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BERT W. O'MALLEY, MD

Interview conducted by
Michael Chappelle
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INTRODUCTION

Bert W. O'Malley, MD, the Tom C. Thompson Professor and Chairman of the Department of Molecular and Cellular Biology at Baylor College of Medicine, directs Baylor's Center for Reproductive Biology and is associate director for basic science at the school's Dan L. Duncan Cancer Center. Dr. O'Malley is revered worldwide for having defined the molecular endocrine pathway and the mechanism of steroid hormone action. Following this landmark research, he went on to discover the "missing link" intermediary factors that implement the transcriptional instructions in the receptors—the coregulators. Dr. O'Malley was also instrumental in establishing the journal *Molecular Endocrinology*, as well as being an initiator of what is now called team science. Throughout his career, he has remained a spokesman of the field and has contributed his own analyses of its historical development. His many and sustained scientific contributions afford him a valid claim to the title of father of the field of molecular endocrinology.

BIOGRAPHICAL SKETCH

Dr. O'Malley was born in Pittsburgh, Pennsylvania, in 1936, graduated from the University of Pittsburgh in 1959, and received his MD degree from the University of Pittsburgh Medical School in 1963. Upon completing his internship and residency at Duke University under the guidance of E. A. Stead, he entered the National Institutes of Health (NIH) in 1965 as a clinical associate in the Endocrine Branch of the National Cancer Institute, then under the direction of Mort Lipsett. In Stan Korenman's lab at NIH, he began his lifelong search for the molecular pathway of steroid hormone action. Working with Dr. Korenman, he employed the chicken oviduct model for the earliest studies on induction of specific protein synthesis. When Korenman departed NIH for UCLA in 1967, Dr. O'Malley was appointed head of the molecular biology section of the Endocrine Branch. Two years later in 1969, he was recruited by Grant Liddle to Vanderbilt, where he occupied the Lucius Birch Chair and became Director of the Reproductive Biology Center. In the early 1970s, Dr. O'Malley elucidated the mechanism by which hormones regulate the functions of genes and thereby regulate the synthesis of new mRNAs and proteins in cells, thus defining the primary molecular endocrine pathway. During that time, he also initiated the Reproductive Centers Program of the National Institute of Child Health and Human Development as the first principle investigator of such a center. In 1973, Dr. O'Malley relocated his lab to Baylor College of Medicine. At Baylor his group went on to biochemically demonstrate ligand-induced conformational activation of progesterone and estrogen receptors, discover the concept of ligand-independent activation of steroid receptors, discover key steroid receptor coactivator intermediary coactivators for receptor function, and define the role of coregulators in selective receptor modulator drug action and in cell homeostasis and disease. This body of work advanced the molecular understanding of the critical role of steroid hormones in normal and abnormal physiology and also generated a base of scientific knowledge that continues to further modern hormonal therapy and disease management. Dr. O'Malley has 600-plus published scientific journal articles, and has received numerous awards and recognitions including election to the National Academy of Sciences, the Institute of Medicine, and the American Academy of Arts and Sciences. He was awarded the National Medal of Science by President George W. Bush on September 29, 2008.

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I. FAMILY BACKGROUND AND EARLY YEARS

Chappelle: Dr. O'Malley, would you tell me a little bit about your family background in Ireland?

O'Malley: Sure. All grandparents came from Ireland. They matriculated to the United States in the late nineteenth century, following the potato famine and the lack of real jobs there. The land was mostly owned by English landowners; they had barely room to raise any food. They really needed work. At that time there was a tremendous exodus to the United States. They came over on both sides. The biggest group was in the O'Malleys, in which many, many came over--on my father's side. They did the traditional things: worked in the steel mills, policemen, maybe a politician or two, whatever they could get jobs at.

Chappelle: Where did they settle?

O'Malley: Our immediate family settled in Pittsburgh, and we had some relatives in Chicago, New York, and places like that. But most of them settled in Pittsburgh. At that time Pittsburgh had a lot of industry--steel mills, coal mills--and there were a lot of jobs there. So that was a good place for them to come.

Chappelle: What about further back in your Irish heritage?

O'Malley: Well, my clan--that the O'Malleys came from--was unusual in Ireland because our clan leader was the only woman that ever was a clan leader in Ireland, Grace O'Malley, or Granuaile. She is a historical, almost mythical figure in Ireland. She was a pirate that preyed on English shipping along the Irish coast. Ships would chase her, she'd go into the inlets where there were a lot of hidden rocks and things, and the English ships would run aground, and they would come back and plunder them. She was so successful that the only way to stop her was [when] Queen Elizabeth asked her to come to England and offered her to be knighted or to receive a ladyhood if she would no longer plunder English shipping, but she was free to work on the French or the Spanish. [laughs] So she did that and grew a clan up in the northwestern part of Ireland.

Chappelle: Does your family talk about its history all the way back to Grace O'Malley?

O'Malley: They do. You know the Irish are great storytellers, and so they have lots of myths and stories all the way back. Of course, most of the time when I was young, I remember them talking about the suppression by the English, and the Black and Tans [a catch-all term for police and army groups that suppressed revolution in Ireland], and how they used to beat them, and jail them, and take land off of them. It was a pretty bitter experience, but they were enjoying the new country, America, very much.

Growing up in Pittsburgh

Chappelle: What did your mother and father do for a living when you were growing up?

O'Malley: Both my parents were from multi-child families. My mother went to high school, but didn't complete it. This was a period of time where very few people went to college. It was an industrial time, and really what you wanted to do was just have enough education to get a job: steel mills, railroads, or things like that. My dad, who was a really smart man and could do complicated math in his mind and so forth, really never got a chance to go to high school. With six kids in the family--actually seven, one died in youth--his mother died of cancer, and his father asked him to quit school and take care of the kids--he was the oldest--which he did and worked. They sent some of the other kids to college, but not him. So he worked in sales for his whole life and was a car salesman--sometimes having his own places, sometimes work with dealerships like Oldsmobile or someplace. That was his life, and he worked till he was eighty-seven.

Chappelle: What was it like growing up in Pittsburgh?

O'Malley: Pittsburgh was a--great! I mean I had a great life. I had no brothers and sisters because my mother had rheumatic heart disease. After her pregnancy with me, she went into mild heart failure and gradually died of that in her early fifties. So she couldn't have any more kids. But where I grew up, there were just tons of kids all over the street. As I became really aware of life--I was born in 1936, that was the wartime. I remember the food stamps, the gas stamps, and the ladies painting their legs with colors because they couldn't get nylon stockings. I remember the victories over Germany and Japan [ending World War II], the celebrations and the kids throwing toilet paper over the telephone wires, staying up late at night and running around the street yelling. But I wasn't old enough to really get into the war. I became a very avid reader of that period later in my life.

Chappelle: History?

O'Malley: Yes, history. I loved history, especially the history of the United States or other countries, rulers, presidents.

Chappelle: What kind of student were you?

O'Malley: Well, I went Catholic school all the way--parents Catholic, Catholic neighborhoods--rather poor neighborhood--we didn't have any excess money--went to Catholic grade school, learned to pay attention and behave myself in school. But I never took school very seriously. It came easy to me. I did very well in school, but I didn't have to study much. I was mainly interested in games and sports and playing--played every sort of sport there was. I was a

member of one of the Catholic parishes; they nominated people to go to Central Catholic High School, and that's where I went. Now, that experience really changed my life a lot because it made me get serious about education and really start to appreciate it and to think about what I was really going to do.

Deciding on medicine

I sort of had an idea I was going to be a doctor. My mother, I think, encouraged that thought. My grandmother used to think I was going to be a scientist or a pharmacist because when I went over to her house--to stay over night or anything--she'd let me go in the kitchen, and I would take everything in her cooking cabinet and put it in a pot and stir it and boil it and cook it and offer it to people to drink, which, of course, they weren't that dumb. I continued the thought, though, that I was going to be a doctor as I went into high school. I thought, I better be sure I get into medical school if I'm going to do that. The Christian Brothers ran the school; they're great teachers, very strong disciplinarians. I played lots of sports at that time in high school; I played varsity football, track, and cross-country, and, of course, many other minor sports, too. But I never thought I was going to do much in sports; I was good at everything, but I was great at nothing. It was just enjoyment that I was in it for.

