Recognition in Moscow and Coming to a Cross Roads

Marshall W. Nirenberg is best known for his work on deciphering the genetic code by discovering the unique code words for the twenty major amino acids that make-up DNA, for which he won the Nobel Prize in Medicine or Physiology in 1968.

Nirenberg was the first government scientist to win the Nobel Prize. The National Library of Medicine and the Office of NIH History has amassed a collection of correspondence, laboratory administrative and research materials, and publications that documents Nirenberg's career as a researcher in biochemical genetics at the National Institutes of Health.

Dr. Nirenberg is featured in The Profiles in Science web site of the National Library of Medicine celebrates twentieth-century leaders in biomedical research and public health. Students appreciate the history, and share some of the excitement of early scientific discoveries in molecular biology. The National Library of Medicine is digitizing and making available over the World Wide Web a selection of the Marshall W. Nirenberg Papers, for use by educators and researchers.

In 2007, the Archives and Modern Manuscripts Program, History of Medicine Division completed a Finding Aid to the Marshall W. Nirenberg Papers, 1937-2003 (bulk 1957-1997). Individuals interested in conducting research in the Marshall W. Nirenberg Papers are invited to contact the National Library of Medicine.

The NLM digital materials and references provide the background for the series of six interviews conducted with Marshall W. Nirenberg, Ph.D., by Ruth Roy Harris, Ph.D., between September 20, 1995 and January 24, 1996.

The "Harris Interviews" took place in Nirenberg's laboratory on the campus of the National Institutes of Health (NIH) in Bethesda, Maryland. Harris also conducted several supplemental interviews, both by telephone and in person, with individuals either involved in the breaking of the genetic code or personally acquainted with Nirenberg: James Pittman, Joan Geiger, Philip Leder, Thomas Caskey, Sidney Udenfriend, and Perola Nirenberg. Interviews with Pittman and Geiger are now in the Marshall Nirenberg Collection at the National Library of Medicine (NLM). Notes from other interviews are held at the Office of NIH History.

A number of individuals and institutions worked on editing the interviews for clarity and content: Sarah Leavitt, Victoria Harden, Caroline Hannaway, Alan Schechter, Robert Balaban, and Alan Peterkofsky. Caroline Leake, Katrina Blair, and Mary Alvarez provided administrative and technical assistance. In 2008, Deborah Kraut edited and formatted the interviews to correspond to the NLM digital materials.

Each Section begins with the NLM digital summaries summaries and references. Additional references, when appropriate are added:

From Profiles in Science:
http://profiles.nlm.nih.gov/JJ/Views/Exhibit/narrative/syntheticrna.html

In August 1961, Nirenberg and Matthaei published their now-classic essay, "The Dependence of Cell-Free Protein Synthesis in E. Coli upon Naturally Occurring or Synthetic Polyribonucleotides," in the *Proceedings of the National Academy of Sciences*. In that same month, Nirenberg presented a version of his findings with the poly-U experiments to a small group of about thirty scientists at the International Congress of Biochemistry in Moscow. Viewers can see the original draft of Nirenberg's address to the Moscow Congress in the Documents section. Francis Crick, who was in attendance at the Moscow meeting, had heard that Nirenberg and Matthaei had found a clue that might unravel one of the central mysteries of molecular genetics. Crick arranged to have the young scientist deliver his paper again, this time to the assembled body of about a thousand people. By the end of the Moscow conference, the discovery made the obscure and mild-mannered NIH scientist a veritable celebrity.
By January 1962, interviews and photographs featuring Nirenberg and Matthaei appeared in scientific journals, newspapers, and weekly magazines around the world. UUU was described as the first word in the chemical dictionary of life, and the key to deciphering the entire genetic code. The poly-U experiments also made Nirenberg a much sought-after speaker at research institutes. He was invited to participate in the first-ever symposium devoted exclusively to the RNA code, which was held at Indiana University in January 1962. Despite the professional and social demands made upon him, Nirenberg also found time to encourage young scientists. In many cases, he invited them to observe and work with him.

