Louis Ignarro: NO Stupid Questions

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Circulation Research *is pleased to inaugurate "Profiles in Cardiovascular Science" with this interview with Lou Ignarro, the son of poor Italian immigrants, who won the 1998 Nobel Prize. Lou is one of my favorite people, a wonderful combination of scientific prowess, human richness, genuineness, and unassumingness, that is both refreshing and rare among medical researchers. Perhaps the most poignant part of the interview is the end, when Lou states that neither of his parents ever attended school; that their son rose to become a Nobel laureate is not only extraordinary but also deeply inspiring. This should be a powerful lesson in motivation for all of us.*

—Roberto Bolli

In the 1970s and 1980s, a series of discoveries made independently by Louis Ignarro, Ferid Murad, and Robert Furchgott established that the highly reactive molecule nitric oxide (NO) was a somewhat unexpected yet important physiological mediator of blood vessel relaxation. First, in 1977, Murad showed that nitric oxide could increase intracellular levels of cyclic GMP,[1] a signaling molecule previously shown to increase when blood pressure dropped.[2] Then, in 1979, Ignarro showed that nitric oxide could relax vascular smooth muscles.[3] Lastly, in 1980, Furchgott discovered a substance released from endothelial cells that relaxes blood vessels[4] that was later discovered by Ignarro to be nitric oxide.[5] This body of work led to the three researchers being jointly awarded the Nobel Prize.

The work of Ignarro and colleagues has established nitric oxide as a key biological messenger. It is now recognized that nitric oxide is a paracrine and autocrine signaling molecule that regulates almost every biological process, including vascular homeostasis, cardiac metabolism, neurotransmission, carcinogenesis, immunity, and stem cell function. Changes in nitric oxide production have been found to be associated with the development of atherosclerosis, diabetes, and hypertension. Several major drugs such as nitroglycerin and sildenafil (Viagra) act by enhancing the supply or the actions of nitric oxide. Since 1980, more than 85 000 original research articles on nitric oxide have been published.

Since winning the Nobel prize, Ignarro, who is now Professor of Pharmacology at the University of California, Los Angeles, has had little opportunity for teaching or research. Instead his time is taken up traveling the globe giving lectures and interviews, a great opportunity for telling people about nitric oxide, he says. Boosting one's levels of nitric oxide through diet and exercise, Ignarro asserts, can lead to lower blood pressure and fewer cardiovascular problems.

Despite his busy schedule (he has just returned from a whirlwind tour of talks in Toronto, Italy and Korea) Ignarro found the time to chat with *Circulation Research*. He told us about his early career, his foray into the drug industry, how he was the first person in his family to go to school, and how his particular third of the nitric oxide Nobel story developed out of an unexpected question.

Into Drugs From an Early Age

What Drew You to Pharmacology?

I always enjoyed biology as much as I enjoyed chemistry. So I thought it would be very natural to put the two together, and that's pharmacology.

And to Cardiovascular Pharmacology in Particular?

That was primarily down to the training I received in graduate school. The department at the University of Minnesota was strong on two subjects: drug metabolism and cardiovascular and autonomic pharmacology. I developed a keen interest in those, and as I read more, I realized how many unanswered questions about cardiovascular disease there were.

Tell Me About Your PhD

I was studying the ways in which the sympathetic nervous system innervates the heart during embryonic development. The Nobel laureate Julius Axelrod had previously discovered that sympathetic nerve endings have storage sites for the transmitter norepinephrine. I investigated when these storage sites appear in the innervating heart neurons and what enzymes they contained.

You Moved to the National Institutes of Health for Your Postdoc. How Was That?