II. UNIVERSITY OF PITTSBURGH (1955-1959)

Chappelle: Why did you choose to attend the University of Pittsburgh?

O'Malley: As I went on in high school, I encouraged myself to medicine. I think I realized I could be pretty good academically, and I definitely was going to go to college. My mother was dead set on me going to college; my father encouraged it, too, but mainly he didn't care exactly what I did as long as I was happy--he would always say. But my mother wanted me to go to medical school. I thought that was a good choice. I liked my family doctor but knew nothing about medicine in any detail. And I certainly knew nothing about science; I never thought about research at that time. I had some good teachers in high school--I was interested in math and English--and they encouraged me to go on. I got scholarships to a number of schools, but I went to the University of Pittsburgh because of, I guess, simple reasons: it was a very good school, it was local and relatively inexpensive, and I had a nice scholarship there. My parents really didn't have the money to be sending me off, and I didn't feel like I should be spending their money--if they scraped it together--to go off to some fancy school. I thought I could do what I needed to do at Pitt, and they had a good medical school, so I even thought I might end up there at medical school.

Chappelle: What was campus life like there?

O'Malley: Well, that was the fifties. Campus life: fun. It was a relatively conservative time. It was postwar, and the economy was expanding--a lot of growth--and we

weren't yet in the Vietnam era. I think, mainly, I was faced with a lot of people who were serious about doing something with their lives--good jobs, not just a job, not just in the steel mills like many people in Pittsburgh, but perhaps going to professional schools. My interests were--I had a ball in college. I fooled around a little too much. I could do the work well, and I decided I'm going to be absolutely certain I get into medical school and to a good school--where I want to go--but after that I wasn't driven to have a straight-A average or graduate summa cum laude or anything like that. So I engaged myself in every kind of campus activity I guess there was, but primarily in fraternity life and school politics. And I, of course, played every intramural sport from track, badminton, wrestling, boxing--I did amateur boxing when I was young, too--that was probably my best sport, but I didn't like to hurt people; I had no killer instinct, so it was clear I wasn't going to make it in that sport. I had lots of fun, lots of enjoyment of campus life, made many good friends, and I learned some things, too. But my eye was on this being maybe the last time I could really have a lot of fun; because I thought when I went to medical school I was going to really buckle down because I was now going to be doing what I was intent on doing for the rest of my life.

III. UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE (1959-1963)

Chappelle: Why did you choose the University of Pittsburgh Medical School?

O'Malley: It was almost the same reason. I got a scholarship; it was local, inexpensive, and it was a good school. At that time, it was growing. It was not so well known as it is now, nationally; now it's a top-ten US medical school. But it was a growing medical school with a good reputation, and I could go there relatively inexpensively. I thought that was the criteria I needed. I did not need to go to--I looked at places like Harvard or other schools, but I didn't think that was going to make a difference in my career. I thought it was really going to have a lot to do with me rather than the school I went to.

Marriage

Chappelle: Did you get married at this time?

O'Malley: Yes. I had the great fortune to meet my wife in college. Now, the last thing I had in mind was to get married. My plan was--after medical school, only--then I'd think about marriage and kids and things. I, of course, wanted a family, but I thought that would be a distraction at the time. And--I never promised my mother, but my mother was very much against me getting married, too, until I finished medical school because she was deathly afraid I would do like all the kids she saw growing up: start having babies, then have to quit what you're doing in education and go into the steel mills or someplace to make good money to support the family. So I dated various girls. And I noticed a particularly attractive and talented young girl in our class, Sally Johnson. Of

course, she was admired by many: she was the homecoming queen at our school; she was in politics and things, too. As it happened, in the politics--I don't know how many people did a triple like this, but I became president of my fraternity, president of [the] interfraternity council, and president of the student body, all at the same time. The student body and the fraternities were antagonistic, so the fact I was president of the two antagonistic groups on the campus was interesting. Sally was president of the women's organization at Pitt. I had seen her to say hello to, but we went to a leadership retreat after my junior year, before the senior year, and for the first time I had a chance to talk to her one evening there, and on the way home we kissed. I don't know if it was love at first sight, but it was love at first kiss because--she was going steady with someone else; I was going with someone else--but after that there was no doubt that we were going to end up together. And a few months later, we got together and became steady partners in senior year and then decided to get married after the first year of medical school, which our two mothers were still very much against, but eventually they realized we were going to do it anyway--so we got married.

Chappelle: What was your wife's career?

O'Malley: She had many talents, but she was in education; she was a teacher and she taught for some years when we first got married and she got out of college. And she was a great musician. She could have done anything she wanted to, but we had--starting the year after we were married--four kids in five years. So, eventually, she quit and took care of the family. We got married after the first year of medical school. At that time I needed to work *and* go to medical school. I was doing fine in medical school, but it was sort of tough working all the extra time, plus having a family, and trying to jam that all in. But it was a great time.

First exposure to laboratory research

Chappelle: What work were you doing?

O'Malley: That was my first introduction to science. After my freshman year in medical school--I got the best grade in biochemistry--so I got offered a plum biochemistry lab job, not plum in terms of any great salary, but they only hired one or two students to work. And I worked that summer. And then I worked continually for the rest of the time, part-time, while I went to school there. I worked for a professor in biochemistry who worked on how steroid hormones are made by the adrenal gland. It was a job; I did not do this with an idea that I was going into science. When I went to medical school, I thought I might be a psychiatrist. And after I got to medical school, I found out what they do, and I decided that was not for me, and I thought I'd be a GP or an internist--no academics.

Chappelle: What was the mode of psychiatry at that time?

O'Malley: At that time psychiatry was very much dominated [by Freudianism], especially at our school, which had a big Freudian institute there. And I think I just couldn't buy the fact that mental illness had a lot to do with toilet training and Oedipus complex. I thought, This has got to be something going on in the wiring or the chemicals in the brain. Of course, that is now realized to be the cause, but I didn't know exactly what was going on, but I just couldn't buy Freudian philosophy. So I decided I'd go and take care of people as a GP or an internist. I went on with my job because I needed the money and spent what free time I had studying and with the kids and my wife.

Mentors

Chappelle: Who was your mentor?

O'Malley: Well, at Pitt--you know, before I went to medical school, I had never met a scientist, met to talk to. I had nothing to do with science. But there were three people in medical school that had an influence on me. One was Klaus Hoffman, a major scientist, a member of the National Academy, who synthesized one of the first hormones, ACTH; [another was] a professor of medicine Jack Myers, who was one of the greatest clinicians of his time--I mean widely known as that. Both of them were very strong disciplinarians, very much perfectionists. I sort of was drawn to perfectionists; I didn't mind them jumping all over me for small imperfections. I took it as a challenge; I liked that. So these two became life-long friends for me.

Deciding on endocrinology and academic medicine

Then in my senior year, we had an elective. And I was thinking of endocrinology, especially; that seemed intellectual to me--a lot of measurements, a lot of tests, deduction of what's wrong, and sometimes you could treat the patients and cure them. It was, I thought, a very interesting subdiscipline in medicine and one that would expand a lot--it looked like it might go into a lot of different areas, too--have an impact on a lot of different areas in medicine. So I took an elective with Jim Field, he was head of endocrinology. He had been at NIH; he was a well-known scientist. Everything changed during that elective; working in the lab was no longer a job. He now allowed me to think about the experiments, in fact, design my own experiments, and make a deduction on the data, the outcome--I wrote a paper during that time--and I really got hooked on research. At that time I decided I was going into academic medicine. I was going to be a part-time physician, teacher, and I was going to do some research.