Viewers can see original documents related to this historic symposium in the Documents section of Synthetic RNA and the Poly-U Experiments, 1959-1962

1995 – 1996 Harris Interviews

MN: After we first found that RNA would stimulate the synthesis of protein, incorporation of amino acid into protein, we published a little note on this assay in *Biochemical and Biophysical Research Communications*. That was in the spring. It was published (a year later) in the spring of 1961, I guess.

I think, in the summer of 1960, there was a meeting at Cold Spring Harbor Laboratory to which Monod, Jacob, everybody, came. I applied to go to the meeting, but was turned down. Instead, I went out to Berkeley and did the work ***with Fraenkel-Conant*** on the tobacco mosaic virus.

It was that summer, actually, that we found that poly-U stimulated polyphenylalanine incorporation into protein.

So Monod and Jacob presented their work at the Cold Spring Harbor meeting. They were the prime people at the meeting. It was all about enzyme induction and repression, and I wasn't there, but I am sure that Gordon Tomkins was there. They must have used the term “messenger RNA” at that meeting. I usually talked about “template” RNA, and I don't think I coined the term “messenger RNA.” I always thought that they had coined the term “messenger RNA,” based on genetic experiments. At least that is the way I remember it.

But while they were talking about it at Cold Spring Harbor, I had demonstrated it experimentally.

RH: You had your result in the summer of 1961 and prepared to present those results at an international meeting in Moscow that August. Prior to the Moscow conference, had you discussed your breakthrough with other scientists in the field of protein synthesis?

MN: Prior to that nobody knew about it. There was one incident where just before going to Moscow, I wanted to characterize the protein product from poly-U to show that it was polyphenylalanine. I thought that this was so exciting and so important that you had to do it right to make people believe it. It has to be done thoroughly, and I didn't know the first thing about polyphenylalanine. I didn't know where to look to find the information. What I wanted to do was to find out about the solubility of polyphenylalanine, and I did two kinds of experiments.

This I did in about one week after I came back from Fraenkel-Conrat's laboratory.
I characterized the C14 product by establishing a stoichiometry between the amount of radioactivity that went into protein and the amount of radioactivity that was recovered in precipitated polyphenylalanine—precipitated with authentic polyphenylalanine.

Then, I hydrolyzed that protein and separated, fractionated the radioactive amino acids, and I recovered greater than 95 percent of the radioactivity, or something like that, that was in radioactive phenylalanine. I recovered the original substrate from that.

I wanted to show that the protein polyphenylalanine had the solubility expected of authentic polyphenylalanine, but I didn't know what the solubility was. Directly under my lab was the laboratory of [Christian] Chris Anfinsen, a superb biochemist. He later won the Nobel Prize. He was an expert on protein conformation. I knew that he had worked with synthetic proteins, polypeptides, and I thought he might know or at least be able to point me in the right direction in the library.

So I went down to ask him where to look for information on polyphenylalanine in the library. He wasn't in his lab, but a visitor from Israel was there, Michael Sela, who I knew had published work on using synthetic polypeptides as antigens for antibodies. I asked him if he knew or could tell me anything about the properties or tell me where to look for information about the properties of polyphenylalanine.

He said, “I don't know much, but I can tell you two things. Polyphenylalanine is extremely insoluble, but it does dissolve in …” He told me about a solvent that was the craziest solvent I had ever heard of in my life, something like hydrobromic acid dissolved in glacial acetic acid. It was just a horrible solvent.

My mouth absolutely dropped open. I couldn't believe that he knew this, and he said, “I just prepared some of the solvent. Would you like some?” I replied, “You bet I would like some!”

He gave the solvent to me, and he explained how he had discovered it. He was the only person in the world who knew that polyphenylalanine was soluble in this solvent because he had taken a sample of polyphenylalanine earlier, and the solvent was a reagent for the C terminal analysis of proteins. He had mistakenly added it to polyphenylalanine and saw that it dissolved in it. He was surprised that it dissolved in it because he had made a mistake by putting this solvent on it.

