Cover Shots
Conversations with Leading Science and Technology Authors

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How did the son of a rancher from West Texas become a scientist? Were there scientists in your family?
Nobody in my family is in science, and I am only the second person in my family who graduated from college. The first was my older sister. We were out here on the frontier in Texas. In high school I ranked high on all the standardized tests. The highest in math, then in science and English. In any event, all those things have helped me. Being good at English meant I could be an editor, and I've edited a number of books and journals. When I went to college the thought was that I would be a rancher, like my father, so I majored in agriculture at Texas Tech.

You received a B.S. in Animal Science, correct?
That's right. As I went along I had to take some chemistry and physics, which I hadn't had at Merkel High School because they didn't offer it. I found out that I was good at those subjects. The electives I took were courses in the biological sciences, and I became more and more interested in that subject. I thought about majoring in nutrition because it had a lot of biochemistry. In my senior year I took an endocrinology course, and I was hooked. It was fascinating! It was so revealing about how organ systems were regulated by endocrine glands. I was interested in the three components of successfully producing animals on a ranch or farm; nutrition, disease and reproduction. I know there are economics involved, but I'm talking about science. In any event, I no longer was interested in nutrition, and I knew endocrinology was what I wanted to study. I went to graduate school at the University of Missouri.

Why did you choose the University of Missouri?
The professor of endocrinology at Texas Tech helped me get into graduate school at the University of Missouri. Being naïve and not long off the farm, I didn't know that given my standardized test scores and my college grades I would have been eligible to go wherever I wanted to go for graduate school. But I went to the University of Missouri and took my Ph.D. there in reproductive physiology with an emphasis on physiological systems. Early on I developed an understanding of how organisms work with the various sorts or organ systems as well as the endocrine system. When I finished my degree there I had become familiar enough with the literature in endocrinology that I wanted to go with one of the best laboratories in the world, which was Dr. Knobil's laboratory at the University of Pittsburgh. I went to visit with him and we hit it off immediately. I didn't want to go anywhere else. It turns out that he and I became lifelong friends, even though we were about 20 years apart in age.

You also had very different backgrounds, didn't you?
Yes, I came off a hardscrabble ranch in West Texas. Dr. Knobil originally came from an upper class family in Germany. Due to the deteriorating political conditions in Germany, the Knobil family left and went to Paris in 1932 when Dr. Knobil was six years old. Later they came to the United States. But despite the different backgrounds, we sort of had the same world view. We viewed science the same way, we were philosophically very similar, and we believed that one didn't understand a system until you could reduce it to mathematics. We both believed strongly in evolution and the importance of reproduction in evolution. A lot of people forget that in evolution sexual selection is probably at least as important as natural selection. That is, the ability to survive versus the ability to reproduce. They are both very strong components in directing evolution. So we were good friends, and good readers of the literature. He was a highly unusual and very wise man.

Then you went on to become co-editors of the first and second editions of *Physiology of Reproduction*.
Dr. Knobil was invited to be the editor by Diana Schneider at Raven Press. He said he would only do it if I agreed to do it with him. It took awhile for Diana to talk me into it because of prior commitments. It was a year or so before I finally felt my schedule was open so I could agree to do it. I had just become the Chairman of the Department of Physiology & Biophysics at the University of Alabama and moved to Birmingham. So Dr. Knobil and I completed the book, and it was the smartest thing I ever did. I think perhaps that was also true of him. I think we will be best remembered for this book. If asked 100 years from now how well humans understood reproduction in the year 2000, this will be the source of that information.

It was in the year 2000 that you were going to plan the third edition. That was the same year that Dr. Knobil passed away.
Yes, we had been trying to get the book away from the company that had acquired Raven Press. They didn't want to do a third edition, but they didn't want to give up the rights either. With the help of Jasna Marcovac, Senior Vice-President of Elsevier who was the executive editor of the second edition, the third edition was finally acquired by Academic Press, an imprint of Elsevier. In any event, Dr. Knobil and I planned the third edition in the year 2000. I went down to visit him, and we knew at that point that he had pancreatic cancer. That's an almost certain death. I went down with the claim to plan the book, and we did, but I really went down to say goodbye to him.

Was that the last time you saw him?
Yes. Toward the end, pancreatic cancer is awful and I didn't want to wait until then. I didn't want that to be my last memory of him.