Chappelle: What research did you do with Dr. Field?

O'Malley: I worked on TSH action--the thyroid-stimulating hormone--how this stimulated the thyroid gland to make its hormones that it secretes: T3 [triiodothyronine] and T4 [thyroxine] hormones. It was an area I never worked in again, but he basically was very important in teaching me the principles of science: hypothesis, the rigidity of experiments, controls, data, ethics.

IV. DUKE UNIVERSITY: INTERNSHIP AND RESIDENCY (1963-1965)

Chappelle: Why did you choose to do your internship at Duke?

O'Malley: Jack Myers had a lot to do with this. I did well in medicine and got the medicine award. So he took me a little bit under his wing after he found out I could withstand his pressures. He asked me what I was going to do. I said I was thinking of going off somewhere maybe in the Northeast for an internship. He said, "Well, you could do that. You'd probably be able to get in good schools up there from where you're going to graduate"--which I ended up graduating at Pitt first in my class--"and that's all fine and good. But if you really want to learn medicine, you'll go to North Carolina to Duke Hospital. They have a friend of mine there, Gene Stead, who's one of the great teachers, and he's building a powerhouse hospital down there in the middle of nowhere, and in every one year you spend there, you'll learn two years of medicine." And I said, "Well, maybe I'll do that." And he said, "You better go down there for an elective and see what it's like, though, because you want to be sure you know what you're getting into; they're going to work your butt off." It was the best training in the United States at that time, and it was the most brutal internship-residency in the United States. You worked long hours every day; you had one half a weekend night off, which got off around 8:30 or 9:00; and you had one half of weekend days, starting at noon, off. And you worked the rest of the time, and you were on call all night, and you did all the laboratory tests yourself, and you worked up many patients during the day. And you checked your ego at the door down there. [Dr. Stead] said, "If any of you kids ever thought you're going to a northeastern school, you better forget about that right now because down here you're just a doctor, and the important people are the patients and the nurses. I can always get a good intern and resident; they're coming out of the woodwork; I can't find good nurses. So you better not have an ego, or you're not going to get along down here."

Chappelle: Who was that?

O'Malley: That was Gene Stead. He was one of the great trainers and, of course, trained many academic people down there, and that hospital grew into a top five US medical school. Lots of people in my classes went on to academics and to careers in research and science.

Chappelle: Dr. Stead. I guess there are a lot of questions to ask about him.

O'Malley: Sure.

Chappelle: What was he like as a scientist?

O'Malley: He appreciated science, but he was not a bench scientist. He was a clinician and a teacher extraordinaire. He commanded different from Jack Myers, who would just chew the daylights out of you if you did anything wrong, or you'd missed a diagnosis, or you didn't do the test right, or you were derelict in any of your clinical duties. Gene Stead was very tall, about six-four; he had these steel-grey eyes that could pierce through you, and he'd just look at you. If you had morning report and you didn't do well with the patient, he'd just look at you and say, "Son, this patient needs a doctor," [laughs] meaning, "and it's not you." So he was intimidating in a different way down there, but I think he stimulated people to go into academics, to compete with the best in the field, so that you always wanted to be around the best and competing with the best. And in medicine, patients are first, not the doctor. That's a good lesson I've never forgotten. He went on to train numerous people and retired as one of the famous trainers. He took a little hospital in the country down there in Durham, North Carolina--small town in the middle of nowhere--and built that medical center into what's now ranked about three, four in the United States. That's impressive.

Chappelle: Did he have any social contact with his students?

O'Malley: Down at Duke? Well, of course, we were having kids. By the time I got to Duke, we had two children--Sally and I--and then she had another one at Duke, and then another one later when I went to NIH; and every minute I had off, I was with the family. But I was also working during the internship because I needed the money and I was interested in getting more research training and accelerating things. I would run down between patients and work in the lab--I worked for a hematologist there and published a couple of papers down there during my internship-residency. When I came home--I'd come home about five-fifteen for about an hour and a half--I would rough house with the kids and do anything they want--play with them constantly. My wife would have the dinner on the table; I'd give her a kiss, give the kids a kiss, and go back to the hospital again. It was a *very* busy time, but she knew what stress I was under. I certainly wasn't doing anything but working or giving some time to the family. The memories of that time are great: a lot of funny experiences. I remember one time my wife had the kids in Pittsburgh for a visit while I was down there, and I was talking to her on the phone. When I got off the phone, I went into the kitchen, and I was cooking some sausage, and it was on fire. I did exactly what you're not supposed to do--I didn't throw water on it--that was one thing I didn't do. But I picked it up to throw it outside, and, of course, the flames went back on my hand and burned it bad. So I went in--this was during my residency--and they taped this all

into a huge big bundle of gauze and tape. So I was working with one hand. And then I went to a resident party and I was doing the limbo and I was off balance and I fell back on the good hand and I broke this hand--the thumb--and that went into a splint. So, Sally was out of town; I had no hands. I was doing residency, and we wore these starched uniforms. We got our uniforms done, and they were starched stiff as anything--that's about all we got; the pay down there was $37.50 a month if you were married, $25.00 a month if you were not--when I went there. But you did get your laundry. But I couldn't get the buttons done, and I had to go into work. And I went next door and the guy had left already. And so I had to get his wife to button up my pants and the front of my coat to go to work. Later that day when I was teaching one of the interns how to do a spinal tap, he couldn't get in there--the patient was screaming and yelling. And as the patient was looking the other way, I said to the intern, [whispers] "Get out of the way." So I sat down and I actually did a spinal tap that time with no hands. That was my greatest achievement in medicine. [laughs]

Chappelle: Did Dr. Stead interact with students outside the hospital?

O'Malley: He did a little, but not much. He or Myers were not drinking buddies with the staff. They had a yearly wine and cheese party, which I think they used to kid that he used the same block of cheese year after year, and have some beer. But he was there for advice if you needed it. He was an onsite type of person. These were not the people that I had personal relationships [with] outside of the hospital or the training facility.

Commitment to endocrinology

Chappelle: Did you have any particular research goals in mind at this time?

O'Malley: Well, endocrinology: I was set on going to endocrinology. That was an advantage of going to Duke, because they had a famous endocrinologist there, Frank Engel, and I was going to do internship-residency and then do a fellowship in endocrinology with him. And during the middle of my internship year--the middle of it--he died. He had a heart attack in the clinic and died. At that point, I thought--I had been thinking about NIH, too--and I thought, I've got to go the NIH. And I called Jim Field, who had been there, and I said, "Can you write a letter for me?" And he said, "Oh, yes; you have a good chance of getting in there." And I decided I'd go from Duke to the NIH, and that was my next big challenge: to get in--number one--and to succeed there.

V. NATIONAL INSTITUTES OF HEALTH/NATIONAL CANCER INSTITUTE (1965-1969)

Chappelle: Why was it such a challenge to get in, and why did you want to get in?

O'Malley: If you wanted to do anything in academics, that was *the* place to go of all the places. See, the US scientific effort really just blossomed in the fifties. It came out of NIH, and NIH itself was strong. The universities did not have as strong a research effort; they were just starting to get money from the federal government like they do now. Eventually, they [the universities] became the strongest, and now are the strongest, not NIH. But at that time it was NIH. The NIH was fed by the developing Vietnam War because you had to go to service, and if you went to the NIH you could get in the Public Health Service, which was a branch of the Navy, get a commission in the Navy, and that was your service time. And as young people, we weren't afraid of being shot at--you think you're immortal anywhere at that time. But what we did get--we would get two or three years of advanced training, instead of just spending time in an Army hospital taking care of patients. So this would accelerate our academic careers. So every person that was any good from all over the country wanted to get in there; it was highly competitive. You went up there for a couple of days of interviews at different places. And I got in.

