Interview with Marshall W. Nirenberg
Wednesday, June 13, 2001
Topic: Nirenberg's transition from genetics to neurobiology
Interview by Jim Tabery

Jim Tabery (JT): There's been some wonderful historical analysis of your work on the genetic code, but that analysis often stops in the late 1960's when you turned to other areas of research. I'm hoping to look at your transition from genetics into neurobiology because you've now amassed 30 years studying neurobiology, and to approach that phase of your work you have to start at the beginning. I'm interested in roughly the years 1966 to 1973. It's your transitional period plus when you got the ball rolling experimentally. I hope I'm not catching you off guard here. I'm sure you haven't thought about much of this work for quite a while

Marshall Nirenberg (MN): Well, that's true, but I can tell you that I was always interested in neurobiology from the time I was a graduate student. When I got a position as a post-doctoral fellow in Gordon Tompkin's office here as an independent investigator I thought long and hard about what I wanted to do, and it ultimately came down to one of two areas: one, either molecular biology (which I eventually went in to), or neurobiology. I decided that neurobiology wasn't advanced enough at that time to really be able to do something important in it, so I picked molecular biology which was the most exciting area in biology at the time. This was in the late 1950's.

I've always been interested in the nervous system because there are really only two systems in biology that process information: genetic information and the brain, the nervous system. So that was the connection, and that was the rational, and actually a number of molecular biologists decided to go into neurobiology: Seymour Benzer, for one.

JT: And then you also find Adler, Stent...

MN: That's right.

JT: I found an interesting letter from Jacob to you from 1970 saying that he's fed up with nematodes and that he's decided to move into the mouse nervous system, so he wanted some guidance with techniques in the area. Did he ever actually turn to neurobiology?

MN: I don't really remember. I applied to him for a post-doctoral fellowship before taking this job. I wanted to go to his lab to study. He's a terrific investigator and a terrific scientist and always has been. But he didn't have space for me, and he later kidded me that his contribution to science was that he turned me down because then I went ahead and did the genetic code work here. But I don't know if he ever went into neurobiology.

JT: Well, it was an interesting letter because he obviously saw that you were having success with neurobiology, and he was interested in maybe doing the same.

MN: Well, you know, neurons don't divide, and so it's logical to assume that tumor neurons might retain the properties of differentiated neurons and then could be used as a model system to study information processing in neurons and synapse formation.

JT: So this is what took you to neuroblastoma?

MN: That's the idea. I thought we might be able to devise a model system that we could use to study synapse formation in cell culture, and we could also study properties of neurons in cell culture. At

this time, the prevailing opinion (up to a year before) was that once you put cells in culture and clone them that the clonal cells dedifferentiated. But a year before there was a paper that appeared that showed that they didn't really dedifferentiate, but instead retained some properties of differentiated fibroblasts (I think). This was a paper that had a real affect on me, and I thought that maybe we could get tumors of neurons and clone them and establish them in culture, and then maybe they would retain enough neural properties to make it extremely interesting and an extremely valuable model system to study neurobiology, so that's what I did. I had never done any tissue cultures before, but I just jumped in with both feet...feet, hands, and everything.

There was a visitor here from the Weizmann Institute, [in Israel], at the time who was a highly experienced tissue culturist, and so I did the first experiment with him. That was helpful because I had never done tissue cultures before. We started and found a mouse neuroblastoma that was a solid tumor that was passed from animal to animal that was known. And, independently, Gordon Sato cloned the same mouse neuroblastoma and established clones of this, and we actually published in the same PNAS journal.

JT: In your first article on neuroblastoma research, you mentioned that you had first spoken with Sato at an NRP meeting about the neuroblastoma work.

MN: I don't remember, but I'll tell you on thing: the NRP/MIT neuroscience program played a very important role for me. I later became a member of the MIT neuroscience program. They had summer courses held in Boulder, CO. I attended and participated in two of them, and they were absolutely wonderful for somebody that was just entering the field and didn't know anything about the thing. The NRP had people who were world famous experts in various topics and would give lectures on the work that they would do. I actually gave a lecture. I don't remember the years exactly, but I attended two of them in Boulder. Boulder's a wonderful place. It's the gateway to the Rockies, and so we drove out into the mountains on the weekends, and it's just so beautiful and gorgeous: the blue skies and wild flowers over everything and the mountainous terrain. It's lovely, and it was a wonderful experience for me.