So he was a big influence on third edition. You put his name in the title and included a memorial article to him.
He and I agreed earlier that the next edition would be called Knobil and Neill's Physiology of Reproduction. In part, to keep our names associated with it, but also because Physiology of Reproduction is such a generic title. We wanted a more specific title. The hope is it will stay that way in future editions. It also memorialized him, as we reproduced the memorial article I wrote in 2000 for *Endocrine Reviews*. The establishment of that journal was one of his major accomplishments as President of the United States Society for Endocrinology.

How do you expect this book will be reviewed?
The book is totally predictable when it gets reviewed. Two things will be said about it: first the reviewer will tell you how many kilograms it weighs and second they will call it The Bible. This book has become the dominant book as a resource in the field of reproduction, and all the people around the world who are taking Ph.Ds in this immense field view this as the primary source for their information. Of course, it also serves as the primary source of background information for professionals who are in the field. I guess I'm bragging, but as Yogi Berra, the baseball player says, "If you can do it, it ain't bragging."

59 authors contributed this edition, and 44 are new. I'm sure this will give the book a fresh review of the new knowledge that has come about during the last ten years since the second edition. What has been the most important change in the understanding of reproduction over the last ten years?
The biggest change is the molecular revolution which has occurred in all the biological sciences, and is epitomized by the Human Genome Project which opened the field for this explosion and investigation at the molecular level. What is different and important about this book is that the molecular detail that has been gathered since the last edition has been woven into an understanding of how organisms and organ systems work. That's what I hope physiology really means; that you understand a whole organism as well as its organs, its tissues, its cells, and the molecular details underlying that. We very carefully chose authors who know the molecular level detail, but also who are sufficiently versed in the field that they know how that applies to organ systems, cells and organisms.

What else is different from the second edition?
The second difference in this book has to do with organismal cloning as exemplified by the cloning of the sheep, Dolly.

The thing that is so key about organismal cloning is not really the cloning per se, but what the discovery told us - that there are stem cells in the mature organism that retain the ability of the fertilized ovum to give rise to a complete organism. That is the importance of Dolly and organismal cloning. They took a cell from the skin of the udder of a sheep, and that cell's nucleus was placed in the ovum whose nucleus had been removed and Dolly resulted. That tells you that this adult cell that they chose retained all of the primordial characteristics of fertilized ova. Therefore, these stem cells are said to be totipotent. They have the ability to give rise to all the various specialized tissues and cells that are in the body. So, now a whole series of stem cells have been discovered in practically every tissue in the body.

I read that molecular cloning was the focus of your research at the University of Alabama.
Yes, in more recent years it was. When I went to work with Dr. Knobil in the beginning we had a big monkey colony and we were trying to understand the menstrual cycle. The first thing I did was to master the measurement of hormones in blood because the hormonal patterns during the menstrual cycle were not known when I arrived as a fellow in his lab in 1965. The first thing we did was to measure the gonadotropins and the steroid hormones in the blood of women throughout their menstrual cycles. We started working on monkeys so we could begin to dissect the interactions between hormones as to how the menstrual cycle was controlled, and obviously you have to use an experimental animal as a model for the human. That's what I did early in my career, and that's where the field and the frontier was. At the end of my career, during my last three or five years in the laboratory I was cloning new receptors out of the genome which we knew were there because we had the whole human genome and you could go through looking for receptors that were similar to receptors that had already been cloned. In fact, we discovered a new receptor for gonadotropin-releasing hormone, that small peptide from the brain which regulates the reproductive process, by searching the genome.

Was that the highlight of your career?
No, the highlight of my career was probably the measurement of those hormones when I began working in Dr. Knobil's lab.

