

A conversation with John Oates

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Conversations with Giants in Medicine

Dr. John Oates of Vanderbilt University was central in launching the field of clinical pharmacology and gave life to the concepts of first-pass drug metabolism and interindividual variation in the way humans process drugs. Oates (Figure 1) also made seminal discoveries on the metabolism, biosynthesis, and pharmacology of eicosanoids. The full interview, with many more stories about testifying before Congress and his love of sailing, can be seen on the JCI website, <http://www.jci.org/kiosk/cgm>. JCI: Can you tell us a little about where and how you were raised? Oates: I was raised in Fayetteville, North Carolina, which at that time was a small town of about 35,000. My mother started out as a schoolteacher before she was married, and my father also began his career as a schoolteacher. He later became a lawyer and a historian. They both had interesting libraries in the home. My mother was attentive to the fact that I might like to read something different from what they read, so she found books that were more appropriate for a boy growing up. One set of books that my mother got for me was called The Book of Knowledge. It was about 10 volumes that were sort of like an encyclopedia but it wrote about subjects in a more interesting way, with a lot of science, geography, or [...]

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One set of books that my mother got for me was called *The Book of Knowledge*. It was about 10 volumes that were sort of like an encyclopedia but it wrote about subjects in a more interesting way, with a lot of science, geography, or history in it. I think I read most of that progressively as I was growing up.

There's an interesting story in the family about how my mother bought these. It was during the Depression and my father had a strict policy that nothing would be bought on credit or by an installment plan that paid progressively over time. But my mother, given the budget, had to buy this on the installment plan, and I think she was concerned that my father would be very upset by this. Fortunately, with her persuasion, he agreed that this could be an exception to his fiscal policy.

JCI: Did that set of books, and particularly the science within it, inspire you to want to pursue medicine?

Oates: Well, it certainly interested me in science. I had an inspiring chemistry teacher in high school who got me excited about atoms and molecules, and I think that also drove me toward thinking about medicine as one way where you can bring science together with the health of people.

JCI: After medical school at Wake Forest, you ended up at Cornell to do your residency. So, how does a proud Southerner — as I've heard one of your colleagues call you — end up in New York City?

Oates: In part it resulted from my exposure to research in medical school. During the physiology course, a research project led me to become interested in the effect of potassium on the heart. I went to my cardiology professor and asked him if could I work in my free time in his laboratory and being very honest he said, "Well, I don't do anything on potassium in the heart. Why don't you talk to the Chair of Biochemistry, Dr. Camillo Artom?" Because of the World War, Artom had come to the US from Italy where he'd been a pioneer in the field of phospholipid research. So, I went to Dr. Artom with the idea that I'd like to work in his laboratory on potassium in the heart and he said, "John, that's very interesting. But why don't you work on phospholipids?" So, being the 1950s, I said, "Yes sir," and that research got me interested in phospholipids. The Chair of Medicine at New York Hospital/Cornell was David Barr, who was quite interested in HDL and its link to coronary disease. I think the congruence of these interests attracted me to Cornell and perhaps vice versa. In addition, the Chair of Medicine at Wake Forest, encouraged me to consider the New York Hospital.

Also, while working briefly in the Merchant Marines, my home port was New York, and I found the city attractive.

JCI: From Cornell, how did you end up at the NIH?

Oates: NIH was fairly new at that time, and one day at the lunch table where the residents gathered, Richard Silver was telling us about his time at the NIH. And I said, "Dick, what's the NIH?" And he told me that he had been able to serve in the doctor draft at the NIH instead of joining the military. I thought that was a good idea and my chairman arranged for me to be appointed to the NIH program, specifically the Heart Institute Program.

We had a choice of which lab we could work in. Although initially I had been interested in the lipid field, when I spoke with the people in Albert Sjoerdsma's laboratory I found they were all having a good time; it was a very productive lab with exciting things going on. He and Sidney Udenfriend

had a collaboration that brought Udenfriend's biochemistry together with the clinical research on aromatic amines. The excitement of that laboratory drew me there.

JCI: Do you mark your interest in clinical pharmacology to that time?

Oates: Very much so. They were doing translational research at that time, related to drugs. We didn't know what clinical pharmacology was but that's what we were doing.

JCI: Did you ever encounter a patient while you were there who shaped your approach?

Oates: At the Heart Institute, our group managed the hypertension service. The studies that we did on aromatic amine metabolism were all in hypertensive patients, because of the general idea that these compounds might be relevant to hypertension.

JCI: How did you come across using methyl dopa to treat hypertension?

Oates: I was working in the Udenfriend laboratory, and he was interested in how we could better analyze the metabolism of aromatic amines in humans. We set up analytical methods based on advances in fluorometry to measure various amines in the urine of humans. We had perfected that as a way of studying the effects of drugs, like the monoamine oxidase inhibitors, to increase amine excretion in patients. Udenfriend had recently been at a conference on the biosynthesis of catecholamines and got together there with Karl Pfister from Merck, whose group had synthesized this α -methyl amino acid, methyl dopa, as part of a cancer research screen. It was then found to be an inhibitor of the aromatic amino acid decarboxylase, an enzyme required for biosynthesis of aromatic amines, including catecholamines and serotonin.

JCI: So it was initially targeted to be screened for cancer?