This was right towards the end of my work on the code. I had been working for six years as hard as I could, and all during this time I had to get out papers every month or every other month, and so it was just the most wonderful sense of freedom. Freedom from doing things that had to be done instead to learning and talking to people that were really knowledgeable about neurobiology. It was a time of tremendous mental activity and thinking and fun.

JT: What was neurobiology like when you entered it in the 1960's?

MN: Well, in the 1960's nobody was doing tissue culture of neurons or any kind of cell lines. The literature in molecular biology is so beautiful. Intellectually, it's gorgeous. The experiments, the design of the experiments, and the work is clean. That work was really breathtaking and really beautiful. Neurobiology, on the other hand, was like walking up to your neck in a swamp. It was horrible! The literature was awful: controls were missing, the people didn't do the experiments properly. But you still had to learn, and so I read everything, but what a difference. It was really in an awful state.

You know, actually, during the coding years, around 1962 or 1963 I gave a talk at the Brain Institute in Los Angeles and wrote a paper on genetic coding, but it was in a Brain Conference. So all during this time I was very conscious of neurobiology.

JT: As I was going through your experimental day books and journals, the earliest mention you make of actively pursuing neurobiology came on New Year's Eve 1965. Later in your journals, everything is titled very specifically, but this one just says "Brain". It was almost like a New Year's resolution because you were really thinking things through for the first time.

MN: [laugh]

JT: Then on January 1st, 1966, you write about where you want to go in the next 6 months, how you want to attack the field, the different systems you want to use. It was really interesting.

MN: Well, I tried two things almost simultaneously at the beginning. First, we set up the neuroblastoma cells, but then we started to work with nematodes. This was before Brenner published anything. Ruth Pertel was a graduate student at Berkeley.

You know, I forgot to tell you: when I was a post-doctoral fellow, I found an old book that was published in 1905 or 1906. This was on tropism in microorganisms: paramecium, bacteria, etc. It was a fantastic book, and the author had made wonderful observations. I got so interested in it that I gave a seminar to our journal club in the lab. I also became interested in an article written by Edward Land from Polaroid, which was published in *Scientific American* on vision. He had a theory of color vision. He took two projectors with black and white slides of the same view. On one projector he put a red filter and on the other one a green filter was placed, and then he combined the images on a screen, and they came out in perfect color. From this, he provided a theory of color vision. I became so interested in that article that I gave another seminar in our journal club on Land's work and demonstrated that it really did work. So I was interested in neurobiology all along. One of the major reasons for my interest was that it was a black box for me. I didn't know anything about the nervous system. I thought that this was an area where tremendous discoveries were going to be made eventually, and I was really, truly interested in it, so studying it and jumping into it was fantastically fun.

I knew I didn't have enough time to do both [genetics and neurobiology]. I couldn't really carry the stuff I was doing (This was around 1966.). I was still working on the code, and there were fantastic problems that still needed to be attacked and that we were attacking at the time, but I had a wonderful associate, a former post-doctoral fellow, by the name of Tom Casky who was in the lab at the time. I gave all of my post-doctoral fellows to him. They had come to me because they were interested in protein synthesis and coding work, and here I was leaving the field, so I gave them all to him, so that I was free to do what I wanted.

JT: How did you communicate that decision to the lab? Did you call a meeting?

MN: Oh yeah. I just told them. Of course Tom was delighted to take them all on, and they were all in problems of their own, so it really worked beautifully. It freed me up. I didn't have any responsibilities then; I was free to explore simple systems in the lab at that time. Shortly after that time, the lab became a little zoo with all sorts of little invertebrates that we took into the lab to see if they would make a good system to study. We had rotifers in the lab, brine shrimp...all kinds of different invertebrates that we could put in culture. Have you ever seen a living rotifer?

JT: Not since biology lab.

MN: [laugh] Well, they're beautiful organisms. Actually, I still have little chambers that have two cover slips that you can screw together. So if you put water in there with a rotifer, you can immobilize the rotifer by pressing down a bit with the top cover slip and so you can see all the internal organs.

I even got some ascaris, parasitic worms, from a slaughterhouse in Baltimore, and Oh my God! They were awful. They smelled so bad. I got a bucket of them and took them to the lab, and Norma Heaton almost quit then and there. They threw up their hands. The smell was horrible. And you can get infected with these things. They're not safe to work with. But somebody by the name of Goldstein around the turn of the century had published these beautiful anatomical drawings of ascaris' nervous system which I had xeroxed. It looked like the inside of a submarine with nerves going in all different directions like pipes. Although Brenner later told me that Goldstein was wrong.

