for someone to receive the Nobel Prize in Physiology or Medicine as a solo individual. In the first fifty-such prizes, sixty percent were to a single individual, and in the last fifty—of which you were a member of that group—only fourteen percent.

SP: Yes.

DL: So it's not common, and you are the *only* clinical neurologist to have ever received the Nobel Prize in Physiology or Medicine [sic].

SP: I think that's right. But, there's that guy—what's his name?—the one who did arteriography... Moniz.⁹⁹

DL: I don't think he was a neurologist [sic].¹⁰⁰

SP: I thought he was. No?

DL: I don't know. I'll have to check. But David Hubel,¹⁰¹ neurophysiologist, did two years of neurology and then said that was enough clinical medicine for him. Rita [Levi-] Montalcini¹⁰² did three years of neurology and psychiatry, but never practiced any clinical neurology, to my knowledge. Those are both dead. So as a living individual, you are the only neurologist to have won a Nobel Prize.

SP: You better keep me alive.

DL: Yes. I'll will do my best.

[laughter]

SP: You better not starve me. [laughter]

[brief discussion of interview logistics]

DL: I think it's fair to say that you're a maverick and an iconoclast. You're an independent thinker. You have challenged traditional thinking in an area. How important do you think that is to achieving something truly novel?

⁹⁹ Portuguese neurologist Antonio Caetano de Abreu Freire Egas Moniz (1874-1955) controversially shared the Nobel Prize in 1949 "for his discovery of the therapeutic value of leucotomy in certain psychoses." In retrospect, Moniz made a greater contribution with his introduction and development of cerebral angiography.

See: Lanska DJ. Moniz, Egaz. In: Aminoff M.J. and Daroff R.B. (eds.) *Encyclopedia of the Neurological Sciences*, 2nd edition. Oxford: Academic Press. 204;3:92-93.

¹⁰⁰ DL had misremembered him as a neurosurgeon.

¹⁰¹ Canadian neurophysiologist David Hunter Hubel, M.D., F.R.S. (1926-2013) was co-recipient with Swedish neurophysiologist Torsten Nils Wiesel, M.D., F.R.S. (1924-) of the 1981 Nobel Prize in Physiology or Medicine [shared with Roger W. Sperry (1913-1994)], "for their discoveries concerning information processing in the visual system."

¹⁰² Italian physician-scientist Rita Levi-Montalcini, M.D. (1909-2012) was awarded the 1986 Nobel Prize in Physiology or Medicine jointly with American biochemist Stanley Cohen (1922-) "for their discoveries of growth factors." In 1952, Levi-Montalcini demonstrated that a substance (i.e., nerve growth factor) harvested from murine tumors caused vigorous nervous system growth in chicken embryos.

SP: I think it's crucial. That's a crucial piece of it, but the *real* piece is luck. You've got to have good luck.

If this had some trivial solution, like there really was an “unconventional virus,” a small virus. Maybe it was a viroid wrapped in protein.¹⁰³ Then you'd say, “What is this?” and you'd have to give it some new name, but it wouldn't be very novel. That's not how it turned out. This turned out to be a whole new world. *Nobody* saw this coming. Nobody thought that after all the work on showing that new traits were all encoded in DNA or RNA... they really did not think that there was going to be anything new. People had worked really hard to work out all the biology from 1944 to 1970... Well, let's just go up to 1995, right? This was the 1997 Prize. That was the golden era of nucleic acid research. People didn't see this coming.

¹⁰³ A viroid is an infectious agent that consists solely of a single strand of RNA, lacking the protein coat (capsid) of viruses. These agents have been documented to be plant pathogens: The first recognized viroid, the potato spindle tuber viroid, was discovered in 1971 by Swiss-American plant pathologist Theodor Otto Diener (1921-) at the U.S Department of Agriculture's Research Center in Beltsville, Maryland. So, since a viroid is infectious RNA lacking the protein coat of viruses, presumably “a viroid wrapped in protein” would be a virus.

Later, in 1978, veterinary geneticist Alan Dickinson coined the related term “virino” to refer to the infective unit of scrapie “which (by analogy with neurinos) are small, immunologically neutral particles with high penetration properties but needing special criteria to detect their presence.” Subsequently, Dickinson, Richard H. Kimberlin, and others used the term virono to refer to “viroid-like DNA complexed with host proteins,” which again is presumably a virus.

Outside of a small group of “scrapie-ologists,” the term virino never caught on, as it was a conceptually problematic effort to explain prion diseases within an existing (and failing) paradigm, akin to the fuzzy thinking that produced “unconventional virus.” Interestingly, it also failed the Prusiner criterion of being at most two syllables long.

See:

1. Diener TO. Potato spindle tuber "virus". IV. A replicating, low molecular weight RNA. *Virology* 1971;45(2): 411-428.
2. Prusiner SB. *Madness and Memory: The Discovery of Prions—A New Biological Principle of Disease*. Yale University Press, 2014:46-47.
3. Dickinson AG, Outram GW. An assessment of the genetics of scrapie in sheep and mice. In: Prusiner SB, Hadlow WJ (eds.). *Slow Transmissible Diseases of the Nervous System*. New York: Academic Press, 1979;1:367-386.
4. Kimberlin RH. Scrapie agent: prions or virinos. *Nature* 1982;297:107-108.

DL: That's all true, but you can't very well *actively* be lucky. Do you know what I mean? You could be a maverick. You could have a novel idea. But lucky? It's hard to recommend that as a character trait, let us say.

SP: No, but most people who do science work really hard, and they do really good work. They're really solid people. They make one or two discoveries, but they don't quite get there.

DL: Yes.

SP: Then, someone else comes along, and either something really important comes out of all that research after a long time or maybe it doesn't. Maybe it has to wait even longer. To get into something and then have it explode into this fabulous nirvana with only a protein, that's just really great luck, because most people don't have that.

After all of this, we first find that it's scrapie and Creutzfeldt-Jakob disease, and then in 1983 I discover that the prions are aggregated into these fibrils, and the fibrils have the tinctorial and ultrastructural properties of amyloid. Then, as a neurologist, I looked at what I was seeing in the light microscope as a resident with Dick Baringer¹⁰⁴ and instantaneously I knew that this was the beginning of a revolution in neurodegenerative diseases, because now you look at plaques, and you look at tangles, and you look at Lewy bodies, and they're *all* amyloids. That's what the brain is dealing with—with these people who get bad illnesses. Then, you know, it's a matter of time to work it out.