A clinical associate at the National Cancer Institute

I didn't get my first choice; I wanted to go to a pure endocrine group in NIDDK [National Institute of Diabetes and Digestive and Kidney Diseases], but I actually ended up in the National Cancer Institute in a branch--Mort Lipsett had a new branch: it was Endocrinology and Cancer. I really didn't want to be associated with cancer--I wanted pure endocrinology--but I learned a lot about cancer at that time and that ended up being a major interest of my future research. So that was fortuitous, also.

Chappelle: How were you able to balance family life with the NIH work?

O'Malley: I had a little more time than [during] the internship. After Duke, working twelve hours a day was nothing. I mean you thought you were on vacation almost, especially if you could have a whole weekend day off or two, here and there, and a vacation. We had four kids, then. I had a very busy time: I was learning clinical endocrinology. My job as a clinical associate was to set up a research program and work in somebody's lab. The head of the branch was Mort Lipsett, who became a good friend--brilliant person--again, not a lab/bench type of person, but great judgment, very intuitive in science.

The search for the molecular endocrine pathway

I decided I was going to work on how steroids act. I had that in my mind for years throughout medical school. And I had this funny little idea: I would go in for--first, I would think I would work for six months and crystallize steroids and learn about the chemistry of them. So I did that, but I didn't really like that; I was working with monkey urine. Oh, it was terrible. Then I joined a young faculty member, Stan Korenman. This was again a fortuitous type of interaction--a good break. He had just come back to the branch, and he was setting up a branch, and he was going to work on how the chicken oviduct worked. He was interested in hormone action--and I was--so we started working together. He was great; he was very smart. We became good friends--still are--I just saw him the other day here at the meeting; he's doing fine.

Chappelle: Why the chicken oviduct?

O'Malley: Well, why the chicken oviduct? First of all, that was an unusual model. At that time people were interested in cell culture and maybe rats or something like that, but nobody was working on chicken. But Roy Hertz had been an old faculty member in the branch I was in, and he had done some work on the chicken oviduct. He had some indications that it made some mucous material that might be egg white and that it became antibacterial when you gave it hormones, which was from avidin. The setting was such that we might be able to show that hormones would cause the synthesis of a specific protein. Now, people knew that there was some general protein synthesis going on in cells at that time--this was very early era of molecular biology--but people did not have specific proteins that they could look at. And the idea was if we got a specific protein induced by a hormone, we could work backwards and see what was made to get from the hormone at the beginning and down stream at the end to the protein. And we could box it in; we could look at the pathway. And so we made antibodies, Stan and I, and I injected chicken at two or three in the morning--at night--injected chickens. It was, again, a busy time--a lot of laughs in retrospect about it. Things went quite well, and we did show you could induce some specific proteins. He worked more with ovalbumin, me with avidin. And then, suddenly, one of the senior people in the branch left, Bill Odell, who went out to set up a new hospital endocrine system at UCLA, and he offered Stan Korenman a job, and Stan left. And so, towards the end of my first year, he was going; we were just getting started and everything, and I didn't know what was going to happen then.

Chappelle: How long had you planned on staying?

O'Malley: Initially, I thought a few years, and then I planned to go to a university. I wanted to be around students, teaching, and patients, and various things like that.

Head, Molecular Biology Section, Endocrine Branch, National Cancer Institute

Chappelle: So you weren't ready to leave yet?

O'Malley: No, I wasn't ready to leave yet. And we had gotten some interesting things, now, and this started to catch the eye of a few people, including the branch chief, Mort Lipsett. So when Stan left, he said, "Bert, would you be interested in staying on a little bit? Things are going well, do you want to just take over that lab?" Now, I was just a first year associate--that was sort of unprecedented. But by virtue of that fact that Stan was leaving--there was no one else and we just had things all set up and started, and I said, "Sure I do." So he gave me a little 220 square foot lab, which also contained the branch dishwasher and the dishwashing lady and my desk. And we jammed a technician and a few postdocs and so forth in there--walking on top of each other, almost in shifts.

Demonstrating that new RNAs are made via hormone action

The first job, then, was [completed]--we showed the protein was made by the hormone--and the next thing was, could we show something occurred in the nucleus that involved RNA. Because I had the idea that it was hormone--messenger RNA--protein. But there was no way to attack messenger RNA directly. So the first thing was to show that new kinds of RNA were made.

Chappelle: Where did that idea come from?

O'Malley: Well, I don't know. You could say it was from bacteria. Jacob and Monod [François Jacob and Jacques Monod] got a Nobel Prize showing it was messenger RNA in bacteria and everything. But at that time that was far from the dominant theory. The major people thought all sorts of things: that hormones acted on the membrane--membrane transport that they worked on; if there was messenger RNA, translation of messenger RNA; or somehow degradation of molecules--protein or messenger RNAs in cell. And it just was not at all certain that they would go in there somehow to the DNA and turn on a gene. But for some reason I became wed to that hypothesis, and I was going to follow it out to see if I was right or not. So I did.

Chappelle: What research did you do? How did you go about following it out?

O'Malley: I wanted to demonstrate that a hormone changed--first, qualitatively--the types of RNA made in the nucleus. Because RNAs come from DNA, so if you made different kinds of RNAs, then it must mean that the hormone was turning on the transcription in different DNA sequences to make these different RNAs. Now, it didn't prove messenger RNA; it just showed that the hormone is acting in the nucleus. And I had to do that first [in order] to limit my thinking to the

nucleus. And we set up new types of hybridization and so forth--I had to go learn off a microbiologist at NIH. We did hybridization and nearest neighbor analysis, which I think nobody in the endocrine field knew what the heck we were doing. That started to catch people's eyes. I did show that new RNAs were made, and that convinced me that the next thing would be to find the messenger RNA.

Pioneering team science and center grants

Chappelle: [Before following along on the messenger RNA thread] I'd like to ask you a little bit about your role [while you were at the NIH] in designing center grants and team science?

O'Malley: Yes. At NIH, I got on a committee appointed by the National Institute of Child Health and Human Development. They were thinking of creating some kind of centers or team science, and I became a strong advisor to the head of the NIH at this time. And the principle was pretty simple--which I believed in, and that's why I was enthusiastic about it: A center is not where you have a big lab with everybody working together in the same lab. A center, or the best team science, is [when] you assemble five or six different people who have their own special areas of interest--their own programs--and then you cross over between the programs: your discussion, your principles, and even collaborations and data, and so forth. And this became the center concept. After I left NIH, I actually applied for the first NIH center and got it because I knew what to say for it--I had helped write the program rules [laughs]--and I've had one ever since. They are now very popular, and we introduced them to Baylor later on in my life when I moved there, too.

Chappelle: Okay. So this work on team science was [happening] at the same time you were there [at the NIH] doing your research?

O'Malley: I didn't start working on the team science; that happened after I left. But the principles were devised at that time. I felt that would be the fastest way to accelerate the pace of discovery.

VI. VANDERBILT UNIVERSITY SCHOOL OF MEDICINE (1969-1973)

Then I started to think, a little bit, about leaving the NIH, but I was pretty happy there; I was in no hurry to leave. And I looked a little at Pittsburgh--where I came from; they offered me a job--and Duke. But you know, I just thought maybe this wasn't [the right] time. [Then] one endocrine meeting I attended--I gave a paper there--and I was in the men's room and I met a famous endocrinologist from Vanderbilt, Grant Liddle, and he said, "You're Bert O'Malley." I said, "Yes. I know you, Dr. Liddle. How are you doing?" And he said, "Can I talk to you a minute?" So I went out with him. First words he said to me--he said, "I want you to come to

Vanderbilt." I said, "Well, I'm pretty happy at the NIH; I'm not thinking of moving--I already looked at some places." And he said, "Well, they're not Vanderbilt. I want you to come to Vanderbilt." I asked him, "Why do you want me to come to Vanderbilt?" He said, "I think you're going to do something famous--I've been watching your papers and reading some of them--and I want you to do it at Vanderbilt because you'll make us more famous if you do it there." And he said, " At least come look at the job." So I did. I came down and I visited a couple of times. The second time I left he said, "When are you going to get back to me?" I told him, "I'll call you in four or five months." He said, "No no no. We've got to accelerate this." I said, "I'm just not quite ready to move, yet; I've got a lot of things going on." He said, "You can do them down here. What do you need?" I told him, "I need to be able to hire some people and put the center concept into play, and I need some stability." He said, "Okay, let me work on it." He called back soon, and he said--we were talking about an assistant professorship, maybe an associate professorship as a first job, which associate professorship would have been quite good. He called and he offered me a professorship and an endowed chair to come down, and money to start up a major program coming from the Ford Foundation, with appointments in medicine, OBGYN, and biochemistry, and some positions to hire some people in--to form this team science center, so I would be head of a center there. I couldn't turn that down. So I went and told Mort. He was disappointed, but he said, "This one you better take." So I left and went down there, and that was the next chapter, and it was quite a ride.