I tried all kinds of simple systems before we finally settled on neuroblastoma. Ruth Pertel, as I began earlier, was a grad student at Berkeley with Dougherty. When you went through the literature, you found that the only invertebrates that you could raise on a defined medium were nematodes, and that was because Dougherty had put years of effort into getting a fully defined medium that would support the growth of nematodes. So nematodes were the ideal invertebrate to approach because they were the only ones with a defined medium. Dougherty, around that time or slightly earlier, committed suicide. And Pertel was just getting her degree, so I invited her to come to the lab, and we decided to start working on nematodes. She was his student, so she was familiar with all the techniques. We still have a couple of racks of nematode mutants that are in the liquid nitrogen. But then I decided that when Brenner came out with his work on nematodes (he was working on the same nematode actually that we were working on because that was the one you could grow). So nematodes were a logical choice for him and for us, but I felt after working a few years with nematodes (We got many mutants, most of them motion or nervous system mutants) that I couldn't really handle nematodes and neuroblastoma simultaneously. It was just too much, and so I felt that I should focus on neuroblastoma cells since Brenner was working with the nematodes.

JT: Was there much communication with the others, such as Brenner, Benzer, and Delbruck...the group that migrated?

MN: There was communication.

[Interruption from post-doc about current research]

MN: We're doing something now that is really exciting. We're screening virtually the entire *Drosophila* genome looking for genes that affect the assembly of the nervous system. And that's using a new technique that has just come up recently called double-stranded RNA interference. If you inject double-stranded RNA for a particular mRNA into the early embryo, there's an enzyme that grabs hold of it and cuts it into pieces about 22 base pairs in length--two turns of the double helix. And a part of that enzyme probably then unwinds the strands. Then they go about searching for mRNA that will base pair with the oligoribonucleotide. If it base pairs correctly, then another enzyme is utilized that will then destroy the mRNA. It's a quick way of getting a mutant phenotype for any gene. And it's an amazing technique. That's what virtually everybody in the lab is doing right now. And we hope to screen most of these genes.

There are 13,600 genes in drosophila, and this technique is so much faster. We were doing the same kind of thing before using an enhancer trap method, which has transposable genes that has a betagalactosidase reporter gene, so that it will transpose into another gene. Then the expression of the betagalactosidase, which we can stain for, is determined by the regulatory region of the gene it's inserted into. We made 500 transgenic lines of flies and found many interesting mutants that affected the nervous system. Anyway, this new method is so much faster than the enhancer trap method, but it's also very laborious because you have to inject embryos with double-stranded RNA, and you have to infect about 40 embryos for each double-stranded RNA. So when you have 14,000 genes it gets to be very time consuming and difficult. But, thus far, we've screened about 350 genes and found 3 mutants, so there's going to be about 1% of the genes that affect the assembly of the nervous system.

But, anyway, we've gotten sidetracked.

JT: Well, I asked you before whether or not there was communication between the molecular biologists that made the neurobiological shift.

MN: Yes, absolutely, and particularly at the beginning. I talked to Adler who I haven't seen for a long time, but was a good friend at the time and Seymour Benzer, who is one of the best scientists in the world. I mean, he is really a terrific scientist. He was the first to actually go into neurobiology with

Drosophila. And we had long discussions about doing it. You know, I remember him saying at the time that this was what he really wanted to do, but he also added that he didn't want to fail. Because when you go into something like this you're an absolute beginner, and you have to learn from scratch, and he was at the top of the field in molecular biology. He was leaving something that he was a world-recognized expert in and going into something that was very uncertain and with an uncertain future. Everybody that made the switch went through exactly the same thing. It took a lot of guts and a lot of courage to do it. I think Benzer is such a superb scientist. He's done so much so well. And he's still at it. I have great respect for him.

JT: And do you think it was the same motivation for them: they were working on the one information processing system, so it naturally led to the other one.

MN: Yeah. The thing was that the big black box was the nervous system. It was there for everybody to look at, and none of us understood what was going on in the nervous system, and we were all interested in information processing, so it was very natural to make the move. Sure we talked about it, and I talked to Julius Adler about it. I didn't really talk to Brenner about it because I didn't really have the opportunity. He wasn't at any of the meetings that I normally went to. Adler has done beautiful work with *E.coli* chemotaxis.

JT: What about Delbruck?