DL: The last thing we'll cover in this part of the interview... Let me ask you about the role that conflict and skepticism played, and whether it had an effect on pushing you to make your science stronger.

SP: Well, I don't know. From my point of view, what I was trying to do was not make a mistake. So this is *à la* Earl Stadtman. I was just trying to understand whether I got it right or whether I got it *wrong*. I didn't want to be *wrong*. So it wasn't about *their* skepticism. I got to the point where I'd had enough of this stuff about other people saying, "Well, you did all this stuff, and it must be wrong."

One Nobel Prize winner, Dan Nathans,¹⁰⁵ who I got to know, came to me one day. This was two or three years after I'd spent a lot of time talking to him at a Howard Hughes Institute meeting. I'd given this big lecture at the NIH, and he came up to me afterwards and he said, "You know, Stan, I don't believe anything you say. It's not right." I said,

¹⁰⁴ Neurologist and neurovirologist J. Richard ("Dick") Baringer, formerly at UCSF, and now Professor Emeritus of Neurology, University of Utah.

¹⁰⁵ American microbiologist Daniel Nathans (1928-1999) shared the 1978 Nobel Prize in Physiology or Medicine "for the discovery of restriction enzymes and their application to problems of molecular genetics."

“What is that you don’t think is right?” My friend Joe Goldstein¹⁰⁶ was standing there, listening to all of this, and he’s not saying anything. I mean, “Joe, what don’t you just tell Dan to go screw himself?” [laughter] I said, “Okay. Look, if you can think of an experiment I should do that will overturn everything, as you say, why don’t you tell me, and I’ll do it.” So two weeks went by, and he didn’t send me anything. I wrote him, and I said, “I’m waiting for you to tell me what to do to show that what I’ve done is wrong.” He wrote me back, and he said, “Well, if I get a good idea, I’ll send it to you.” I said, “Okay. Fine.” I didn’t write him back. There wasn’t any point to write him back, and he never came up with an idea. He died. This was typical.

DL: That kind of gets back to my earlier point that the skeptics don’t convert, they...

SP: Yes, exactly. This was really a surprise. I thought that after two hours of talking to him at this meeting in Florida, one-on-one, that he was convinced, and then just out of the blue he comes and he attacks me. I said, “Well look, you just tell me what I need to do.”

[notice given that designated time for interview was reached]

DL: We’ll conclude this at this time. It’s been truly a privilege and an honor to have talked with you this morning.

SP: You’re very kind. Thank you for taking the time.

[End of the Private Portion of the Interview]

¹⁰⁶ American biochemist Joseph Leonard Goldstein (1940-) received the Nobel Prize in Physiology or Medicine in 1985, with fellow University of Texas researcher Michael S. Brown (1941-), “for their discoveries concerning the regulation of cholesterol metabolism.”

Interview with Doctor Stanley Prusiner Resumes

Interview by Doctor Doug Lanska in front of an audience at the Boston Convention Center

Stanley Prusiner - SP
Douglas Lanska - DL

During audience discussion:

George Perry - GP
Unidentified audience participant - AP

DL: Welcome and good afternoon everyone. It is indeed my privilege and honor to talk with Dr. Stanley Prusiner today, the 1997 sole recipient of the Nobel Prize in Physiology or Medicine for that year.

In the first fifty years of the awarding of that prize, sixty percent were to a sole individual. But in the last fifty years, the number is fourteen percent. Dr. Prusiner is the sole clinical neurologist [sic],¹⁰⁷ certainly the sole living clinical neurologist, to have been awarded that prize.

Dr. Prusiner is currently professor of neurology at UCSF and has been since 1984, where he directs the Institute for Neurodegenerative Diseases. He spent three years at NIH and did his neurology residency at UCSF, where he began his academic career in 1974. In 1992, he was elected to be a member of the National Academy of Sciences. In 1994, he received the Albert Lasker Award for basic medical research. In 1997, again [noted], he became a Nobel laureate.

SP: That was a hell-of-a-roll.

[audience laughter]

DL: That was a hell-of-a-roll, exactly.

I would say that there is a group of neurologists in Germany who have won last year the Ig Nobel Prize [for Medicine],¹⁰⁸ but that does not compare to Dr. Prusiner's accomplishments in winning the *true* Nobel Prize.

¹⁰⁷ Egas Moniz also was a clinical neurologist. See footnote 99.

¹⁰⁸ Neurologists from the University of Lübeck, Germany (Christoph Helmchen, Carina Palzer, Thomas Münte, Silke Anders, and Andreas Sprenger), won the 2016 Ig Nobel prize for Medicine “for discovering that if you have an itch on the left side of your body, you can relieve it by looking into a mirror and scratching the right side of your body (and vice versa).”

[audience chuckles]

He has also won many of the major awards of the American Academy of Neurology. In 1987, he received the George Cotzias Award for Outstanding Research in Neurology. In 1991, he won the Potamkin Prize for Alzheimer's Disease Research which was bestowed here in Boston that year. In his monograph, he wrote, "[M]y exile from the biological establishment had come to an official close when the American Academy of Neurology awarded me its 1991 Potamkin Prize for Alzheimer's Disease and Related Disorders research. The prize was bestowed in Boston..."¹⁰⁹ So it's fitting that, today, we discuss some aspects of his career. He also received the American Academy of Neurology Presidential Award in 1993, became a fellow [of the American Academy of Neurology] in 1996, received the Distinguished Achievement Award [of the American Academy of Neurology] in 1998, and became an honorary member [of the American Academy of Neurology] in 2003. He has authored or co-authored more than 500 academic scientific papers and has received 12 honorary degrees.

Please, join me in welcoming Dr. Prusiner today.

[applause]

SP: I might elaborate for a moment...

DL: Please.

SP: ... on the Potamkin Prize here in Boston. One of my friends, Frank Westheimer, who was a professor of organic chemistry at Harvard—I knew him really through family ties—he came, and we went to lunch afterwards, and he said, "Who made those slides for you?" And I said, "I made those slides." He said, "They're horrible! You can't read them."