Chappelle: You were occupant of the Lucius Birch Chair there.

O'Malley: Yes.

Chappelle: And Director of Reproductive Biology?

O'Malley: That's right.

The Reproductive Biology Center

Chappelle: Would you sketch out the state of the Reproductive Biology Center when you arrived?

O'Malley: Yes. I had a general interest in reproduction. I wasn't a traditional reproductive biologist, but I was working with female hormones--estrogen and progesterone--so that was close enough--and reproductive tissues: the uterus, oviduct, and some breast--some tissues like that. So I fit the general model of the new branching area of molecular reproduction. I actually oriented the center to that, and that was a new break in reproduction. There was some question, initially, by people--the site visit team that came back to look had [inaudible], What's a chicken have to do with humans? We really would like to

find out what these hormones do in humans. I said, “Look it”--I convinced them that if you find out how a hormone works in any cell, just *really* how it works, those principles are going to be repeated in all species--“we just can’t do it in humans, but I can do it in a chicken.” So I got the grant--I got additional grants, and we found out we could raise quite a bit of money down there. We hired people. Tony Means, who came with me just as I left NIH came down with me and helped me build the center down there, and he was a lifelong--well, not a lifelong partner, but a partner there and through early Baylor. And some other bright, young people: Bill Schrader; Jeff Rosen; and a young chromatin biologist, Tom Spelsberg; a receptor person, Dave Toff, out of Gorski’s lab came down. They all had their own labs and so forth; we had a tremendous interaction. Things started growing, and papers started flowing, and I set out to find the messenger RNA.

Setting out to find the messenger RNA

Chappelle: Would you sum up, again, what you had accomplished at the NIH?

O’Malley: Basically, when I left the NIH, we had--at least to my satisfaction, not to necessarily everybody’s--proven that the hormone acts in the nucleus. So now I could forget about the rest of the cell and concentrate on the nucleus. And, of course, in the nucleus there’s DNA and synthetic reactions, which is RNA, and that really put me right where I thought I wanted to be. And the next thing I had to do--and someone had to do--was show a hormone could cause the accumulation of a specific messenger RNA off a specific gene.

Chappelle: How did you go about that?

O’Malley: Well, there weren’t really methods to do that at that time. We set up translation assays. Tony Means and I worked very closely on this, also Jeff Rosen and Bill Schrader. I worked more on the receptor side at that time. But we were mostly after the messenger RNA, then. The first assays were a little scary. We were using millions and millions of radioactive counts--putting it into a tissue--and we were getting what we thought was the message with fifty counts in it. This is sort of dangerous in terms of what you would call a background in the assay. We were sure we had it, but it was such small amount being made in our translation system--where we translate the message and made the protein--that we were just barely over the detectable background. And then we had a little breakthrough--where we learned how to purify that one step--and suddenly the counts jumped up to four or five hundred, and later into the thousands, and we were on our way. We showed both: the estrogen induced ovalbumin messenger RNA and the progesterone induced avidin messenger RNA. And we finished that first goal there at Vanderbilt.

Chappelle: Did you come up against any dogma?

O'Malley: Well, we came up against *all the other dogma that existed*. You know, science is suspicious of new observations and should be--they make you prove it over and over to the n^{th} detail--and there were some other interpretations. People said, Maybe it's really not the synthesis; maybe you're just changing the half-life of the message, and it's accumulating and increasing that way, and this is not working at the DNA level, like you say. I argued mathematically that this was impossible because you could calculate that there was virtually no messenger RNA in the cell before the hormone, and it accumulated to such a high level so fast that--and you could measure the half-life of the message--you could not mathematically do this. That was a mathematical proof, though, rather than an actual proof. Later, we had to go on to actually measure the exact number of molecules in the cell and to show that it was all new synthesis.

Chappelle: Is it possible at that time that you could have been mistaken?

O'Malley: Sure, it was possible to be mistaken all the time, and I certainly don't want to give the impression that everything I ever thought was right, it's not. My mind changed many times, and I have been wrong different times. But I was right on this, fortunately. I guess with youth, you don't fear being wrong; you fear not moving forward and doing what you really think is right and making the deduction you think is correct.

Chappelle: What if you had been wrong?

O'Malley: Well, I would have had a short career, and I'd have been taking patients now into my office instead of talking to you. [laughs]

Chappelle: What happened to the field after this?

O'Malley: Well, at the same time, Elwood Jensen's work was going on with receptors. And we were working some with receptors, too, but he was the major domo in that area. And we realized--I think I realized that these come together: that the hormone was probably going into the cell, binding the receptor, the receptor was actually the molecule binding to the DNA, and then that event was inducing the messenger RNA, and that that was the pathway. So I think our next effort over the seventies was to prove that was the pathway in this system.

VII. BAYLOR COLLEGE OF MEDICINE (1973-present)

Chappelle: Why did you move your lab group to Baylor in 1973?

O'Malley: When I went to Vanderbilt, I expected to be there a lot longer, but it ended up only being a little over four years. I think we were a product of our own success. The lab grew so much--so many trainees--the faculty programs of

others grew, and we just ran out of space. People kept saying, Bert, we can't work in this; we've got to have more space. Why don't we move, because there is no space at Vanderbilt? Vanderbilt was very nice about it; they did not want us to go, but they had no space. There was no place to put us except where we were, and we just were jammed packed in there.

Chappelle: Was that still Grant Liddle?

O'Malley: Grant Liddle, yes. And he was very disappointed I was leaving, of course. He tried to do some complicated things to keep us there. I didn't want more salary money; I didn't want more research money.

[Interruption]

Well, Grant Liddle was disappointed I was leaving, and so were other people; we had good friends at Vanderbilt. Finally, I decided we had to move somewhere. So I looked at three opportunities; we had some good ones at the time: Rockefeller, Harvard, or Baylor College of Medicine in Houston. Of course, Rockefeller and Harvard were very famous at the time, and Baylor was a little bit of--I don't know--a frontier town at the time, growing--a medical school and hospital that was famous for cardiac surgery, but not much science. So I looked at those three places, and I guess a lot of people were surprised I picked Baylor College of Medicine. I just had a--I wanted flexibility and an ability to do new things. At Rockefeller the attitude was, Here's the way we do it at Rockefeller. It was a good job, good money, good salary, but you sort of had to fit in--"this is the Rockefeller style." At Harvard, I was talking to people, and I found out this person was fighting with that person--and [people were saying things like] Don't collaborate with him; collaborate with that person over there. I just didn't have a good feel for the places. And Baylor offered me good money, and I could bring my people that wanted to come. And we brought seven of them. Key people were, again, Means, Rosen, and Schrader; they came down with us. Spelsberg went off to Mayo; he established a good career. Dave Toff went to the Mayo Clinic also, established a laboratory. Frank Chytil [was] the only person in the group who decided to stay at Vanderbilt. He said he was getting too old to move around, and he had a good career down there. So we're off to the "cow town" in Houston to make our fortune. It was in some respects more than I bargained for, but it was very successful.

Chappelle: What was the state of the department and the center when you arrived?