MN: [laugh] Delbruck. I only met him once actually. I attended a meeting at an abbey in France with him where I presented the work on poly-U, so this was the early 1960's. He was the chairman of that particular session. This was the first time I had ever seen him. This was only months after I had initially reported [the poly-U discovery], and when I finished he looked at me and said that he tried to use poly-U to direct the synthesis of polyphenylalanine and it doesn't work. So I looked at him and said, "Well, I've made probably 75 preparations of cell-free extracts. There's a little variation between the activity of one prep and that of another prep. Some are better than others. But every one of them worked. So make these solutions. Throw out all your old solutions and try it again." I said, "I'd be glad to help you. If you have trouble with it, come to my lab or send somebody to my lab and I'll run through it with them." And that was the end of it. I never heard anything more.

JT: He seems to be famous for making those kinds of abrasive comments.

MN: Very, very abrasive. This was before the entire audience. I asked him a few questions about his methodology, but it was clear that there was some trivial kind of error that they had made, and I'm sure that there was no problem trying to figure it out.

JT: Now, was there any communication with Stent.

MN: Stent used to come to these NRP meetings.

JT: So, when you talk about having opportunities to meet and speak with the others, was it often at the NRP meetings?

MN: With Stent, yes. Have you read his new book? This is a book he just published recently, and it has the worst title I've ever heard in my life. It's autobiographical: *Nazis, Women, and Molecular Biology*. I mean, it's the kind of thing you want to get in a brown bag. I ordered it through Amazon.com, and it came to the lab, and my secretary looked at me when she handed it to me and didn't say anything. It is interesting, though. He's from Germany originally, and his family was refugees that came to the United States, so he spoke German. Immediately after the war, he was hired by the army as a civilian to

go into Germany and find papers and scientists on various scientific projects. And so the book is about his experiences going back to Germany immediately after the war. I heard he had it privately printed. It's an interesting book, but it's got a terrible, terrible title.

JT: So there was communication with him at the NRP?

MN: Oh yes. He and his wife were there, and I spoke with him and everybody there. Those NRP meetings were terrific. They lasted a month, and it was a wonderful way of getting a solid introduction to the field.

But once we had these neuroblastoma cells, it was clear that I had to learn electrophysiology to sample them and also a lot about the methods of tissue cultures, of cloning them. Takahiko Amano came to the lab at the time as a post-doctoral fellow. He was an expert at tissue cultures and cloning. He had a green thumb. And total dedication to the work, so he took over the cloning, and he cloned all of the neuroblastoma cell lines. He's really a wonderful tissue culturist. And, you know, one of the great things about the NIH is that it's easy to have collaborations with people: Phillip Nelson, who is an expert neurophysiologist, used to be in the basement of this building. We started a collaboration to do electrophysiology of cultured neuroblastoma clones, and that was wonderful. That was the reason I moved from building 10 to this building: because he was here, and because the space had just become available in this building. This building is full of the neurosciences.

JT: Was there any communication or collaboration with Axelrod?

MN: I knew Axelrod. I've known him for many, many years, but I've never collaborated with him. He was mostly working on trying to find new enzymes in the nervous system. I see him about every month. We have lunch together.

JT: So as far as actual collaboration, Nelson is the only one at the NIH?

MN: Well, Nelson is the major one. There have been two major collaborators...actually three that I've collaborated with on neurobiology. Phil Nelson was the first one, and for years we worked together and it was very productive. The major problem was learning a new scientific language. I had to learn electrophysiology, and he had to learn molecular biology, and so we were teaching one another. He gave me things to read; I gave him things to read, and so it proved to be a wonderful collaboration that made us both better scientists. It was wonderful.

Later, we collaborated on a whole series of papers with Werner Klee, who used to be in this building. Werner had wanted to know if any of our neuroblastoma cell lines have morphine receptors.

JT: So was he the catalyst that turned the work over to the morphine studies?

MN: Yes. He came to me and wanted to know if we had anything that had [morphine receptors]. We had so many cell lines. We have probably more cell lines than anybody else in the world. We have a cell bank here. What we did later, after we established the initial neuroblastoma clones, was then to try and characterize them to see if they had neural properties. That meant that we then had to set up assays. We studied them electrophysiologically. We looked for electrically excitable membranes for ion channels, and found that they could generate action potentials, and that the excitable membranes were regulated, and we could shift populations of cells from a dedifferentiated to a differentiated state by upping intracellular cAMP levels. Then we simultaneously set up all these enzymatic assays to look for neurotransmitters. This took a couple of years. It was a major project in the lab at the time as we tried to establish all of these assays that could be applied to the cultured cells. We devised methods for tyrosine hydroxylase and many others.