Oates: That's right. The Merck scientists found that it had absolutely no effect on blood pressure in experimental animals, and concluded that it would not be an antihypertensive agent. Udenfriend and Pfister decided that if Merck would do the toxicology studies, we would then investigate the effect of methyl dopa on aromatic amine biosynthesis in humans. The initial plan was to study it in patients with pheochromocytoma and carcinoid syndrome, to evaluate effects on catecholamine and serotonin biosynthesis. But, none of those patients were in the hospital when the drug



Figure 1

John Oates on April 27, 2013, in Chicago, Illinois. Image credit: Karen Guth.

arrived and our chief was on a sabbatical. So we decided, why not determine whether it would block aromatic amine biosynthesis in hypertensive patients? We had very carefully dose-ranged the drug until we got to a point where we were inhibiting the biosynthesis of tryptamine and tyramine in the patients. In looking at the patient charts, the blood pressure obviously swings up and down during the day, but we had the impression that on average the blood pressure was coming down over several days' treatment. I then went back to the lab at night and plotted out these data, which showed in fact that we were getting a very clear reduction in blood pressure in that first patient. It was a very exciting graph and I called my collaborator, Louis Gillespie. He was at home but came into the lab and we looked over this data and decided that this was something we needed to pursue with additional studies. That was a eureka moment in the methyldopa story.

JCI: You moved in 1963 to Vanderbilt. What made you leave what sounds like it was a Shangri-La for research and discovery at the NIH?

Oates: The Clinical Associates, of which I was one, typically are there for three or four years and then move on; it was simply time for me to migrate out of the NIH. Fortunately, Allan Bass of Vanderbilt knew the work that was going on in the Udenfriend group and contacted him.

JCI: Where you established the first Department of Clinical Pharmacology?

Oates: The first in that institution, yes. It was a Division of Clinical Pharmacology in the Departments of Medicine and Pharmacology. We were very careful not to set ourselves up as something separate.

The attractions for me at Vanderbilt were the things that have kept me there all these years. It was an institution where the Pharmacology Department was really committed to including human pharmacology and clinical investigation. The Department of Medicine Chairman, David Rogers, was also committed to interdisciplinary science. One of the first Clinical Research Centers in the country had been established at Vanderbilt; it mirrored on a smaller scale the Clinical Center at NIH, so that gave us the infrastructure for our clinical investigation. Those were the things that drew me there and, as our program grew with a number of collaborations in the Pharmacology Department, it was a very productive place to work.

JCI: Much of your focus was on the biology, metabolism, and synthesis of eicosanoids. How did you get interested in eicosanoids?

Oates: My interest in hypertension and in the vasoactive compounds that effect blood pressure drew me into the area of the prostaglandins, which are extremely potent. I asked Sune Bergström, who was one of the discoverers of the prostaglandins, why he invested so much in elucidating their structures. He said it was because when he purified them to a point where you could no longer see anything, there was still an extremely potent biological activity. That was intriguing to me. It was difficult to address prostaglandin research in patients because you couldn't measure the levels in blood. We became interested in measuring prostaglandin biosynthesis by assessing their metabolites, which would not be interfered with in artifacts of blood collection.

When I was with Udenfriend, he told me many stories about his experiences with his mentors, and one of whom had developed the first radioactive isotope-dilution assay. We had a mass spectrometer in the Clinical Pharmacology Division, and it occurred to me that we could apply isotope-dilution technology to measure prostaglandin metabolites using stable isotopes instead of radioactive isotopes. We had already developed assays with stable isotopic methods for prostaglandin E₂ itself in human urine, and showed that it is derived from the kidney. But, we wanted to learn about prostaglandin biosynthesis in the body as a

whole, not just the kidney. So, that led me to a sabbatical in Sweden with Bengt Samuelsson to learn how to biosynthesize the stable isotopic metabolites that we used for mass spectrometric analysis. Once I came back from Stockholm, we utilized analysis of the major PGE₂ metabolite to demonstrate excessive biosynthesis of PGE₂ in patients with lung cancer for the first time.

JCI: Beyond your work on prostaglandins, you are also recognized for elucidating the concept of first-pass metabolism.

Oates: We had undertaken a study with Ciba Geigy. They had an antiarrhythmic drug, and we were interested in cardiovascular drugs. They were having some trouble in development because patients appeared to be getting different responses to the same dose. We agreed to investigate its metabolic fate and pharmacokinetics, if they would synthesize a radioactive tracer for us. We gave the drug both orally and intravenously to the same individuals. Pharmacokinetic analysis at that time was based on mammillary models where you have compartments, and arrows of rate constants going between them, but there was nothing in these models about what happened to the drug before it reached the systemic circulation. These studies demonstrated that, when you gave the drug by mouth, all of the drug was absorbed but the levels in plasma were a tiny fraction of what occurred when you give it intravenously. That was something that wasn't built into the previous pharmacokinetic models and led us to the concept of "first-pass metabolism," involving metabolism in the gut and in the liver before the drug reached the systemic circulation.

JCI: Did this lead to your discovery that there are vast interindividual differences in the way that humans process drugs?

Oates: First-pass metabolism amplifies those differences and our group came up with the general concept that if you have very high first-pass metabolism, you're likely to have great interindividual variation in plasma levels, and that was the case with this antiarrhythmic drug. There were such wide differences in the plasma levels that were achieved that it was clear that you couldn't use this drug with a low-therapeutic index for treating patients with arrhythmias.

JCI: Do you think you ever would have chosen a different vocation?

Oates: I don't think so. Those of us who are involved in medicine and medical research are very fortunate.

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