See:

1. Helmchen C, Palzer C, Münte TF, Anders S, Sprenger A. Itch relief by mirror scratching. A Psychophysical Study. PLoS ONE 2013;(8)12: e82756.
2. Tanne JH. Neurologists win Ig Nobel prize for discovering that scratching the other side relieves itching. BMJ 2016;354:i5193.
3. Winners of the Ig® Nobel Prize: The 2016 Ig Nobel Prize Winners. <https://www.improbable.com/ig/winners/?#ig2016> Accessed 12-13-17.

¹⁰⁹ Prusiner SB. *Madness and Memory: The Discovery of Prions—A New Biological Principle of Disease*. Yale University Press, 2014:177.

[audience chuckles]

SP: Just yesterday, I told this little vignette on the phone to a young man who has got some fabulous data that I think will help march us forward in trying to develop drugs for Alzheimer's and Parkinson's. I said, "Carlo [Breda], those slides that you just sent me are unreadable." [chuckles] I said, "The letters and the numbers are so small that no one can read them." Then, I told him the story of Frank Westheimer, and I said, "So, now you can join in good company here, and you need to fix it."

[audience chuckles]

SP: That's my little story.

DL: Fair enough.

Stan, your interest in what have become the prion diseases began as part of your clinical career with a specific patient. Can you tell us what stimulated your interest in this group of disorders?

SP: I had a patient with Creutzfeldt-Jakob disease [CJD]. I had no idea what the disease was about in that patient. I couldn't make the diagnosis, but it was readily made by older neurologists. I had already seen this book by Kirschbaum called *Jakob-Creutzfeldt Disease*, a monograph, in 1968.¹¹⁰ That's the same year that [D. Carleton] Gajdusek and [C. Joseph] Gibbs published their seminal paper on the transmission of CJD to apes and monkeys.¹¹¹ Once I knew about the disease, and then a little bit more, it was really [J. Richard] Dick Baringer, who was the second attending to see the woman, who said to me, "There's a lot of interest in chemistry. There's a lot of interesting data. You should look it up," and he gave me some references. That's really what started me thinking: Wow! This is really a great problem. The more that I delved into this, the more I read about it, the more excited I became.

I had done something, which a lot of people don't do. I had made up my mind that when I did a residency for two years, I was not going to go into the laboratory and try to do experiments, because I decided nothing I would do with the few hours that I might be able to steal from taking care of patients would lead anywhere. But it gave me a chance to read exhaustively. So I read everything I could find about scrapie. We had a good library

¹¹⁰ Kirschbaum WR. *Jakob-Creutzfeldt Disease: (Spastic pseudosclerosis, A. Jakob; Heidenhain syndrome; subacute spongiform encephalopathy)*. Amsterdam and New York: Elsevier, 1968.

¹¹¹ Gibbs CJ Jr, Gajdusek DC, Asher DM, Alpers MP, Beck E, Daniel PM, Matthews WB. Creutzfeldt-Jakob disease (spongiform encephalopathy): transmission to the chimpanzee. *Science*. 1968;161(3839):388-389.

at UCSF and UC-Davis. So I could read all the literature. So I got more and more excited about this.

DL: But you switched very quickly from [being] Creutzfeldt-Jakob-disease focused to scrapie focused. Tell us how that came to be.

SP: When I started to add up the bills for monkeys or chimpanzees, and I compared those to mice, it was pretty clear that I wasn't going to get anywhere doing these experiments with apes and monkeys. Mice were clearly much better than apes and monkeys, and clearly much better than sheep. So, it was no leap of genius to figure out that I should use mice.

DL: Scrapie was a good problem for you and allowed you to use your skills that you developed at the NIH, allowed you to focus things very quickly on solving some aspects of the characterization of the scrapie agent. Can you tell us about that?

SP: The prevailing ideas at the time were that this was an infectious particle and that it must be a virus because it's very small. It goes through filters, classically bacteria were retained by these filters, and it must be that there has to be some sort of virus that creates scrapie, CJD, kuru, and other similar diseases. There had been a lot of attempts to demonstrate this "virus" and find this "virus" using classical techniques like cesium chloride gradients.

Not being able to find such a "virus," I set out to take a more simple-minded approach. That was, let's figure out what it is. Let's try to separate whatever it is away from all the things that have nothing to do with it. That's called purification. That was my focus and that's where I went with the problem, and that's what created all the advances that I was able to make. That was the route.

DL: So what you did originally was try to identify the size of it, purify it. You purified it from some...

SP: He's a good student. I've been filling him full of this for three hours.

[audience chuckles]

DL: We had a long chat this morning.

You started out with purification of some 30-fold of infectivity and wound up with more than 5,000-fold.

SP: Well, that's not atypical for most proteins. Only when some protein is highly over expressed is it about 100-fold purification. Most proteins are [purified] 1,000-, 5,000-, 10,000-fold until they become pure.

DL: To characterize this further, you tried to eliminate possibilities of whether it was just a protein or a protein with nucleic acid. How did you approach that?

SP: I went after the nucleic acid by six different approaches. I kept trying to knock out the infectivity by destroying nucleic acids. At the same time, I tried to knock out proteins by similar approaches. So either I was chemically modifying the protein, chemically modifying nucleic acid with different chemicals, using different enzymes, proteases to kill proteases and nucleases and UV light and other approaches for nucleic acids. What I kept finding was that, the more I purified the infectious agent, that I eventually called prion, the more readily I could destroy it with techniques that modify proteins. But no matter what I did, the nucleic acid techniques did nothing to alter the infectivity.

DL: You had a classic, landmark paper in *Science* in 1982¹¹² that not only outlined some of those results, but also proposed a new term. Tell us about how you came up or derived this new term.

SP: Well, what happened was that I kept saying to myself, calling this a virus, calling it an “unconventional virus,” calling it an atypical virus, calling it an unusual virus, a small virus, a big virus, this led nowhere. It confused me. It confused the field. It confused the people working with me. And I thought we needed something better.

About two years before the paper was published, Frank Westheimer—the same professor of organic chemistry that I was telling you about, who said, “You can’t read the text of this” in this very building—he said to me, “Stan, look, you’ve really discovered something very important here. A few more experiments, and you need to publish this, and you need to make sure that you pick a good term to describe this infectious particle that is not anything like a virus. If you pick a bad word, someone else will come up with a better word, and they’ll get the lion’s share of the credit.” Then I started to get really nervous, shaking.