Then, he asked me why I wanted to know about this polyphenylalanine, so I told him that we had found that polyuridylic acid is the template which directs phenylalanine into protein. Sela went on to become president of the Weizmann Institute and a very well known immunologist. He wrote a preparatory chapter for an annual review of immunology, in which he reminisced about his work in science, and he said that at the time I told him this story, he didn't believe me. But he didn't tell me that he didn't believe me then. But he just didn't believe it was true.

So in a matter of just days I had the entire characterization of the protein product done. This was just before the Moscow meeting, and I thought it was important to pin it down, and it really was important. I had some 20 different solvents, a slide made with 20 different solvents, every one of them negative except the hydrobromic acid in glacial acetic acid. It was an incredible solvent.

When we published the paper on poly-U, I included a footnote thanking him for information about poly-U. I didn't realize that this was unpublished information, nor did I realize that he was the only person in the world who knew this. What is the probability that you would go to the only person in the world who knew something and ask him for that information?

Moscow Conference

RH: Dr. Stetten insisted that you publish your work before he would sign off on letting you go to the Moscow conference. Can you give your version of the story?

MN: I remember one thing he told me. “Marshall,” he said, “this is going to be a very important publication.” He said, “Write it well!” when I sat down to write it, and I think that was very good advice. I also think it was good advice that he gave me to have the paper in press before leaving for Moscow. So we got the papers written and in press immediately before I left for Moscow.

I needed a member of the National Academy of Sciences to sponsor the papers for publication in the *Proceedings of the National Academy of Sciences* [*PNAS*]. I knew that Leo Szilard, who was a physicist-turned-biologist, was a member.[1] I wanted him to sponsor the first two papers that we had. The first was describing the protein synthesizing system. The second was the poly-U paper. I called him on the phone, and he invited me to come down to the Dupont Hotel at Dupont Circle. His office was basically the lobby of the Dupont Hotel. He was remarkable. He did all the work for his Ph.D. in two weeks while he was mountain climbing in the Alps. He had an idea that related information and entropy, and he worked it out while he was on this mountain climbing trip. I felt privileged to be able to spend even a little time with him because he was so well known as the originator (with Albert Einstein) of the letter to President [Franklin D.] Roosevelt that started the Manhattan Project.

Szilard didn't know anything about protein synthesis, or about what I was going to tell him, so I started from scratch. I spent the whole day with him. He seemed to know everybody. Everybody that would come through the lobby there would wave and say, “Hi, Leo,” and they would talk for a few minutes about something that I knew nothing about. He had a wide circle of acquaintances who passed through that hotel lobby, and in between these conversations with other people, I told him what I had done and the implications of it. But after listening to me for the whole day, he said that he simply didn't have the background and didn't feel right about publishing and/or sponsoring these two articles.

I finally got [Joseph] Joe Smadel, who was an administrator at NIH at that time and whom I had never met, to sponsor the first two papers in *PNAS*.[2] They were sent in immediately before I left for Moscow. I wanted to have the papers in press before leaving for Moscow.

RH: Was the paper that you gave in Moscow about the breakthrough that would lead to deciphering the genetic code?

MN: Yes. This paper showed that it was absolutely clear that we had a way of doing this. We had already deciphered the first word with poly-U. It was clear that a number of U's corresponded to phenylalanine, three or more U’s. It couldn't be two because there wasn't enough information, so I thought most likely it had to be three. We already had deciphered the first word and had devised a relatively simple method of deciphering the codons for every other amino acid as well. So it was clear that by using randomly ordered polynucleotides with different proportions of bases that we could determine the base compositions of codons for all the other amino acids as well.

RH: Could you please tell about what happened in Moscow from when you arrived and about you giving your first talk there?

MN: I remember sitting in the airplane next to somebody who was from the NIH. As we approached, he asked me what I was doing. I told him what I was going to present at the meeting, and it seemed to go in one ear and out the other. I don't think he really understood because he immediately changed the subject to something else.