JT: There was also the dual regulation of adenylate cyclase.

MN: That was with Werner Klee. To rescue gene expression from the nervous system we used somatic cell fusion with neuroblastoma cells. We found that most of the neuroblastoma cell cultures are relatively dedifferentiated if you grow them in log phase. They don't have excitable membranes; they don't express neural properties. So we had to first learn how to grow the cells by upping intracellular cAMP, so that they shifted to a more differentiated state. But to try and rescue gene expression from the nervous system we fused neuroblastoma cells with cells from the normal nervous system (retina, hypothalamus, peripheral nervous system, etc.) to make somatic cell hybrids. We got many cell lines generated, and we characterized about 30 that looked like they had the most neural properties. And one of them was NG108-15, a somatic hybrid cell (neuroblastoma X glioma). This was a glioma that actually Gordon Sato was the first to publish and describe. This hybrid cell line turned out to be loaded with morphine receptors, and so we asked ourselves if we could make the cells dependent upon morphine if we cultured the cells in the presence of morphine. Would they become dependent upon morphine? That lead to a whole series of really interesting papers where we showed that adenylate cyclase was regulated, that morphine inhibited adenylate cyclase, and that if you cultured the cells for a day in the presence of morphine they become dependent upon morphine because adenylate cyclase activity increases, so that the morphine inhibits it and it becomes the control level. So then if you remove the morphine the enzyme becomes sky high and tremendous amounts of cAMP are produced, so that it takes a long time to return to normal.

JT: And that's the withdrawal?

MN: That's the withdrawal.

JT: The NIDA (National Institute on Drug Abuse) came about in 1974. Was there any collaboration with them?

MN: No. We got some drugs from them, but nothing else.

JT: Really? You would think that they would be interested in that work.

MN: Well, one of the wonderful things about the NIH is that people are very helpful, so I talked to a lot of people during this whole time, and people were helpful if they knew how to do something that you didn't know how to do.

Anyway, we worked for a number of years on the opiate dependence problem, and we also found the same phenomenon with both musc. receptors--if you place them in the presence of a compound that activates the receptors. And noradnergic receptors, that if you cultured them in the presence the compound it will do exactly the same thing: inhibit adenylate cyclase and then become dependent on the neurotransmitter that's present. So it's a very basic phenomena that doesn't only work with opiates but also works with normal neurotransmitters like acetylcholine and norepinepherine.

JT: I want to turn the conversation back a few years because one of the first things that I saw in your work that got me interested in your transition was the phase where you were comparing and contrasting the neural code with the genetic code. You seemed very interested in their analogies. Can you tell me a little bit about that?

MN: Well, I had come from spending years intensely thinking about genetic information transfer, so the obvious thing was to contrast how genes work with how the nervous system works. So I was interested in that. I had a lot of interesting ideas and a lot of wild ideas.

JT: Did any of them evolve into anything else that was productive?

MN: Well, when you say "productive", I think everything is productive in the sense that it shapes you and makes you ask more questions. Maybe people work differently, I don't know, but for me, the way I work is to generate hundreds or thousands of questions. Some of the questions are awful; they really stink. Others are mediocre, and others are okay or pretty good. And then a few of them really hit the bull's eye. So, if you like throwing darts at the dart board, then you cover the wall with dart holes, but a few of those questions are really terrific questions. That's just part of generating ideas.

JT: So where does the genetic-neural analogy fall into your hierarchy?

MN: Well, there are major differences between the nervous system and the genes, and they're obvious, but I still think it's interesting to think about it and to compare them. I spent a lot of time doing that. It's a lot of fun to do it.

You know, we found in the cell lines that Amano had established a number of neuroblastoma cell lines that made acetylcholine, and this was totally novel and new at the time. It was thought before then that only adenergic sympathetic neurons did this, but we found cholinergic neuroblastoma cell lines that could do it. Later on people looked for cholinergic cell lines in children and found them.

JT: If you had to think of your 3 big contributions to neurobiology could you list those or would it be too difficult?