[audience laughter]

SP: I said, “Well, that’s not a good idea to have somebody else steal all this hard work.” So, I started to spend time on this idea.

Then I went to [Philip H.] Phil Abelson, who was the editor of *Science*, at the time.¹¹³ I spent two hours on the phone with him, and he said, “That’s great. I’ll look forward to an article.” So I had a *lot* of space, five or six pages, to develop the whole story.

¹¹² Prusiner SB. Novel proteinaceous infectious particles cause scrapie. *Science* 1982;216:136-144.

¹¹³ See footnote 83.

I said, "Okay. I've got to spend time on this word," because Westheimer had said to me, "Don't take this lightly. You need to come up with a great word." I knew a lot of Latin, but no Greek. That was a serious problem, I thought. I kept thinking that I could go to Berkeley, and I could find some person who was a master of words. I kept saying, "There's got to be somebody that designed a word like Exxon." I thought that was a great word.

[audience chuckles]

SP: Before there were *introns* and *exons*, I thought two x's like that, boy, that's just fabulous! My model words were virus and quark [pronounced correctly as *qwork*]. I thought Murray Gell-Mann¹¹⁴ was terrific with that, stealing that from Lewis Carroll [sic]. So I looked through *Alice in Wonderland* for another one, but I didn't find one.

¹¹⁴ American physicist Murray Gell-Mann (1929-) received the 1969 Nobel Prize in physics "for his contributions and discoveries concerning the classification of elementary particles and their interactions." Gell-Mann coined the term *quark* (which he pronounced *kwork*) in 1963 to refer to the fundamental constituents of the nucleon (i.e., either a proton or a neutron, considered in its role as a component of an atomic nucleus), with the spelling derived from a whimsical poem in *Finnegans Wake* (1939) by Irish writer James Joyce (1882-1941), and not from the fantasy novel *Alice's Adventures in Wonderland* (1865) written by English mathematician Charles Lutwidge Dodgson (1832-1898) under the pseudonym Lewis Carroll.

In Gell-Man's account (1995):

In 1963, when I assigned the name "quark" to the fundamental constituents of the nucleon, I had the sound first, without the spelling, which could have been "kwork". Then, in one of my occasional perusals of *Finnegans Wake*, by James Joyce, I came across the word "quark" in the phrase "Three quarks for Muster Mark." Since "quark" (meaning, for one thing, the cry of the gull) was clearly intended to rhyme with "Mark", as well as "bark" and other such words, I had to find an excuse to pronounce it as "kwork." But the book represents the dream of a publican named Humphrey Chimpden Earwicker. Words in the text are typically drawn from several sources at once, like the "portmanteau" words in *Through the Looking-Glass [and What Alice Found There]* (1871), the novel by Lewis Carroll]. From time to time, phrases occur in the book that are partially determined by calls for drinks at the bar. I argued, therefore, that perhaps one of the multiple sources of the cry "Three quarks for Muster Mark" might be "Three quarts for Mister Mark", in which case the pronunciation "kwork" would not be totally unjustified. In any case, the number three fitted perfectly the way quarks occur in nature. (Gell-Man, 1995, p. 180)

Similarly, in an account by Merriam-Webster of the origin of Gell-Mann's term,

[audience chuckles]

Whenever I would go to a boring lecture, I would write on a piece of paper, “Protein. Infectious. Agent.” I kept going through this, and I would pull out letters, so I could have some minor rationale about this.

I came up with p-i-a-f, *piaf*. I said, “Yes, that’s a great word because of Edith Piaf, this unbelievable singer.” “Sparrow” was great.¹¹⁵ So I laid that out, wrote the paper that way. Then, I sent it to one of my friends,¹¹⁶ who was the director of Roche Institute, which was a place that existed for about thirty years, and then Roche closed it because they never got a single drug out of it. He wrote me back, and he said, “Stan, this is an *American* discovery, not a French discovery. You’ve got to get rid of that.”

[audience chuckles]

According to his own account he was in the habit of using names like ‘squeak’ and ‘squork’ for peculiar objects, and ‘quork’ (rhyming with pork) came out at the time. Some months later, he came across a line from Joyce’s *Finnegans Wake*:

Three quarks for Muster Mark!
Sure he has not got much of a bark
And sure any he has it’s all beside the mark.

The line struck him as appropriate, since the hypothetical particles came in threes, and he adopted Joyce’s spelling for his “quork.” Joyce clearly meant quark to rhyme with Mark, bark, park, and so forth, but Gell-Mann worked out a rationale for his own pronunciation based on the vowel of the word quart: he told researchers at the Oxford English Dictionary that he imagined Joyce’s line “Three quarks for Muster Mark” to be a variation of a pub owner’s call of “Three quarts for Mister Mark.” Joyce himself apparently was thinking of a German word for a dairy product resembling cottage cheese; it is also used as a synonym for quatsch, meaning “trivial nonsense.”

See:

1. Gell-Mann M. A schematic model of baryons and mesons. *Physics Letters*. 1964;8(3):214-215.
2. Gell-Mann M. *The Quark and the Jaguar: Adventures in the Simple and the Complex*. New York: Henry Holt and Co., 1995:180
3. What Does ‘Quark’ Have to Do with *Finnegans Wake*? How a word used by James Joyce became the name for an elementary particle of matter. Merriam-Webster, 2017. <https://www.merriam-webster.com/words-at-play/quark> [Accessed 12-12-17]

¹¹⁵ See footnote 89.

¹¹⁶ Sidney Udenfriend. See footnote 90.

So now I got rid of that, and I got rid of the word *agent* because it's so non-specific. There are FBI agents and... I didn't know that they could make someone president.¹¹⁷

[audience laughter]

SP: They're more powerful than I thought. Maybe I should have left *agent* in there.

[audience laughter]

At any rate, what I then did was to get rid of *agent*. Now, I had two words: protein and infectious. I started moving letters around. I don't know how many times I came across the same word. I have no idea, but this one time, it stuck, and it was p-r-i-o-n. I said, "You know, that looks like a good word, because there is *ion* in it—i-o-n. That makes it very fundamental. It's got two syllables. It looks very fundamental. It looks good." So I then put that together.