In the 1960's?
Yes, it was very important and it wasn't known at the time. Every textbook you look at now has that in it. There were surprises to it. There was a person in the lab measuring the growth hormone. We all thought we knew what growth hormone levels would be like; it would be highest in children because they grow faster, and low or non-existent in adults. As it turned out, there wasn't any difference at all as far as we could tell between children who were growing fast and adults who weren't growing at all. Looking more carefully and measuring growth hormones throughout the day and night, you can finally see a difference in children verses adults. Children

have higher levels, but it's a pretty subtle difference. And yet that subtle difference makes a very large difference in the growth rate of these two groups. It began to teach us that the differences in endocrinology were much more subtle than we had ever anticipated. I guess I'm trying to make the point that you had to have the hormone levels as they normally existed if you had any hope of understanding a process such as the menstrual cycle. It was very, very basic. That was probably the most important work I did in my career. It was also the most exciting and fun. Dr. Knobil had a very large lab of people and he was so wise. He understood intrinsically the principles of physiology. He taught me how to do research, not by saying to do this or that, but by me watching him. That is classically what you do as a postdoctoral fellow or as a resident. You learn from people who know how to do it, but who can't really articulate what it is they do. You have to watch them do it, and you have to go through the process many times. As a result, I spent four years in his lab. It was lots of fun, it was very edifying and I got a tremendous education from it, and moreover, I was learning to do what I was going to spend the rest of my life doing. I also learned about writing papers. I learned that you don't tolerate any errors, and I don't mean a few, I mean none. This man was driving for perfection. That's what happened in Dr. Knobil's lab for me, and for many others, of course.

And then you continued learning from each other when you left and went to Atlanta and then Alabama?
Right, I went to Emory University in Atlanta and spent ten years there, and then went to Birmingham as the Chairman in the Department of Physiology. He and I always kept in close contact.

I want to go back to cloning. How do you feel about the risks involved with cloning?
Well, I obviously feel we should do it.

Molecular cloning or organismal cloning?
I obviously don't have a problem with molecular cloning. I think most of the world had the same kind of concerns about molecular cloning as they now have about organismal cloning. It turns out there was really no danger. I think we will see later that the same thing is true of organismal cloning, with one exception. I exclude the cloning of humans. That is, letting them grow to be adults. To use embryos, which are a by product of in vitro fertilization, and throw them down the drain and not use them as a source of stem cells is just crazy. Stem cells may turn out to be not as important as we think they will be. At every point along scientific history you never know for sure whether in fact things are going to turn out to be as important as we think they may be. It's hard for me to believe that stem cells are not going to be important, however. Furthermore, to classify an early embryo as a person is just a simple lack of understanding of biology or a mis-application of philosophy.

With the mapping of the genetic code, is it possible now to identify from birth diseases that a person may develop?
Yes, they are in the very early stages of that.

On another note, is it possible to identify imperfections in fetuses and how reliable is that kind of genetic testing?
At this point the genetic testing for defects or diseases is in its infancy. But of course, that will improve with time. As an example of the sort of things that are coming out of the Human Genome Project, the National Institutes of Health has announced that it's going to start testing for all of the genes that are associated with cancers. That's going to be a difficult problem, but I think it's worth the effort so we know to look out for the development of disease. It's already possible to know whether you are carrying the gene which predisposes you to a minor form of breast cancer. Some people will choose not to test for it, but if their parents show it, they almost always choose to do it. It's also possible now to detect a form of high blood pressure which has a very high incidence in African Americans. However, there is a big controversy about whether in fact we should test that because now you begin to look at differences among races. Well, if that isn't a case where we need to look at differences among races, I can't imagine what would be.

What do you think will be the biggest changes for the next edition?
There is absolutely no doubt it's going to identify the proteins and understand what it is they do. We will get past the notion that one protein serves one function. We are already beginning to see that it takes a hundred or maybe a thousand proteins to serve a given function of the body. There are complex regulatory networks of proteins that we are already beginning to get glimpses of, and that will be the major focus of the fourth edition.

Will the challenge be to simplify that?
If it can be. My fear is that it can't be simplified because there are a very large number of proteins relative to the number of genes. There are only about 30,000 genes, but there is a lot more proteins than that because one gene can give rise to a bunch of different proteins. So there is going to be a very large number of them, and one is going to have to begin to identify all the proteins that are involved in a physiological process. An example of this is a chapter on ovulation in the book, where JoAnne Richards, who is one of the section editors, has looked and found the very large number of RNAs, which give rise to proteins that are involved in ovulation. There are some real surprises in there. You think what in the world is that protein doing in that process? This prompts the question of how do all these proteins work in this process of ovulation. When you really stop and look at ovulation we don't think it's that complicated. Well, I think we are just being foolish. The human is a very complex organism. Remember what we are trying to explain. We are trying to explain an organism who has consciousness. That is, it realizes that it exists. It says, "I think, therefore, I am." We are trying to figure out how all these proteins can make that happen. If you stop for a moment to think about that, it gives you some sense of the overwhelming complexity that we have to deal with. Moreover, the main tool we have to understand the brain, is the brain.