MN: Sure I can list them. I'll tell you what the areas were that we worked in that I think are really important. First, we established simple systems/clonal lines of cells that have neural properties, and our objective was to find cell lines that form synapses, and we did that. We found 5 cell lines that synthesize acetylcholine and that form synapses with muscle cells. We could innervate every muscle cell on the plate. And so they're wonderful systems for studying various questions relating to neural information transfer. They're electrically excitable; they have neural transmitters and receptors that form synapses, and they've been used by many people throughout the world as simple systems. We characterized lots of these properties including the opiate receptors and dependence. So that's one area. People write to me all the time and ask for cultures of different cell lines which we send them. We send them all over the world.

Another thing that we studied was the generation of monoclonal antibodies in retinal cells. We spent a lot of time studying the retina, and found that with a chick embryo retina you can disassociate the cells in the retina. Then, when you reassociate them, they form synapses during development that look exactly like the normal synapses, so we used this as a model system to study synapse formation for a long time. You know Roger Sperry, the grandfather of neurobiology, in the early 1960's wrote an interesting paper hypothesizing that you cold give every cell in the retina a molecular address by two gradients of different kinds of molecules at right angles to one another. So we looked for molecular gradients by using monoclonal antibodies. We took little pieces of retina from different positions in the retina (dorsal, ventral, etc.) and injected them and made monoclonal antibody cell lines that synthesize antibodies, and each cell line would synthesize a different kind of antibody. And then we tested them and looked for antibodies that would recognize an antigen more abundantly in one part of the retina than in another part of the retina. And, low and behold, we found one. We found an antigen that we turned "top" for "topographical" that was much more abundant in dorsal retina than in ventral retina. And, in fact, there was a concentration gradient throughout the entire retina. This was a membrane protein. We purified the membrane protein. And it was the first time anybody had ever found a gradient protein in any system, and so we had a lot of fun with that. I tried to clone the antigen, but failed. We couldn't detect it with the antibody we were using. Maybe we didn't try hard enough. But then I figured that it was too complicated; that trying to do it in the chick embryo was just too complicated, and that's why I went into drosophila.

So the idea was to look for new homeobox genes in drosophila. We found 4 new ones. One of them, which was NK2, seemed to be expressed at such an early time in the nervous system that I thought that maybe it's the first step. And it turned out to be true; it is the first step. The expression of this gene initiates neural development in part of the ventral nerve cord in the embryo.

JT: Have homologous genes been found in other organisms?

MN: Yes, the mouse has 7. And, actually, there's something called the NK2 family of homeobox genes that are found in all kinds of organisms from Xenophis to zebra fish to planaria, tape worms, chicken, and the mouse, as I said, has 7. We study many aspects of NK2 because it really initiates neural development in the most ventral part of the medial ventral nerve cord. And it turns out that there are 3 different homeobox genes. Each one initiates neural development. Like an anterior/posterior stripe of cells in the drosophila nervous system. And a fourth, the most ventral, is another gene regulator, which initiates neural development in the mesectoderm, which divides right and left halves of the nervous system. So we've studied NK2 because it really initiates neural development.

JT: It's really at the top of the hierarchy.

MN: Absolutely. It starts it. But there are 3 other independent initiation events, so it's like a sandwich. Right from the very beginning the gene expression differs in the neuroectoderm and neuroblastic form from each. The most ventral one has one kind of initiation event, and then comes NK2, then comes IND--a different homeobox gene, and then MSH--a dorsal neuroectoderm. And the regulation of each of these genes is very logical. We found that single-minded represses NK2. Others found that NK2 represses IND. And IND represses MSH. It's very logical and efficient. Now we've been trying to find out how a pattern of NK2 neuroblasts is formed in the nervous system. We do that by taking pieces of the DNA from the 5' flanking region of the NK2 gene and then linking it to betagalactosidase, a reporter gene, whose activity can usually be visualized by staining, and make transgenic flies that express...I have pictures at home that show some of the beautiful patterns that are made. We've identified different regions of DNA from flanking regions that are responsible for these patterns. So it's something that we're still working on.

JT: When I look over the span of your work from the code, to neuroblastoma, and even now, you seem to be constantly looking for the simplest system to approach problems. Is that a common theme for you?

MN: Absolutely. That's a common theme: to have a model system that can be used to ask questions. You know, I was trained as a biochemist, and, although I'm pretty much a molecular biologist now, they're pretty much the same. You definitely use the simplest system because the nervous system is so complicated, and you also need genetics as a handle to be able to sort out the complex events, so I think pretty much everybody in the field feels that way.

JT: Well, this has been extremely helpful. I want to thank you.