O'Malley: Well, no center. And there was a--I was going to form a new department. I wanted to form a department of cell biology, which was sort of a new discipline right at that present time--that was where you put all kinds of things in the cell, together. I thought I'd move the center there, too, which they wanted me to do.

I got there, and there were two-fulltime faculty and two part-time faculty, and one of the faculty had one grant. The two people that were there, actually, I kept. I got rid of one and then had to rehire them when I found out they were teacher extraordinaire that I needed. And the two part-time people, one was a priest and one was a nun. And, of course, that wasn't going to fit in with our--we needed high-level research people. I guess I had to fire them, but in a nice way--relieve them, get them to move on. I remember going home that night and said, "Sally, I just got rid of a priest and a nun. I might be going to hell." [laughs] This was not the way to start out--a good catholic boy. But then we started hiring people, and the new people started up their labs. It grew and grew. Today, the department is the number one basic-science funded department in the United States with over thirty million dollars of research, and two hundred and forty-some line item projects, and seventy-five students and thirty-three faculty. It's very successful.

Chappelle: Did you have goals for molecular and cellular biology beyond your department at that point?

O'Malley: Yes. I was convinced that molecular biology needed to be brought out of bacteria or yeast [and] into the animal world and into humans, and that the principles were the same. And so that was the guiding principle for our department. We really became a molecular and cellular biology department--which was the name of it now--but oriented also to physiology and disease. This was sort of a successful undertaking; it caught a wave of new growth, and we became very well funded through those roots. I took a hit in my research for a four or five-year period, I think. We continued--I mean we were successful in publishing papers, but I wasn't that happy because I had to spend an awful lot of time recruiting faculty and wining and dining them and establishing programs, and doing administrative things, which weren't my number one priority, but that I took responsibility for, and I had to do. But the Baylor people were quite supportive, and those things got done, and I got my mind back to my next goals in science.

Tidying up the pathway

Chappelle: What was your next goal at that point?

O'Malley: We had established the major steps in the pathway by the time I left Vanderbilt, so we had three jobs in the eighties: one was to substantiate them. When you come up with a hypothesis, and then data, and then a theory that you develop, you can't just publish it once and then say that's it. You've got to keep supporting that, and you've got to keep going into more detail on it to convince people. And then, eventually, they buy it. Nobody buys it off one publication or one announcement. So we stayed on that. And we got into the new cloning technologies, and we were one of the first labs cloning genes. We cloned the

target genes for the hormones, like ovalbumin and avidin. And we developed ways of measuring the number of molecules of the message in the cell and looking at the actual synthesis rate of the hormone--things we needed to tidy up the pathway.

VIII. COREGULATORS

But all this time I had my mind on a missing link to all this. And the missing link was the coregulators or coactivators.

Chappelle: How did you know there was a missing link?

O'Malley: Well, again, it was some lucky deduction or logic in my mind. I call it logic. As I started to think about this at the time of Vanderbilt and the message, I thought, Things are very complicated in the nucleus and turning on a gene has got to be a complicated process, and it's not going to be just the hormone and receptor that does this; there must be a lot of helper proteins. So we began looking for proteins [that] we called at that time acceptor proteins. They would accept the receptor onto the DNA, help it on the DNA, and help it do its function. We actually devised assays--Tom Spelsberg and I--and we actually showed there is a fraction of the proteins that do this in the nucleus, but we could never purify them. We put them on gels and purification schema, and there were peaks all over the place, and it looked like it was aggregating or breaking down. I was looking for one or two of these proteins I thought existed--that would accept a receptor and help it work in there. I had no idea the [degree of] complication. But anyway, we couldn't purify them, so I dropped it. But it was in the back of my mind all through the eighties while we were working with Bill Schrader on purifying receptors and showing that a hormone when it binds to a receptor changes its shape and becomes an inactive form. And we cloned receptors--Orla Conneely in the laboratory did this--cloned progesterone receptor. And, of course, other labs were cloning receptors; we weren't the first to do that. We found out some more things about how the receptor is activated and that you can activate it with mechanisms other than hormones--which was exciting--by ligand independent mechanisms.

Ligand independence

Chappelle: What happened with that aspect of it--the ligand independence?

O'Malley: That was a side issue. But, again, it got us mired in a lot of controversy. We had helped--with others--build a dogma up that receptors are hormone-activated molecules and they bind hormone, which they did, and the hormone activates them. And the fact that they could be activated *without* hormone by other pathways in the cell was *very* surprising. These were some studies done with Bill Schrader, Nancy Weigle, and so forth, in the laboratory. And when

we published that, some people chose to ignore it, and others just to doubt that it was true [and assumed] that we were doing something wrong. But we eventually did show that was correct. And in fact, that's now known as "cross-talk": where a pathway, say from a hormone that works at the membrane level, can send signals through kinases and phosphorylation cascades down to the receptor, activate it without the hormone [inaudible], and then the hormone goes and does its job on genes. So that was a fun thing.

The first steroid receptor coactivator

But what I really was after at that time were the coactivators.

Chappelle: How did you go about finding them?

O'Malley: Well, I had a bright, young postdoc, Donald McDonnell--part of the Irish connection; we had a lot of people come from Ireland for a period of time there, and they were very good workers in the lab. And we started working in yeast. He [Donald McDonnell] went away to get trained in yeast--the plan--and then came back to the lab. And we started work in yeast to develop the principles that such a thing as a hormone receptor coactivator or [a hormone receptor] corepressor existed. And we established this in yeast, and he published two key publications that solidified our thinking that this was true.

Chappelle: When was this?

O'Malley: We started in the late eighties, and this was in the early nineties. And then what we really needed to do was to find a--from a human cell, or mammalian cell--we needed to find a specific coactivator, clone it, and prove that it existed.

Chappelle: And when did you do that?

O'Malley: We started that in around '93--postdoc Sergio Oñate in the lab--and in collaboration with two of my really *long*-term collaborators since I came to Baylor, Ming and Sophia Tsai, wonderful people, wonderful collaborators. Donald had left--he went off to Duke--and Sergio used some yeast two-hybrid methods, and we were good at cloning. To make a long story short, we cloned the first of these hormone receptor coactivators, SRC-1, steroid receptor coactivator 1, and that was very exciting.

Biochemical and animal evidence

Chappelle: Would you explain a little more about what SRC-1 actually does?

O'Malley: Sure. The coactivators are the helper molecules for receptors. So the hormone comes into a cell, binds to the receptor, changes its confirmation to an active form; the receptor goes on to DNA and searches up and down the DNA to find the

genes that it's to turn on or off, and then it has one more job--it does not do this directly; it does it by recruiting other proteins called coactivators to turn on the gene, or corepressors to turn off the gene. We established the biochemical evidence that corepressors existed, and we cloned a coactivator all in one year. So we had a good year there at that time. And this molecule, then again, when you took it away from cells, the hormone didn't turn genes on; when you gave it back, it worked again. If you gave extra of it, it turned the gene on very high. And we had other criteria for proof of a coactivator, all of which were satisfied. We published that in *Science* of that year. Very quickly, though, we knew we had to do one other thing. We had to prove this wasn't some phenomenon of cell culture, but that it happened, also, in living animals. And a young postdoc, Jianming Xu, made deletions of SRC-1 and another member of the family, SRC-3 genes in mice, and showed that if you take those out of the mice--delete those genes--the hormones will no longer work. They become resistant to hormones. So we now had coupled in-the-cell evidence with the animal evidence. This met some resistance, but, basically, I think people were ready to believe this, and it achieved pretty good acceptance and a lot of notoriety at the time.

Reconceptualizing coregulators

Chappelle: Had this, then, completed your goal that you had since the NIH days?