I went and looked in a dictionary and—oh boy!—there was a bird. The bird lived in Tasmania.

[laughter]

SP: The bird could fly from Tasmania to the Antarctica. I said, "Who the hell has ever seen this bird or heard of this bird?" It's pronounced *pry-on*. It has a saw-tooth beak. That's where the word was derived from, from the Greek word for saw. I said, you know, "Only a few ornithologists will be upset by this. It's just no big deal. So, forget it."

So I went on with it, and I called it *pree-on*. I said, "If I'm right, that will be the number-one definition of p-r-i-o-n," forgetting about how it's pronounced. That's where it is. That's how it happened.

I have to say that then this journey... I'm going to tell a little more of the story, since this is all kind of folksy. When I wrote this book called *Madness and Memory*¹¹⁸... I was trying to give you guys little bookmarks, but they didn't come. Fed-Ex killed the story. What happened was that in trying to put this book together, called *Madness and Memory*,

¹¹⁷ FBI Director James Comey sent a letter to Congress on October 28, 2016 in which he wrote that the FBI had "learned of the existence of emails that appear to be pertinent to the investigation" into the private email server that Democratic presidential candidate Hillary Clinton used as Secretary of State. Reports of this letter disrupted the news cycle, soon halved Clinton's lead in the polls, and were subsequently felt to have ultimately cost her the election.

¹¹⁸ Prusiner SB. *Madness and Memory: The Discovery of Prions—A New Biological Principle of Disease*. Yale University Press, 2014.

published in 2014... I'm trying to sell copies still. It's hopeless, but I'm still trying. What I did was, I looked up in Google p-r-i-o-n, because now Google was becoming easy to use. I went to Imperial College to do a sabbatical in London, so I could actually get this book written that I'd dreamed about. But I clearly never needed to go to the library, because Google was there on my computer. It was *fantastic*. I looked up everything. I even looked up p-r-i-o-n. There's an entry and then there's a picture under it. I think that picture is still there—of a boat. Behind the boat, in the water, is a little island. It said, “P-r-i-o-n, Prion Island” [pronounced *pry-on*]. I said, “Oh, my god! I've got to go there.”

A few years later, I went to the Antarctica. I went with a group from the [National Research Council for the] White House on the expenditure of funds. I was the only non-polar scientist. I had a really big function because, after every meeting or [during] every break, people would come up to me who were polar scientists, and they would say, “We're so happy you're here because you're the only one who can ask questions about things we're supposed to understand, and we don't understand.”

[audience laughter]

SP: So I went to the Antarctica. I went to the South Pole, but I couldn't go to that island. That island is in South Georgia, and I had no understanding of the distances. I'd never really looked this up in detail. I just thought, okay, I'm going to be in the neighborhood. [chuckles] Well, there's no airport on all of South Georgia. This is where [Ernest] Shackleton went to get a boat from the whaling station when he went and saved all the crew from the *Endurance*.¹¹⁹ So it has this long, beautiful history.

Then, this past summer... Two years ago, I met a man who decided that what he wanted to do was do was do a circumnavigation of the Antarctica. What he then did was he went to Putin,¹²⁰ because he knows him, and he rented a Russian icebreaker. I was always scared that I was going to be in a storm, and I was not going to come back. Well, this boat was 500 feet long. It rocked a lot, but nevertheless, I got there. I saw it [Prion Island], but I never stepped on it, because we were in the middle of a cyclone. The waves were too big. But I've seen this island in person.

[audience chuckles]

SP: Maybe that's a point where we should stop, and you should take over.

[audience laughter]

DL: That's fine, but you did see plenty of whale birds or prions [pronounced *pyr-ons*].

¹¹⁹ See footnote 9.

¹²⁰ Vladimir Vladimirovich Putin (1952-), President of the Russian Federation since 2012, after previously holding the position from 2000 until 2008.

SP: Yes.

DL: You have at least one picture with a dead one, right?

SP: I was scared I wasn't going to get any pictures. I didn't realize that ornithologists, when they buy cameras, they buy lenses like this [motions to indicate a long lens] and then they can get high-speed pictures. I had a little camera. I have to say that I went from a big camera, when I was in India. I was buying some rugs, and there was some guy who wanted to talk. He said he was from Oakland, California. I said, "So what do you do?" He said, "I'm a photographer." I said, "So what kind of pictures do you take?" He said, "I was Margaret Mead's photographer."¹²¹ I said, "So what kind of camera do you use?" He said, "Oh I have just a little, tiny, light camera." So since that time, I got rid of all these heavy cameras. I just have that [small camera]. But these birds were not within my reach. Anyway, the guy, he's in Cape Town, and he just sent me a large number of files. I have prions [pronounced *pry-ons*] coming out my ears. They're great.

DL: Hopefully, not prions [pronounced *pree-ons*], just prions [pronounced *pry-ons*].

[audience laughter]

SP: Exactly! Correct. You got it.

DL: But in Grytviken, you did get a picture, right?

SP: I got a picture in a museum [in Grytviken of] a big plaque that says there are twenty-two million prions. I kept saying, "Why the hell don't I have a lot of pictures of these?"

¹²¹ Ken Heyman (1930-) was a student of American cultural anthropologist Margaret Mead, Ph.D. (1901-1978) while attending Columbia University, and submitted a photo essay for a term paper assignment in her course. Upon Heyman's graduation in 1956, Mead invited him to go with her to take pictures in Bali. Heyman and Mead collaborated for more than 20 years. His photographs appeared in two books co-authored with Mead: *Family* (1965) and *World Enough* (1975). Heyman has also photographed various celebrities, including Ernest Hemingway, Pablo Picasso, Elizabeth Taylor, Andy Warhol, and Marilyn Monroe. Shows of Heyman's work have been held at the Museum of Modern Art in New York City (1963), the Hallmark Gallery in San Diego (La Jolla) (1965), the International Center for Photography in New York City (1976), and the Zabriskie Gallery in Paris (1995). He resides in Oakland, California.

See:

1. Mead M, Heyman K. *Family*. New York: Macmillan, 1965.
2. Mead M, Heyman K. *World Enough: Rethinking the Future*. Boston: Little Brown and Co., 1975.

But, then, it dawned on me that you've got to go fast [with a] big lens. Right next to it was a prion, stuffed, in the museum. I took a picture of that.