The NIH is an excellent place to do a postdoctoral fellowship. If you pick an individual laboratory, you are going to one person, and there may or may not be some other good people

E-mail ruth.williams@absw.org.uk
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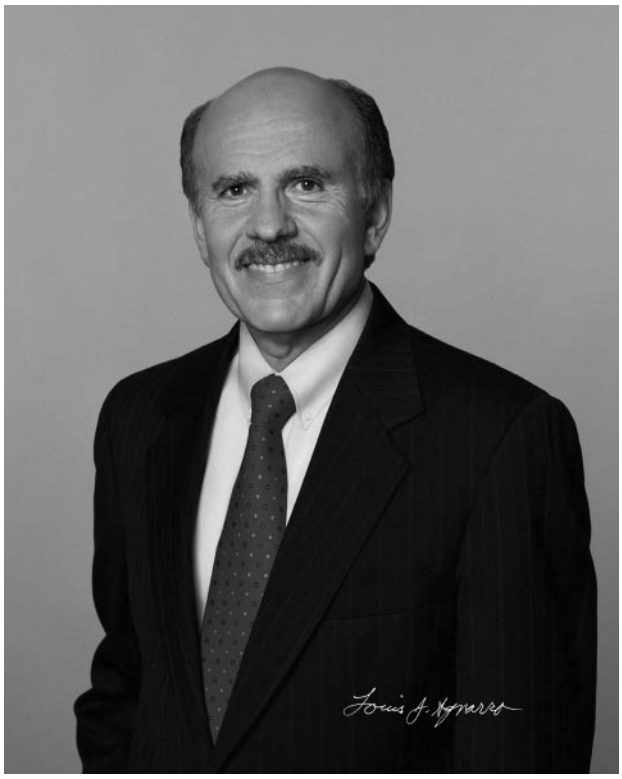

Figure 1. Personal portrait of Louis Ignarro.

around the university. At the NIH, however, you have literally floors of excellent investigators. I saw it as an opportunity not only to do my research but also to visit other laboratories, meet people, see what they were doing, and learn from them. And that's exactly what I did. It was a very rich and rewarding experience.

What About Your Project?

Ah, well, that was another story. At the time, there was virtually nothing known about the alpha and beta adrenergic receptors, which control a number of things including heart rate, and so my mentors, Elwood Titus, and Bernard Brodie, thought that in 2 years I might be able to isolate, identify, and characterize both of these receptors. We were all rather naïve. It was exceedingly difficult. At the end of my postdoc, I wound up with just one publication: a rude awakening after the success of my PhD, when I'd published lots.

The benefit was that in those 2 years, I learned a great deal about working independently. It made me think logically. It helped me to plan better projects for my own graduate students and postdocs down the line. In short, it truly helped me to understand the scientific method.

A Brief Exodus

Was There a Point in Your Postdoc That You Thought You Might Quit?

I never give up! But after the first year, I did think about switching projects. I talked to Julius Axelrod about working in his laboratory, but with only a year left, it was deemed a bad decision to switch. So, I stayed and got the most that I could out of it.

Figure 2. Louis Ignarro accepting the 1998 Nobel Prize in Medicine or Physiology.

But Then You Did Quit Academia for a Drug Company

I did, and that upset a lot of people. It certainly upset the people at the NIH, and it also upset my PhD supervisor, Fred Shideman. He wanted me to get an academic position and had been working toward that.

I didn't leave readily. Geigy (now Novartis) came to see me three times at the NIH, before I agreed to join them. They wanted me to direct the pharmacological development of antiinflammatory drugs, but this wasn't my area of expertise. I asked why they wanted me, and they said they'd talked to people at the NIH about me and had decided they needed someone fresh with a sharp mind. They asked if I would at least consider it.

The salary they were offering was twice what I would have earned in academia. On top of that, I wouldn't have to apply for any research grants, they were going to provide me four technical people in my own laboratory, and I would also be supervising two other labs. I thought, maybe it would be a good experience. If I didn't like it, then after 4 or 5 years, I could always return to academia. I also thought, well let's see how good I am, because if I'm a really good scientist, then I should be able to do something.