But, once I got to Moscow I saw [James] Jim Watson, and I introduced myself and told him about the work and what I was going to say.[3] Watson told his colleague [Alfred] Tissières, who was from Switzerland and who was working with Watson at the time, about the work. Tissières actually came to the talk that I gave, and was totally convinced by the data I presented. This was a talk that was in a small amphitheater, with an enormous projector, as big as a person. I gave the talk, and relatively few people came to it. Almost nobody — maybe there were 25 people. But Tissières, who was there, saw the data and he told Watson that it was solid.

RH: Did Watson come?

MN: No. He didn't come. And neither did [Francis] Crick. I ran into Crick in the halls later on. He said he had been searching all over for me and was glad to see me, and he invited me to give the talk again in a large symposium that he was chairing.[4] So I gave the paper twice.

The second time I gave the paper it was to a very large audience. The reception was really remarkable, fantastic. I remember [Matthew] Matt Meselson, who was sitting right up front. I didn't know him at the time, but he was so overjoyed about hearing this stuff that he impulsively jumped up, grabbed my hand, and actually hugged me and congratulated me for doing that.[5] I could have been part of a rock band or something! That meant an awful lot to me. It really meant more to me than all kinds of awards and what-not because it was genuine and spontaneous. Since then, whenever somebody in the lab does something really good, I have always made it a point to try to congratulate them in a spontaneous and sincere way. I think that kind of thing means a lot to people. So it was a terrific reception.

I met some Soviet scientists, but I never really got to know them. Years later, the man who translated my talk at the Crick symposium came to the NIH and introduced himself.

He told me he had been the translator at the time. Later on I met numerous Russian scientists. There was one delegation of Russian scientists that visited the NIH that I am absolutely positive was mostly KGB men. They all wore black, identical hats and identical suits. I was asked to give a little welcoming talk to them. I had a technician, Teresa Caryk, who came from the Ukraine, so I asked her for a phrase in Russian, a welcoming phrase, for these guys. I don't know what the phrase was. I memorized it and said it, and they burst out laughing to such an extent that they almost fell out of their seats. I had no idea what I had said, but whatever it was, it was very funny.

While I was in Moscow, I saw the parade in Moscow of Yuri Gagarin, the first man put up in space. When he returned, they had an impressive parade for him which I saw. But Moscow was so dreary. I was depressed to be there. I had this sense of dreariness in Russia: it was a depressing place at the time. A little boy came up to me in Leningrad, and he said, “Are you a capitalist?” I looked at him, and I felt I wasn't really a capitalist, but that I felt I had to defend the honor of the United States, and I said, “Yes.” He wanted to sell me his watch, or he wanted to buy my watch, something like that. I didn’t do business with him.

I remember when I flew out and landed in Finland and we saw in the coffee shop a table with a rose on it, or a flower of some kind, a single flower, that it looked so beautiful. It was so different from the dreariness and drabness of Moscow.

Perola and I got married just before I left for Moscow also, and we decided to honeymoon in Europe. She was going to meet me in Denmark after the meetings. I thought that was the worst time in the world to take a vacation, but I felt that you only get married once, and it was worth it. We took several weeks and traveled in Switzerland, Denmark, France, and Italy and we had a wonderful time.

We didn't have a reservation in Copenhagen, and, to tell you the truth, I didn't have any money, really not enough with which to get married. When I was a postdoctoral fellow, I was making $3,000 dollars a year. In 1961 I had become a postdoctoral fellow of the Public Health Service for one year, simply because they didn't have a position available for me at the time, but I wasn't making much more. My expenses were really minimal. I could live on what I earned, but I certainly didn't have enough money for a wife or a honeymoon in Europe.