[audience chuckles]

DL: I informed him in our oral history discussion this morning...

SP: He likes that part of the story the best, right? He's excited about this stuffed bird in this glass case in South Georgia.

[audience laughter]

DL: I am excited about it. What intrigues me is your pursuit of prions [pronounced *pree-ons*] and prions [pronounced *pry-ons*] in any form, whatsoever.

[audience chuckles]

SP: But *now* what you've discovered is fantastic. Tell them what you told me.

DL: There's also a mountain in Turkey that's named Mount Prion. It was named such because of its saw-toothed character after, again, the Greek word for saw. So now he has another agenda, don't you?

SP: Yes, but the problem is whether I will outlive [Turkish President, Recep Tayyip] Erdoğan.

[audience chuckles]

It's not so clear that it's very safe to go to Turkey right now.

DL: No. Perhaps not.

Well, one more thing we should probably say about the derivation of the word prion is the reaction that a reviewer gave it when you submitted your paper to *Science* that was published in 1982. If I may, he wrote, "The term Prion is capitalized as if it were registered as a trademark. It carries unfortunate echoes of the author's name, *Prusiner ions*."¹²²

[audience chuckles]

¹²² Prusiner SB. *Madness and Memory: The Discovery of Prions—A New Biological Principle of Disease*. Yale University Press, 2014:90-91.

SP: My reaction was, well, then we need to get rid of protein and Prusiner, and how are we going to separate those out? I didn't want to give up my name. I'm sure that people in the sciences and the non-sciences didn't want to give up the word protein. It had a long, long history.

DL: Perhaps not. Yes.

SP: Anyway, it went nowhere.

DL: Yes.

Prion was introduced, and it had a lot of kickback, didn't it?

SP: Yes.

DL: Why do you think it had such a lot of negative kickback?

SP: This was a field that was stagnant. It wasn't going anywhere fast. It was slow. In fact, it was not progressing much at all. I don't know why somebody else didn't figure this all out. Some people said, "You usurped the name. You gave it a name. You just took over the whole field. You were supposed to be quiet about this. It should be called a *Gibbs* or a *Gajdusek*, not a *prion*." In science, you need to go as fast as you can. It's a competition. It's more than a competition, because in science there's no rediscovery.

Whoever wins [the NBA finals]... The [Golden State] Warriors are going to win, of course.¹²³

[audience chuckles]

SP: It could be the [Cleveland] Cavaliers. No, no.

DL: Cavaliers, I'm saying.

SP: George [Perry]¹²⁴ is out there [in the audience]. He might be rooting for the [San Antonio] Spurs, sometimes.

¹²³ Prusiner predicted correctly. The National Basketball Association (NBA) finals in June 2017 were played between the Western Conference champion Golden State Warriors and the Eastern Conference champion Cleveland Cavaliers. The Warriors won the finals 4-1 over the Cavaliers on June 12, 2017.

¹²⁴ George Perry, Ph.D., Dean of the College of Sciences, Professor of Biology, and Semmes Foundation Distinguished University Chair in Neurobiology at the University of Texas at San Antonio College of Sciences.

GP: And Cavaliers.

SP: He lives in San Antonio—can you believe this? [chuckles]—and he’s going to root for the Cavaliers. God!

[audience chuckles]

Anyway, it doesn’t really matter because in the next year, there’s going to be another playoff series, and we’re going to be entertained by it. It really makes no difference who wins this in reality. But Curry¹²⁵ is a really good guy, so root for him.

[audience chuckles]

In science, you can labor your whole life, and you can be unlucky, and you’ve worked and worked and worked, and you’ve never had quite the right approach, or you’ve not been able to get the support that you needed when you were going down the perfect path. Then, somebody who is doing science in Dongguan—that’s way, way west of China, near the big desert—that person can come up with a whole story, and figure it all out. They didn’t do anything wrong. They didn’t steal anything from anybody. They figured it out. And the person who’s been working on this for twenty years, who didn’t quite figure it out, but worked so hard, did so much work, they’re left with nothing, because they didn’t get there first. That’s science. That’s the way we’ve constructed science. There’s no rediscovery. The second discoverer or the fiftieth discoverer is in the same place.

I think people were worried about this. At that time, I had to take some guesses, but I had a lot of information. Maybe nobody else had a Frank Westheimer, but I had one, and he told me what to do, and he was right, and I did it, but there were some people who weren’t very happy because they realized what I had done. So, there’s a lot of negative reaction with something like that. The stakes were pretty high. So that’s how I view it. Maybe I’m wrong. Maybe you have another view.

DL: No. I think that’s an interesting perspective. One of the things we talked about this morning was whether this is really a Thomas Kuhn-type revolution in science, and we’re having difficulties switching from one paradigm to a new paradigm and that the people doing so-called “normal science” in the old paradigm can’t see the possibilities of that new paradigm, because they’re stuck in that old framework.¹²⁶

¹²⁵ Wardell Stephen Curry II (1988-), commonly known as Stephen Curry and sometimes as Steph Curry, is the point guard for the Golden State Warriors. In 2014-2015 and 2015-2016 seasons, Curry won the NBA Most Valuable Player Award. Curry led the Warriors to two NBA Championships, in 2015 and 2017. In 2016, the Warriors lost to the Cleveland Cavaliers in the finals.

¹²⁶ See footnote 41.

SP: I think that's true. Most people who are still working in this field never adopted the new approach, that this is *only* a protein, and that the protein had all of this different biological activity, all of these different strains of scrapie agent or CJD, and now multiple system atrophy, synuclein, A β , tau. They haven't thought about it like that. So it's been really hard to make this change. I think for a lot of people, they just could *not* adopt the idea that all of this biological activity that is conformationally driven and replicates, that each little change represents a different strain, a different biological property. To take all this in and then use it has been very, very difficult, because the techniques for three-dimensional structure analysis are really the most difficult.

Now, I think this is going to change with what's called cryo-electron microscopy, because we're going to be able to get the structures of all these different proteins that become aggregates and are difficult to deal with. They cause these horrible neurodegenerative diseases and some other degenerative diseases. We're going to understand the structures. When that happens, we're going to move toward drugs a lot faster. And I think once we really get drugs, just like with HIV, we're going to be at a point where we stop wondering if a mycobacterium is the cause of AIDS. We're going to see a revolution over the next ten or fifteen years.