During my time there, we managed to get a drug approved for further study: it eventually went on to become the widely used antiinflammatory, diclophenac. I was pleased I'd delivered them a drug before I left. It had been four and a half

years, I had learned a lot, but I was highly motivated to get back to studying cardiovascular pharmacology, and I wanted to teach, so back I went to academia.

Do You Recommend Industry Experience to Your Own PhD Students and Postdocs?

Before I recommended industry, I spent an equal time in academia, so that I could properly compare and give students informed advice about both. Academia is much harder than industry. You have to lecture students, you have to apply for grants, you have to join committees. When you're starting out, they load you up with everything and still expect you to have a successful research laboratory. I think that it's the hardest job on the planet and certainly the lowest paid. But if you love to teach and train new scientists, as I do, then you have to go to academia and suffer!

You Choose Tulane University. Why There?

I was always interested in understanding how drugs worked and what signaling mechanisms in cells they affected. When I was thinking of returning to academia, the signaling molecule cyclic GMP had just been discovered. One of the main people working on it, William George, was based at Tulane, and there was also a very good cardiovascular person there: Philip Kadowitz. George had shown that when you decreased the heart rate (and blood pressure) using acetylcholine, cyclic GMP levels went up. I didn't know exactly what we were going to study, but with this team, I knew something good was going to happen.

Something Good Happened

How Did You Get Into the Nitric Oxide Story?

I was lecturing students at Tulane on cardiovascular pharmacology. I told them about various drugs that lower blood pressure, including nitroglycerin. Nitroglycerin was commonly used to treat angina, because it is a vasodilator, but it was originally used by Alfred Nobel to make dynamite: it is an explosive chemical.

After the class, a group of medical students asked, "How can an explosive chemical be a vasodilator?" I told them that no one knew how nitroglycerin worked. But it got me thinking. I went back to my office and spent two full days reading everything I could on nitroglycerin, nitrates, nitrites, but there was no clue as to its vasodilating mechanism.

I decided to go after it. At the same time that we were working on the problem, Ferid Murad, with whom I shared the Nobel Prize, had just made an accidental discovery that nitric oxide elevates cyclic GMP in cells and tissues. He went on to test other nitro compounds and found that they also increased cyclic GMP. My brain started to click. I thought maybe one of the nitro groups on nitroglycerin gets metabolized to nitric oxide, and that this is the vasodilator. We did the experiments and the rest is history.

So, It Was a Very Good Question From the Medical Students

Exactly! Sometimes in lectures students will raise their hand and say, "Dr Ignarro, I have a stupid question." I tell them there's no such thing.

When Did You Find Out That You'd Won the Nobel Prize?

The date was October 12th, 1998 (Columbus day, here in the States). I was traveling from France, where I'd just given a lecture, to Italy, where I was about to give another lecture. I was at the airport in Nice and was standing in line waiting to board the plane, when one of the airport attendants made an announcement: "Is there a Professor Ignarro here?" I raised my hand, the attendant came over, handed me a telephone and said, "You have a very important phone call." I got on the phone, and it was one of my physician friends from UCLA. With the help of my wife, he had managed to track me down to the airport (it was 3 AM in LA).

The thing is, this particular friend had been telling me year after year, "Oh, you know, this year is the Nobel Prize for you." So, when he told me the news, I thought he was joking again. The telephone reception was poor and we got disconnected, and then I had to board the plane. I sat through the flight thinking, "This is the second week in October. That's when they announce the Nobels. Why would my friend call me and track me down at the airport if it was a joke?" When I got off of the plane in Naples and walked down the stairs to the tarmac, there were three or four dozen photographers taking pictures. So, then I knew for sure. I almost fainted. It was 11 years ago and I'm still celebrating!

You know, both my mother and father were born in Italy and were completely uneducated. They never even went to first grade. I was the first person on either side of the family who ever went to school. Period. I was able to climb to the top of my profession without their help, only with their support and motivation. When I get invited to give talks around the world, I love to tell that story, because I hope it inspires the young and underprivileged to aim high.

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