O'Malley: In a sense, yes. In essence, we had assembled the pieces of the pathway: starting with a hormone and ending up with a function. And that was the missing link: the coactivator or corepressors, which we call--as a group--coregulators. But when this happened, some strange things started to occur. I had people working in the lab, and we quickly cloned another coactivator and then another one and then another one. And some other people started cloning them. And the numbers started growing, and I started to think, What are all these molecules doing? What is this about? There is something more than just a protein that comes and helps this receptor. There must be a lot of these, and they must be doing a lot of things we don't understand. So we devised a concept, then, that in fact the coactivators don't just help you turn the gene on, but they do everything in the nucleus that has to do with transcription: they come in and they remodel the chromatin, move the nucleosomes, they cause initiation of transcription, they move polymerase along the gene, they regulate the splicing of RNAs at the gene, and even--there's a group of them that come in at the end--which was a big surprise; we found this early--some coactivators come in and their job is to destroy all the other coactivators and the receptor. And this seemed counterintuitive to our thinking at first glance, but then I realized it's beautiful: it's the failsafe way to turn a gene off. The natural state of the genome is off; if you send active molecules into the gene to turn it on, you don't want to let those hang around in there when they're not needed, and the best way to stop the process is destroy them, not recycle them somehow. And if you want the gene on, you send more new molecules in to the gene. The soldiers go into the battle to die at the nucleus. That was a lot of fun, and we

went on and showed that they were involved in these steps. And this greatly expanded the role of coactivators. But also, now, a little light went on in my head, That's *why* we couldn't purify *the* coactivator--because there are many of these. In fact, now there's over three hundred and fifty of them known--probably end up with five hundred. So all those little peaks and all those little things we were looking at on the columns, they were all coactivators, and we just couldn't believe that there wasn't more than one or two or three of these.

Master genes

Then one day, I was thinking about all this and I thought, You know, there's more to this than just transcription. These molecules may be the molecules that really have created the mammalian and human species.

Chappelle: At this point you have all of these coregulators, and you've looked at each one of these steps that the coregulators can do. Did you build those [realizations] up one at a time and then come to an overall concept/theory, or did you have the overall concept [somewhere in the back of your mind] and start to plug in all the different things that [the coregulators] could do?

O'Malley: I guess there were some basic things. We were learning about the human genome at the time; we were learning that there's a surprisingly few number of genes in the human genome. There are only around twenty thousand plus genes. A yeast cell, a fungus, or worm has the same number of genes. Look at what we can do, compared to them. So it's not the number of genes. Somehow we know how to play the piano a lot better. So if you think of genes--the twenty thousand genes [not as genes but as keys on a piano]--there's eighty-eight keys on a piano, and the combination of the keys is what produces sound and, of course, the combinations together produce function, which is music. And that's essentially--I started to think--that's what the coregulators are doing. They are assembling the groups of genes to work together, not to just turn them on and off, but they've evolved these individual coactivators to produce functional goals in the cell: goals such as inflammation, growth, reproductive processes, cell death, metabolism; processes that are inherent parts of our physiology, but that require the coordinated actions of many genes, and that these may be the missing master genes.

Chappelle: Excuse me, just for a second--I know you're right in the middle of a thought. But following up with the piano analogy, you're going from playing individual notes to playing chords--

O'Malley: And then chords together for a musical piece and, eventually, a symphony; it's just beautiful when you think about it. I remember in 1969 I was reading an article in *Science* written by [Roy] Britten and [Eric] Davidson--it was a theoretical article, no doubt. And they postulated there was some sort of master genes that set it above all the genes in the cell and that they could perform

major functions; they could put the genes together for functions. It was ignored because their data never really came out for it. And one day that popped into my mind. I thought, That's what they are; that's why they evolved; we're working with all the things that they do on transcription and so forth--that's the details--but there's a big picture here. The big picture is why do they exist and what functional advantage does that provide to humans that other species don't have. Because the worms don't have the coactivators and the bacteria don't have the coactivators and the yeast don't have the coactivators--or just a couple--it's a product of the animal cell.

Chappelle: So the yeast and the other things you just mentioned, they're playing single notes? They're not playing the chords.

O'Malley: They're playing notes in succession. There's some interaction; one of the genes--one of the notes may produce something that goes over there and turns another gene on, but they can't get the simultaneous coordination of the master molecule coming and [doing what it] could do. And you'd say, why have it all in one protein? Well, *why not*? That's the way to coordinate it best. If you have one protein responsible for coordinating the genes, then nothing gets out of sync. If you activate that protein and you signal to that coactivator and that makes different transcription factors or receptors work together on different genes, now you've put everything together in the same time frame you need for a response.

Chappelle: So the master gene--

O'Malley: I have written about that. And after some smiles, initially, I think people are starting to--they're not smiling about it anymore, and they're thinking, Well, maybe they are [functioning as I have postulated]. [laughs]

Chappelle: Is that where it is right now--

O'Malley: Yes. I think--I would say it's a mild acceptance.

Chappelle: Okay, can we leave that area of [your] work now, or is there more to say--

O'Malley: I'll say one more thing. Then I started to think, How did we evolve? And that if the animal species have these and others don't, why did they have them and what were the driving forces. And the driving forces are metabolism and growth, and the response to food, and so forth. And then we got into what are the signaling pathways that activate these. We then went on to show that many stimuli from the environment can activate these coactivators, and each of them produces a different code in the coactivator, and it's a posttranslational modification code, like phosphorylation or ubiquitylation or acetylation or something, and this code in the protein makes it work with different sets of genes. So all the way outside of the cell and from our environment, signals can

come from there all the way down to the gene, and--again--use the same coactivators, but when they're coded differently, they go to different genes and they do different functions. So that's where we are now.

Therapeutic implications

The last thing I'd say is, along with that thought, you realize if these are that important, then they're going to be really important for disease. So in the last few years--and for the near future--we work a lot on how diseases co-opt these coactivators or corepressors to their own purposes. And, in fact, of the three hundred and fifty known coactivators, now, about one hundred and eighty-five of them have already shown themselves to be important in human disease, and so they have great relevance to pathology, especially cancer.

Chappelle: I was going to ask you, what diseases are you--

O'Malley: Genetic diseases, reproductive diseases, metabolic diseases, and cancer--big time. For instance, SRC-3, a coactivator we've worked a lot with, is overproduced in over two-thirds of human breast cancers. Now, why does the breast cancer go after that gene to make more of that product? Well, because it's a master growth coactivator. So if you make a lot of it, it now goes and puts together all the growth responses in a cell to grow rapidly, and that's what the cancer cell wants to do. So the cancer cell has two ways to evolve: go after every single little one of these genes and mutate them and take them under its control, or go for the biggie, go for the master gene and overproduce that. Now, suddenly, you've got a growth advantage.

Chappelle: What are you looking at that can turn the coregulator on?

O'Malley: Well, signals for growth will turn it on. And what we want to do--take cancer for instance--since the cancer cell is dependant on this, if we can find a way to block the activation of the coactivator that the cancer cell is using, we can stop the cancer from growing. And, in fact, it becomes so dependant on it [that] if we shut down that coactivator, the cancer cell kills itself. So that will be a future drug development target for us in the laboratory.

IX. MENTORING: A COEQUAL PASSION

Chappelle: Will you talk a little now about your philosophy of mentoring?

