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INTERVIEW
Nature or Nurture – Is A Successful Neuroscientist Born or Created? Interview with Rusty Gage

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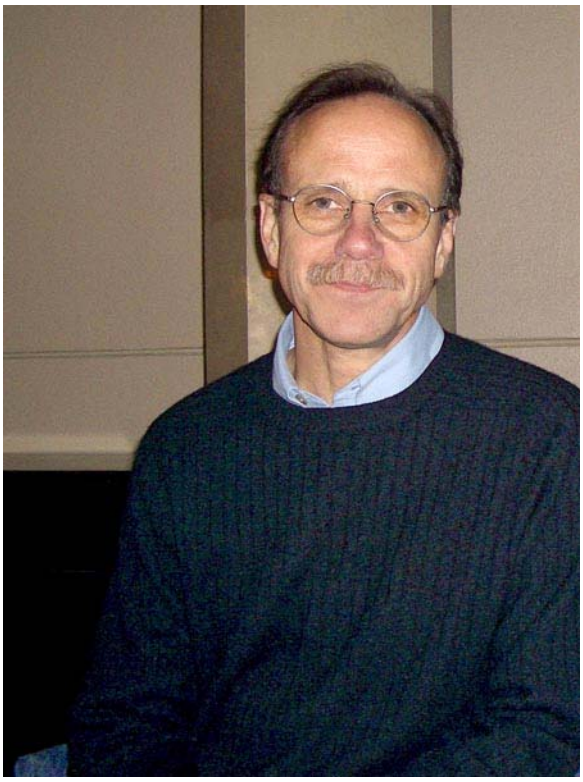

In the continuing series of interviews with famous Neuroscientists, I had the pleasure of meeting with Fred (Rusty) Gage at the last SfN meeting in Washington, DC. I was accompanied by a former student of mine, Anne Fagan, who had also been a graduate student in Rusty's lab when he was at UCSD. Again, my main question was: "How did you become a famous neuroscientist?" I gave Rusty the choice of answering questions or just telling us about his life – he chose the latter.

CA: Tell me about your education:

RG: I went to high school at St Stephens' School in Rome. This school was founded by a math teacher from Philips Academy, Andover, a science teacher from The Choate School, and an Episcopal priest as Headmaster and provided a classical liberal arts education, taking full advantage of its location in the historic center of Rome.

CA: And after that international experience, where did you go?

RG: I had planned to stay in Rome and improve my Italian, (I also speak some German and more recently learned Swedish). However, I started at the University of Florida at Gainesville in 1968, since my father and my sister went there.

At Gainesville, I mostly floundered around. However, one day I met someone in the back of the bus whom I had known in Frankfurt, Germany, where my parents lived at the time, and he was working in Bob Isaacson's lab (Bob is a well known hippocampologist). On my friend's recommendation, I got my first summer job at this lab, doing electrophysiology in rabbits. There was a lot of down time so I ended up also running rats in mazes. I worked there for three years doing lesions and electrophysiology. At one point I had a very bad auto accident and was seriously injured and hospitalized for months. The graduate students from the lab came almost every day and tutored me in my course assignments. They really put time in with me; they were a community of people who rallied around while my so- called "friends" ignored me. This was a very important period since their help allowed me to graduate on time and I appreciated belonging to this community.

CA: And what happened after undergraduate school?

RG: I applied to graduate school at Johns Hopkins University, to Dave Olton's lab. Dave Olton was one of Bob Isaacson's graduate students who finished his doctorate at the University of Michigan after Bob left for Gainesville, and Dave went to Hopkins without post-doctoral experience, which was not so unusual in those days. I was his second graduate student.

Since I was accepted early at Hopkins, I continued to work at Bob Isaacson's lab for nine months. I had no homework, I was making money and I had the greatest time. I did a lot of interesting experiments such as recording single units in hypothalamus and researching the cause of mirror focus epilepsy. I published my first paper in 1971, which involved tracking down these pathways.

CA: So how did you like graduate school?

RG: After my second year, I never thought about doing anything else. I decided that I would do this as long as it's fun, and it still is fun. When I get talked into administrative work, it is not as much fun. Then when I am back in the lab and sit down with data I still get that rush. I get to spend my life figuring stuff out that other people don't know. For example, with Bob, we studied recovery of function: how could we recapitulate the regenerating responses of the developing brain in the adult brain? Another example was working with Ulf Stenevi on neuronal sprouting.

Back to graduate school. In Dave Olton's lab, in one project we mapped the anatomical basis of spatial memory by making many microlesions. I became a pretty good surgeon and, even with slight variations in lesion placement, we could see deficits in various behaviors and, amazingly, we often observed recovery from these deficits in around ten days. Also we noted that the amount of

external stimulation affected the rate of recovery after septal lesions, which Mountcastle and Brady had discovered caused a syndrome that they called "septal rage."

Johns Hopkins is a good place to do graduate work. It has a strong tradition of doing neuroscience: Adolph Meyer, Curt Richter, Harvey Cushing, and Walter Dandy are only a few of the early pioneers in Hopkins Neuroscience. Sol Snyder was a young professor there when I was a graduate student.

CA: And after Hopkins?

FG: From Hopkins I went to Texas Christian University in 1976, as an Assistant Professor, as I was offered the Associate Directorship of the newly established Neuroscience program at TCU. I had a very productive time there and was able to pursue my interest in multivariate analysis that I had developed will working part time with Warren Torgerson at Hopkins.