Fortunately, Perola had saved some money. I was looking for the cheapest hotel that you could possibly imagine. I had never been to Europe. I had never really traveled. I didn't realize it might be difficult to get reservations. So I had some crazy idea that Perola would arrive before me, that she would have plenty of time, she could look around and pick a good hotel, a cheap one preferably, and then come out to the airport and meet me. She came out to the airport and, for some reason, started to leave before my plane had arrived. I was very lucky that I was able to find her before she left the airport.
I think the plane was just late. It was an Aeroflot, a Russian plane with a rococo Greek pillar holding up the roof of the airplane.

RH: What happened when you got back to NIH from the Moscow conference? What was the reaction here?

MN: After I got back from Moscow, one of the first things I did was to give a talk at the Rockefeller Institute in New York. Fritz Lipmann, who was a hero of mine, a marvelous person and the best biochemist of his generation, actually had invited me to give a talk in his laboratory at the Rockefeller Institute, which I did. I was introduced to him earlier when he came out to the University of Michigan to give a talk. But the first time I had a chance to talk to him was in Moscow. I had to go up to Lipmann. When I had met him in Moscow, I was fumbling around, sort of looking for the hem of his robe to kiss. That is the way I thought about him — he had done marvelous things in biochemistry. Actually, Lipmann was very kind to me.

When I went up to give the talk at the Rockefeller Institute, I asked him for some intermediates of some enzyme preparations that he had that were involved in protein synthesis. One of the things I wanted to do was to show that phenylalanine tRNA was an intermediate in polyphenylalanine synthesis. This had never been done before. Nobody had proven it. It was a real question. Is aminoacyl tRNA an intermediate in protein synthesis? Lipmann had tried to do that and had failed. So he gave me the intermediates.

In one week I did all the experiments, and in another week I wrote a paper on it. So in two weeks I showed that phenylalanine tRNA was required for polyphenylalanine synthesis. But I always regretted that. I always thought I made a mistake, because that was not the most important thing. Even though it was an important thing to do, it was not the most important thing for me to do. What I should have done immediately was to start working on the code.

Watson invited me to give a talk at the Massachusetts Institute of Technology (MIT) in Boston. This was either the first talk or second talk that I gave after I returned from Moscow. When I went there, the place was packed. It was a large auditorium, and there was standing room only. I had taken a day to organize my latest data, another day to make slides, and a third day to go up to give the talk to Boston. So I gave the talk, and during the talk Watson, as he always does, was sitting in the front row with the *New York Times*. In the middle of my talk he unfolded the *New York Times* and vibrated it like he was terribly angry. I had heard that he did this during talks whenever somebody said something he didn't like, that he disagreed with, and I thought it was funny. I had never seen this before.

But only after I thought about it did I understand what was going on. Let me just say, if I go to a talk and I don't want to get stuck in the room, if I think that the talk is not going to be any good, I will sit in the back. I will take the last seat next to the door so that if the talk is no good I will duck out the door without disturbing the speaker. But, Watson always sat down in the first row of the presentation, brought a newspaper with him, and vibrated the newspaper in the middle of the talk presumably at something he didn’t like.

What I should have done, if I had thought about it, was to immediately confront him with this: “I see Jim Watson is rattling his *New York Times* there, and there is something that he doesn't like. What don't you like?” I would pin him down. The thing that struck me was that when he rattled the paper, it was totally inappropriate. I was speaking about new data that I had obtained since I had gotten back to NIH. It was relevant to the work that I was doing. But Watson knew nothing about that. I hadn't reported that. So it was inappropriately timed.

When I thought about it, I said, “Why in the world would a person do a thing like this?” To me it seems that if somebody gives a talk and says something wrong, or is no good in any way, everybody immediately understands. What is the sense in saying anything about it? Watson was a negative cheerleader. I think what he was doing there was setting himself up as a judge of everyone who passed through giving a talk, and basically saying, “This guy is no good, this guy is a turkey,” or “This piece of work is no good,” and saying that he is better than the speaker. He is trying to tell the audience that there is something wrong and that he, Jim Watson, says that there is something funny about this work. I don't know any other reason why he would do something like this. It was in the middle of the talk, and very clear to everybody in the room, and purposely so.