O'Malley: Yes. Often people say, Bert, I know why you're so turned on in your career, you have this passion for science and discovery. That's true, but there's one equal thing: it's the young people, the trainees in the laboratory. They keep you alive, and they, of course, do the work. And it is great fun working with them and training them. And I've trained over two hundred and fifty of them; they're all over the world in successful positions of professorships or heads of

companies, CEOs, NIH directorships, or positions abroad. That's been a great part of it. People often ask, what's my philosophy for training? And I always say [that] there are five things for success in science--and these same five things are required for success in life--I mean special success. One is IQ. But the IQ is overblown; you can't IQ your way to success. All you have to be [is intelligent] at a certain level, and after that other things make the difference. And when you get into a graduate school--training or something--you've already met the IQ level; so you've got the intelligence. The next big separator is industry or hard work. You've got to work hard and for a long enough period to school yourself in the discipline you're going to be an expert in. If you're not going to put the time in, and be compassionate and dedicated to it, you're not going to achieve your ultimate success. You can have some success, but you will hit your capacity. The third thing is judgment. Judgment is the most elusive of the five things. When I say that to a trainee, they say, What do you mean by judgment? Judgment is knowing what to do and when, what to say and when, how to interpret data, what direction to go on, what's a logical hypothesis, what's illogical, and how far do you go on something before you stop. You can't stop before you might just get the breakthrough. So it's judgment calls. But, of course, judgment is important for success in life, too. People with poor judgment don't do well. You see that all the time. Fourth is a strong code of ethics. In science that's absolutely sine qua non: you must have a strong code of ethics. Data must be exact and precise and direct and reliable and repeatable. And I think that carries onto your personal life, too. Because you can succeed, I think, to a limited degree without a code of ethics, but the human conscience weighs heavily, and you're not going to be happy. And the fifth thing is--well, you have a number of terms for it--opportunism, thinking out of the box: be ready for the unexpected, and see opportunities in the unexpected, see opportunities in negatives. If something doesn't work that you expected--and you get immediately depressed, Unh, I thought that was the way that worked, and it doesn't work--you repeat it. And if you get the same data, then it's telling you something you never knew before. That it's not the way you thought; you better change your thinking. And that might be the breakthrough. And that's of course how many things have been invented or many successes in life--people doing that in all phases of life--opportunities, thinking out of the box. Like Art Fry at 3M: the guy next to him is making super glue; he has a failed experiment and the glue's terrible; it doesn't hold anything. He's about to toss it; Art Fry says, "Give me some of that." And he puts it on the back of little pieces of paper and makes Post-its. And Post-its are still being sold all over the world for millions of dollars. You put them on and you can take them off, and they don't destroy anything. That's opportunism; that's out of the box thinking.

Chappelle: How do you present this to your students? Do you do it by example or do you actually teach--

O'Malley: I think you establish a relationship with them, number one. And the best way to teach anything is by example, yes. I mean, if I tell you something, [for instance] this is the way to do it, or this is the way to live, and then I live opposite, you're not going to pay that much attention to it. So the best teaching is to model, but also you've got to communicate your philosophy. You'll find the good students want to know. They want to learn about judgment. They want to learn--why do you think that way? They wanted to know--back twenty years ago--why did you think this, why did you do that? And they are refining their own judgment through those kinds of experiences.

X. THE NUCLEAR RECEPTOR SIGNALING ATLAS (NURSA)

Chappelle: What is NURSA?

O'Malley: NURSA is a Nuclear Receptor Signaling Atlas; it's a NIH consortium. A while back, NIH was thinking they've got this expanding field of nuclear receptors, and one of the people at the NIH, Ron Margolis--and [also] Phil Smith--talked to me about the possibility of forming a country-wide consortium of labs that work together to provide data that couldn't be done in individual labs, make it available to the public, and to advance the whole field. This is in addition to our own laboratory stuff that we do. I talked to Ron Evans, who is another leader in the nuclear receptor area, and together we are co-PIs on NURSA, and there are seven or eight schools involved in there now. It's supported primarily by NIDDK but has had money come in from a number of other institutes, too.

Chappelle: When did this get started?

O'Malley: We're in our seventh year, now. It's very successful. It took a while to get started--it was started from scratch--but it's really now fulfilling its purpose. We don't get money out of it; in fact, it's a lot of extra work. But Ron and I are both people that feel we got a lot out of the field and we can give something back. So we put effort into that.

XI. THE ENDOCRINE SOCIETY

Chappelle: What were the most compelling issues that you were involved with when you were president of the Endocrine Society?

O'Malley: Oh, that was a fun time, too. That was in the mid-eighties; I guess from late 1985--I could be off a year. When I first went to the Endocrine Society, I think there were about four hundred and some people in it then, and there are fourteen thousand now. Well, in the eighties it was still relatively small. When I was elected, there was one administrative assistant, Nettie Karpin, and she had one assistant. And the president had a lot of authority and could move the Society one way or another. Now it's a very large bureaucracy--it is successful; I'm not criticizing it, but it's just a different horse, now. So when I became

president--each president wants to do something--my idea was to move endocrinology away, totally, from the principle that this is a society for endocrinology itself as the traditionalist describes it; that is, an organ makes a hormone, it goes in the blood stream, and acts somewhere else in the body. And that [idea entailed moving endocrinology and the Society towards more complex and inclusive thinking about how] hormones could be made in cells and act on nearby cells in the same tissue, or even could come back in the same cell and act, which we call paracrine and autocrine, and that all kinds of factors being produced by cells were really hormones. And there wasn't, like, a couple of hundred hormones; there were thousands of hormones, and the field of endocrinology was giant compared to what people were thinking. And that's gradually--I wrote some articles at the time on that--and that principle has gradually grown now and people now realize that. The other thing was to introduce and champion an area that was developing with our work of molecular endocrinology. I wanted the Endocrine Society to capture that field, not let it be captured independently by another group, or stand alone. There were a number of ways to encourage this: by the program, making special things on the program, actually considering it a subdiscipline of endocrinology. But one of the ways I thought I could establish this was to have a journal called *Molecular Endocrinology*, so that we now had our clinical endocrinology journal, our fundamental biological endocrinology journal, and the new journal *Molecular Endocrinology*. I pushed that through with good support from my council members, but a lot of pushback from the publications committee, which thought, Well, I don't know if that is going to be successful, and why do we need another journal? They were not clear about this whole field of molecular endocrinology at that time. But I just did everything possible to push it through, and, of course, it's a major part of endocrinology, now. It's quite successful, I think--the journal.

XII. CURRENT VIEWS ON ENDOCRINOLOGY

Chappelle: What are your current views of the field?

O'Malley: Current views are very positive. Endocrinology is like a body of water that seeps into all the cracks in the hillside and fills every crevice and impacts everything. It has extended from a field dealing with a limited number of hormones, but it's in everything now. I mean it's a major force in cancer, inflammation, metabolism, genetics, reproduction, and the brain. The brain is the new area going forward, too. These are the outgrowths of endocrinology; it really metastasizes into everything. It's a fundamental discipline. You work with the heart; that's the heart [gestures to chest]--you could be cardiovascular and work with the blood vessels, too, but with endocrinology you're into every organ and every function in the body. And it's very exciting for that reason. In hormone action in the 1960s, there probably would have been a couple of hundred people in that general field; the last I looked--which was a few years ago--there were over a hundred thousand people working in that field,

worldwide. So it's really grown. How hormones work has had great interest to people, but primarily because when you know how they work, you encourage the drug companies to find new ways to develop new drugs for new diseases or old diseases. You also have new intervention ideas for diseases; and lots of new drugs and so forth have come out of the field. Just the nuclear receptor area, which I work on--I believe something like twenty-five percent of the prescription drugs in the United States work through those kinds of receptors. So it has a big impact. It's been nice to see the pharmaceutical companies grab hold of this and make a lot of new agents to turn on receptors and turn off receptors. And the next challenge will be how to turn on and off coregulators.

Chappelle: Thank you.

O'Malley: Okay.

[End of Interview]

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Interview History—Bert W. O'Malley, MD

Dr. O'Malley was interviewed by Michael Chappelle on June 11, 2009, during the Endocrine Society's Annual Meeting held at the Walter E. Washington Convention Center in Washington, DC. The interview took place in a conference room at the convention center and lasted ninety-eight minutes. The transcript was audit-edited by Mr. Chappelle and reviewed by Dr. O'Malley prior to its accession by the Oral History of Endocrinology Collection. The videotape and transcript are in the public domain, by agreement with the oral author. *The original recording, consisting of two (2) 45-minute mini DV cam tapes, is in the Library holdings and is available under the regulations governing the use of permanent noncurrent records*. Records relating to the interview are located in the offices of the Clark Sawin Library's Oral History of Endocrinology Project.