Do you plan on keeping up with the research in your retirement?
I plan to read *Scientific American* because they will simplify the research and keep me up-to-date. To stay up with the literature is a full-time job. I'm 66 years of age, and I don't have the energy it takes to do that any longer.

You went back to West Texas to retire. Did you always know you were going to return to Texas?
No, I thought I never would.

Why did you come back?
Well, let me tell you why I left. I had a good brain. The frontier in Texas is about as non-intellectual as you can get, and I just had to get out of here and go participate in that great big beautiful world which I got a glimpse of when I was in college at Texas Tech. I never had any idea such a world existed when I was chasing cows and doing all the things you have to do when you work on a ranch. My great fear was that I would not be able to escape the clutches of West Texas. I went away and now I philosophically understand what being alive and what being human and what the universe is about. It doesn't have anything to do with religion. I was a doubter when I was a kid. Doubters become scientists, it doesn't happen the other way around like people think. Doubters are still at the bottom of the hierarchy out here. But I moved back, and I'm still an outsider because I'm a skeptic. But my family is here, and my brothers and I have always been best friends. My wife and I came back because we felt something was missing in our lives, and we found it. It was West Texas, as god-awful as it is.

Are your brothers ranchers?
No, one was a teacher and then became a Superintendent of Schools. My youngest brother, who was the smartest kid in the family and a mathematical genius, became an electrician and now runs a company that sells electrical equipment and supplies. He could never bring himself to leave West Texas.

Do you currently live on a ranch?
Yes. The closest neighbor is 3 miles away.

Is your wife from Texas?
Yes, she's from Merkel.

Did you go to Merkel High School with her?
Yes. We've been married for forty five years and only have two children. One of the characteristics I think I see in reproductive physiologists is that they reproduce themselves really quite poorly. [laughter]

I've heard that you have a side business, windmills that generate electricity for farmers?
The ranch I bought, which is about a mile and a half from where I grew up, has a wind farm on it. Florida Power & Light developed the wind farm and put GE wind turbines on it. I learned a lot in the process, and I was looking for something else to do when I retired. I sat around for about the first six months after I retired and it was clear that wasn't going to work. I need to be busy doing something and making my brain work. I started developing wind farms myself, visiting ranchers who had good properties for wind farms, signing them up, and offering it to wind farm developers for a small part in ownership.

And you've been successful?
Yes, twice now. The funny thing is how easy it is compared to the science I did. That was really hard work. The reading involved just to stay up, and the pace keeps increasing. This is so easy, and besides that, in two years I will have accumulated an income equal to my current retirement income which took me forty something years to accumulate.

What makes you successful at this?
I know the culture of these ranchers. I know what they think is important. My dad was that and I grew up being that. One of the problems that other wind farmers have run into out here is they don't understand that they are dealing with a very peculiar group of people. They have a very unusual point of view, and I'm privy to that because I grew up in it. I interact with these guys really well because I know what to say. I'm honest and I live up to what I say. I just use run-of-the-mill academic ethics, which are so honest compared to business ethics. The ranchers don't like the business ethics. I came by academic ethics naturally. That was how I was raised and that's what I believe in. You do things right, and that is the ethic out here.

What's next for you?
I'll do the windmill farms until I'm about 70, and then we'll start traveling. We've been lots of places in the United States when our kids were growing up, and we'll go back and visit all of those. Then we will visit the classic places in the world. I've been all over the world, but I've never been to Greece. I also want to go to Big Game Africa, and see the wild animals. I want to go to the Galapagos Islands to pay my dues to the origin of evolution which is one of the only principles of biology that is somewhat similar to the principles of physics and chemistry. I also want to go to China, because I haven't been there. I guess I'll keep reading philosophy, because the philosophy of Christianity they tried to teach me when I was 10 or 12 years old just didn't stick. We are also restoring this big beautiful ranch house we bought with the ranch. It's been a lot of work. And finally, we have worked ourselves into the local art community. We collect art from the local artists, and we don't buy original art unless we know the artist. The local art scene is really quite active. I've become a member of the board of trustees for the Center of Contemporary Art. We're having lots of fun.

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