There is one thing that I want to say about the talk at MIT. At the end of my talk, Peter Lengyel stood up. Severo Ochoa had sent Lengyel, his postdoctoral fellow, from New York to Boston to attend that talk and to give results from their lab on the work as a sort of question after my talk.[6] I don't know how he had heard about it. So Lengyel got up and showed data using synthetic polynucleotides. The rumors I had heard that he had synthetic polynucleotides and he had found other amino acids going into protein and he was ahead of us were absolutely true. Just the fact that Ochoa would send someone to give a talk after my talk was a remarkable thing. I had never heard of anything like that. It was very depressing at that time because it was clear that they were way ahead of us in deciphering the code.

I guess I very rapidly learned not to accept talks because it kills you. Now, I accept one maybe every few months. It takes time to prepare the talk and to make the slides, and it takes you away from the laboratory. I didn't want the distraction so I have severely limited the number of talks that I gave simply to have the time to be able to work, to do things.

When I took the plane back from Boston to Washington, I was terribly depressed because I thought I had made a big mistake spending two weeks proving that phenylalanine tRNA was the intermediate in polyphenylalanine synthesis when I should have been working on synthetic polynucleotides. I didn't even know how to make synthetic polynucleotides.

The next day was a Saturday, and I went to Heppel's library just around the corner ***(from my lab)*** to look up and to find out how you make synthetic polynucleotides. I felt I had reached a crossroads here.

I felt that either I would pull out and let Ochoa take it away, let him do the code, or I would really dig in and compete with him.

[Robert] Bob Martin was a postdoc in Bruce Ames's lab at the time, a young guy, and for him, to think is to do.[7] He was filled with energy. I told him what the situation was, and impulsively he said, “I'll help you. Let's look up how you make synthetic polynucleotides. We'll make the solutions today. We'll make the polynucleotides this weekend, and Monday you can be doing the experiments.” That is exactly what we did.

Bob galvanized me into action. At the end of that weekend, we had all kinds of synthetic polynucleotides that we had made, and we used them in successive weeks. That was a real crossroads because I had to decide then whether I was going to pull out or fight to compete on this problem.

The footnotes that appear below will be placed in a separate digital file for linkage to this file.

1**information needs to be reinserted.**

[2] Joseph E. Smadel (1907-1969) earned his A.B. at the University of Pennsylvania and his M.D. at Washington University. Before joining the NIH, he investigated infectious diseases at the Walter Reed Army Medical Center. He was elected to the National Academy of Sciences in 1957.

[3] James Dewey Watson (1929-) won the 1962 Nobel Prize as the co-discoverer of the DNA structure. He studied zoology at the University of Chicago and earned his Ph.D. at Indiana University. Watson taught at the California Institute of Technology and at Harvard and was director at the Cold Spring Harbor Laboratory in New York.

[4] Francis Harry Compton Crick (1916-2004) shared the 1962 Nobel Prize for his work with Watson in explaining the structure of the DNA molecule. A physics graduate of University College, London, he earned his Ph.D. in biology at Cambridge in 1953. In 1977 he became a professor at the Salk Institute in San Diego, California.

[5] Matthew Stanley Meselson earned his A.B. at the University of Chicago in 1951 and his Ph.D. from the California Institute of Technology in physical chemistry in 1957. Along with Franklin Stahl, Meselson conducted a joint demonstration of semiconservative replication of DNA. With Jerome Vinograd, Stahl and Meselson developed a technique that extended what Crick and Watson had done. In 1960 Meselson joined the biology faculty at Harvard University.

[6] Peter Lengyel (1929-) graduated from the Budapest University of Technology and Economics in 1951 and earned a Ph.D. from New York University in 1962. In 1969 he was a professor of molecular biophysics and biochemistry at Yale University.

[7] Robert G. Martin (1935-) is a molecular biologist with the National Institute of Diabetes and Digestive and Kidney Diseases. He earned an A.B. in 1956 and an M.D. in 1960 from Harvard Medical School.