DL: As that revolution transpires or develops, the people that were in that prior paradigm or framework traditionally haven't really come around. They've stuck with their old framework. As Thomas Kuhn wrote, they usually were eliminated by dying off. Do you see them coming around or is that really going to be kind of a Kuhnian change?

SP: Well, a lot of these people retired, so they don't have labs. I didn't mean to be flippant about that, but that's the reality for *those* particular people, who were my contemporaries in that era. There are lots and lots of new people. This is an *enormous* field.

George, how many papers published on Alzheimer's disease? Do you know?

GP: Seventy thousand.¹²⁷

SP: I guessed a hundred [thousand]. That's a lot of papers, and that's a lot of money spent to get all 70,000 papers, and we still don't have one drug that stops Alzheimer's disease. I can't sit here, [and] George can't sit here, and say, "We *know* what we should have done." We don't know what to do. There's a lot of different opinions. Somebody is going to be right. That means a lot of other people are going to be wrong. But, at the moment, we don't have anything. It's horrible. The disease just keeps increasing as we live longer, and we have more people on the planet.

¹²⁷ See footnote 30.

DL: As you were doing this work, particularly early on, before that landmark paper, you had a big struggle as a clinician/scientist trying to garner enough resources, enough lab space, enough support staff, working in a clinical department where it wasn't always perceived as the goal of the department to the point where at one point Robert Fishman wrote you a letter giving you notice that, perhaps, tenure was not going to be coming unless some changes were made. Tell us about that struggle.

SP: I never knew about the changes. I didn't know what those changes were. I just knew that I was trying to do what I wanted to do. This was a *hard* transition from the idea of a virus to a protein. So Bob had the same difficulties as many people, and he wasn't helped by the rigidity of other neurologists who would weigh in on this periodically, because he was trying to make sure that he wasn't doing something stupid. It was very hard. He didn't have the background to read the papers, but, on the other hand, he had the responsibility to try to decide whether he was going to have to spend his life working in a clinic to pay the salary of a tenured professor, who didn't want to go to clinic and didn't have any money to do any research, so he was just sitting there, looking at the sky, and contemplating his navel.

[audience chuckles]

SP: This was really rough on him. It was very hard. I think I make it pretty clear in the book that he wasn't evil.¹²⁸ He wasn't somebody who was trying to be problematic. He was trying to do what was best for a clinical department, who had this guy who didn't quite fit. But the guy didn't quite fit in the biochemistry department. Eventually, this all got ironed out, because the dean became involved, and some people from other institutions got involved, and I ended up with a lot of money from the tobacco world, from R.J. Reynolds. That just pushed everything over the top. So I was lucky! I didn't know what I was going to do if I had to leave. I'd have to recreate this huge animal colony, and I'd have to get a large staff with really talented people that I'd accumulated. I was not very happy during that period. Fortunately, it came to a head within a period of about six months. Yes, I don't know what else to say.

I wrote about it, I thought, pretty accurately. Wherever there was a lot of bile [in what I wrote in my memoir], it was edited by my wife, significant other. She took the first crack, and then a professional editor got involved. Then, three lawyers from Yale University Press read it, and it got cleansed a lot—not just that part, the whole book.

[audience chuckles]

¹²⁸ Prusiner SB. The battle for tenure. In: *Madness and Memory: The Discovery of Prions—A New Biological Principle of Disease*. Yale University Press, 2014:65-80.

DL: Tell us briefly what happened to you when you received the call that notified you of the winning of the Nobel Prize.

SP: Well, it was in the middle of the morning around 2:00 a.m., 3:00 a.m. I talked to the secretary of the Nobel committee, Nils Ringertz. He said, “Do you remember me?” I said, “Yes.” I told him exactly where I’d had dinner [with him]. Afterwards, I said, “God! I was stupid. I should have said to him, ‘Where did we have dinner? Then, I’ll know it’s you,’” because there are circumstances where reporters call up and tell scientists that they’ve won the Nobel Prize, and it’s nothing but a hoax. I didn’t do that. Anyway, he told me a lot of things, but nothing that was going to identify him as unique. Then, he said, “We’re giving you the entire prize.” I was blown away by that. Before he hung up, he said, “I hope you can make time in your schedule to come to Stockholm.” I never thought anybody like Dylan...that I’d be like that and not show up and have my own ceremony six months later.¹²⁹

[audience chuckles]

SP: I turned on CNN, because I wanted to know whether this was real, and there was nothing. Now, it was four o’clock in the morning and there was nothing. Then, it was five o’clock in the morning, and there was nothing. Then, it was six o’clock in the morning, and there was still nothing. It got to be pretty clear that it was *not* real. Then, at seven o’clock in the morning on the *radio*—this was not even at the level of TV; this was on the radio—it was real. So I was very happy. Every time I talk about this, I say to people, “I recommend this. It’s good. Don’t turn it down.”

[audience laughter]

SP: It’s a good thing to have happen to you. You’ll enjoy it. There’s nothing negative about it, even if there are a few people who want to say, “Ahhh! *That* guy should have *never* won a Nobel Prize.” I don’t care.

¹²⁹ American singer-songwriter Bob Dylan (1941-) won the 2016 Nobel Prize in Literature “for having created new poetic expressions within the great American song tradition.” Dylan missed the official award ceremony on December 10, 2016, due to “previous commitments.” He finally accepted the Nobel prize at a private ceremony in Stockholm on April 1, 2017.

See:

France-Press A. Bob Dylan finally accepts Nobel prize in literature at private ceremony in Stockholm. *The Guardian*, April 2, 2017.

<https://www.theguardian.com/music/2017/apr/02/bob-dylan-finally-accepts-nobel-prize-in-literature-at-private-ceremony-in-stockholm> Accessed December 12, 2017.

[audience chuckles]

SP: That's a summary.

DL: That's a summary.

I would think it's fair to label you as a maverick and an iconoclast, certainly an unorthodox, independent-minded person, who has attacked what were previously cherished beliefs. How do you think it's important to be that kind of person in terms of generating truly new and revolutionary ideas in science?