Meanwhile, I applied for a Fogarty fellowship to go to Anders Björklund's lab in Sweden. Björklund had established that sprouting existed: when the fornix is lesioned, thick PNS fibers grow into the hippocampus. This was a "big phenomenon." While at TCU I had worked on this phenomenon with Chris Fredrickson at UT Dallas and linked the sprouting to a high concentration of zinc in the hippocampus, leading to the zinc hypothesis. And since zinc is the element in the dimerization of NGF, we hypothesized that NGF might be involved with this CNS sprouting. This was pretty exciting.

After hearing Anders give an excellent talk in Brighton, England, at the UK Society for Neuroscience, I decided to accept the Fogarty and go to work with him at Lund University in Sweden. When I got there (1981), Anders was planning to take a sabbatical in Cambridge. I didn't have to teach, there were no post-docs but there were five technicians, all the equipment I needed, and some very ambitious medical students. With all these resources and the amazing skill of Ulf Stenevi, I quickly learned transplantation technology. There were many experiments that we wanted to do and the good thing was that we had the resources to do most of them. Working with Anders and our colleague in Lund for those four years was a very exciting and productive experience. While I was there I was asked to apply for a very prestigious Swedish Medical Research Council professorship. There were only 25 such professorships in Sweden and when you are awarded the professorship, the King signs the official document and you can take the professorship anywhere you want, in Sweden. In analyzing my application, the Swedish officials wanted some external validation of my value as a scientist elsewhere, so they requested that I get job offers from abroad.

Well - I got an offer at NIH, was asked to select my dream team at the University of Miami, and then was also recruited by Robert Katzman at UCSD. While I was interviewing at UCSD and sitting on the beach drinking beer in late November with some wonderful scientists, my wife was pregnant with our second baby in Sweden, the pipes were frozen in our house, and I was being offered a tenured position in sunny California.

CA: Do you think you made the right decision?

RG: Yes, I knew I was doing the right thing. I then went back to Sweden and they said, "All the paper work's done for your professorship," but it was too late. If I hadn't had to validate myself with job offers, I'd be in Sweden now. I still have a close friendship with Anders. He is the godfather of one of my kids.

I stayed at UCSD for ten years (1985 – 1995) and it was great. We really had fun and the work in our lab was very well recognized.

CA: So what came next?

RG: I began my work in gene transfer and therapy in the late 1980s and in 1995 I was encouraged to head up the new Gene Therapy Institute at UCSD. At that time I was collaborating with Inder Verma at the Salk Institute, and he suggested that we join forces and start a new Laboratory that would focus on basic principles gene transfer. Soon after that, I was invited to join the Salk Institute and co-direct a new Laboratory of Genetics with Inder, which included remodeling the bottom floor of one of the buildings and hiring a few new faculty members. So I gave up tenure at UCSD (no one has tenure at the Salk). I just felt that I was at a time in my own research that I wanted to do more, to go in new directions. I needed to be in a new environment and there are no walls at the Salk. It was great from the moment I got there. Francis Crick was the negotiator for the position, and he told me, "We're not hiring you for what you're doing, we're hiring you for what you are – just be great!" That's what happens at the Salk. You need to ask yourself: is this really the most important question I can be asking now? The other thing Crick would say is to consider how you are going to prove your theory wrong. Think about the critical experiment that can destroy your hypothesis. We have a tendency to hang onto our own hypotheses much longer than we should.

I have been very fortunate in my career decisions. Going to Lund was a good decision, and leaving UCSD when the Salk recruited me was very good for my career.

We then had an in-depth conversation about his latest theory that newly born neurons are timekeepers… I will leave that to you to read about in the literature.

CA: What is your advice to a young neuroscientist?

RG: I think they need to establish a real commitment. This is not a job; it is a complete life commitment. You need to have other things that you are interested in, have a supportive family, and live in a place where there's lots of science. But if you really want to do it, and it really gives you joy, then you just have to stay with it, through all the down times. Bear in mind that you learn more from your mistakes than your successes. I have met people who have never had a failure in their life, and then they end up having a failure in my lab… I'd much rather have someone "screw up" as an undergraduate! Don't go to graduate

school immediately. Go get a job. Work in a lab, see what it is like to be a real scientist in a laboratory. Then if you want to go to graduate school, you will have an idea of what you like and what you are also good at. If you don't have good hands, don't try to be a surgeon, be a computational neuroscientist. But if you don't like computation, don't go there. However, if you really know what you want to do and then you find that you're not good at it, then train yourself. Just work very very very very hard. There is absolutely no way around it. Read, study, think and work; and do experiments; go do experiments; don't over-think it. You learn so much from doing experiments. When you do an experiment, you'll learn a lot more about what you're thinking about. Then you can come back and formalize it a lot better. There is nothing like a good pilot experiment.

CA: What are you thinking about now?

RG: What I'm very excited about right now (you should read the paper in *Nature* last summer) is retrotransposons or what are called mobile elements. It's a very hard, difficult story, but basically our hypothesis is that junk DNA is a potential mechanism for generating individual diversity between neurons. It is somatic evolution - a mechanism for generating a small amount of diversity in every cell in the brain so that, as you evolve, it selects on that diversity and makes every neuron potentially different from every other neuron, due to some random insertion in the genome. It only occurs in neurons. It doesn't occur in any other tissues. But that's another story.

Rusty had to go; this is a shortened version of the interview. Anne and I tried to digest the science that he had whipped through in passing – 'what did he mean when he said …?' We had been in the presence of a very intense, gifted and successful scientist. I hope I have given you some flavor of what makes him who he is.