SP: I don't know what I'm supposed to say to that. What do you want me to say?
[laughter]

I think...it's very hard to pick a problem. I discuss this all the time. I discussed it in the book about how to pick a problem,¹³⁰ because most scientists don't do very well with this. They continue on with something that was in their Ph.D. studies or their postdoctoral studies, and they don't dare to go off and do something [new], because the study sections are going to say, "Well, you don't know anything about this." This is a real problem. It seems to me this is one of the most important issues that a scientist has is what problem to study. Then, after that, you've got to start out, and you've got to make things happen. If you do work where other people have already shown you the path, and there's a huge lore, and you've mastered it all, you'll only think about things that way.

I remember thinking many times the luckiest thing that happened to me was that when I first started out, I had too many expenses. It was much too expensive to pay for all these animals. Carleton Gajdusek would, a few years later, win a Nobel Prize.¹³¹ He was a big deal at the NIH. He had *enormous* resources. I tried to convince him that he should give me a lab and that I should be a section chief—I didn't have one paper in the field—and that I should do my own work. I didn't want to work for him. He went on and on about how he doesn't want his lab to get bigger, because he likes to travel in New Guinea and everywhere else across the planet, and he doesn't want to be around taking care of a lot of people, and on, and on, and on. I was really disappointed. Years later, I said, "My god, what a favor he did for me." I would have heard nothing but "This is the way it is... This is the way it is... This is the way it is... This is how unconventional viruses behave."

¹³⁰ Prusiner SB. *Madness and Memory: The Discovery of Prions—A New Biological Principle of Disease*. Yale University Press, 2014: xv-xvi, 23-24.

¹³¹ Daniel Carleton Gajdusek, M.D. (1923-2008) shared the 1976 Nobel Prize in Physiology or Medicine with Baruch Samuel Blumberg (1925-2011) "for their discoveries concerning new mechanisms for the origin and dissemination of infectious diseases." Gajdusek studied the transmission of prion diseases (although he opposed that conceptual framework), while Blumberg discovered the hepatitis B virus, and later helped develop its diagnostic test and vaccine.

Nobody ever knew what that is, [or even] still what an “unconventional virus” is. This is a really, really important thing to talk about with young students. This is *crucial*—not to get swept up in everything from the past. Come up with new approaches, new ideas, new ways to go. But it takes a lot of courage and *a lot* of push to do this.

DL: Do you think that the skepticism that you engendered with your work made your science stronger by forcing you to channel or develop better arguments? Do you think that helped or do you think that hindered?

SP: Yes. I think it helped a lot. I had some people...and I write about Charles Weissmann in detail.¹³² One aspect of Charles Weissmann is that he thinks like a Talmudic scholar. He wants to see everything over, and over, and over, and over again. This was *wonderful*, because it forced me to do a lot of experiments that I might have just thought were there and important, but I needed to really focus on them. I think that was very, very useful.

DL: In the last couple minutes, Stan, can you tell us where you think prion disease work will lead us in the next decade or so?

SP: Yes. I think it's very clear, from my point of view that it's going to go right to Alzheimer's and Parkinson's. The stakes are huge there, because there are so many people...and there's nothing to treat them with. We as a country, we as a planet, need to solve this problem. I think that's the place where I hope most of the resources go. We won't be spending all of our money on something about which we're saying, “We can't do anything about Alzheimer's. We can't do anything about Parkinson's. But we're going to work over here in X, Y, and Z.” I hope it goes just down that road on Alzheimer's and Parkinson's. We need some medicines that work to stop these diseases. They're a death sentence, horrible. One that goes on year after year after year. It's just horrible.

DL: Well it has truly been my privilege, pleasure, and honor to have talked with you today. I thank you for speaking with all of us.

SP: Well, thank you, Doug, for doing this.

[applause]

DL: We have just a minute or two if there are a couple questions. We can try and answer them.

AP: Parkinson's. Alzheimer's. What about ALS?

¹³² Prusiner SB. *Madness and Memory: The Discovery of Prions—A New Biological Principle of Disease*. Yale University Press, 2014: 130-138, 148-149, 168, 176-183, 215-217.

SP: Sure. It's all part of the same spectrum of neurodegenerative diseases. I think, you know, ALS is really, really exciting now, because there's this whole series of new experiments with RNA granules.¹³³ That's where prions feature in all of this, with these low-complexity sequences. I think there will be big progress in ALS.

AP: Your own story started with CJD, but we still don't have a treatment for CJD. How do you think we need to approach that question?

DL: His question was, "There is no treatment yet for CJD?"

SP: Right. There's a real problem, and the problem is a fifty-year old problem. Once Gajdusek and Gibbs transmitted the disease, nobody since that time has been able—they couldn't do it either—nobody has been able to create a cultured cell system or any other kind of high-throughput rapid assay for CJD. So we, and others, have made more than a dozen drugs that prolong the lives of animals. We double or triple the lives of animals with scrapie, but when you try to use the same drugs on transgenic mice that express human PrP, they don't work. So we need other drugs that will work with human PrP. That's the root of this. We've worked *really* hard on this. We've stopped for the moment, because we don't have any more good ideas about how to make a cultured cell that will replicate human prions. Once we get that, it will go very fast, because we have all these drugs that work in scrapie, and we'll make a bunch of analogues. But we have no way of figuring out which analogues to pursue as we go, because it takes too long. We can't wait for every single iteration for 100 days. That just doesn't lead us down a good path.

DL: Thank you all for coming.

[applause]

[End of the Interview]

¹³³ See:

1. Liu-Yesucevitz L, Bilgutay A, Zhang YJ, Vanderweyde T, et al. Tar DNA binding protein-43 (TDP-43) associates with stress granules: analysis of cultured cells and pathological brain tissue. *PLoS One*. 2010;5(10):e13250.
2. Wolozin B. Physiological protein aggregation run amuck: stress granules and the genesis of neurodegenerative disease. *Discov Med*. 2014;17(91):47-52.
3. Fan AC, Leung AK. RNA granules and diseases: a case study of stress granules in ALS and FTLD. *Adv Exp Med Biol*. 2016;907:263-96.
4. Mitsuhashi K, Ito D, Mashima K, Oyama M, Takahashi S, Suzuki N. De novo design of RNA-binding proteins with a prion-like domain related to ALS/FTD proteinopathies. *Sci Rep*. 2017;7(1):16871.

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