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JOHN T. POTTS, MD

Interview conducted by  
Michael Chappelle  
June 15, 2008

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## **INTRODUCTION**

John T. Potts, Jackson Distinguished Professor of Clinical Medicine at the Massachusetts General Hospital (MGH) and Harvard Medical School (HMS), is a pioneer in the chemistry and biology of parathyroid hormone (PTH) and its role in clinical disorders of bone and mineral ion metabolism. As the Director for over 40 years of the NIH Program Project grant, "Hormonal Control of Calcium Metabolism," Dr. Potts leads a staff of distinguished scientists and clinicians, in addition to a number of outstanding research fellows. Throughout his career, he has remained a spokesman of the field and has contributed his own analyses of its historical development.

## **BIOGRAPHICAL SKETCH**

John Potts was born in 1932 in Moorestown, New Jersey. He attended LaSalle College in Philadelphia and in 1957 received his MD from the University of Pennsylvania. Upon completing his internship and residency at the MGH in 1959, he then went to the National Heart Institute at the National Institutes of Health (NIH) to work with Nobel Laureate Christian Anfinsen in protein chemistry. Dr. Potts began his work on parathyroid hormone (PTH) and calcitonin at the NIH, becoming Chief of the Section on Polypeptide Hormones. In 1968, he returned to the MGH as Chief of the Endocrine Unit. He served as Chairman of the Department of Medicine and Physician-in-Chief from 1981 to 1996, and as MGH Director of Research from 1995 to 2004.

An internationally recognized authority on calcium metabolism and the hormonal mechanisms that govern it, Dr. Potts has pursued the clinical application of his basic research on PTH. Beginning with the early development of the radioimmunoassay for PTH, he and his colleagues applied this technique to study the abnormalities in parathyroid production that occur in hyperparathyroidism, including the development of a two-site immunoradiometric assay for PTH which measures only intact, biologically active hormone and can separate hypercalcemic patients with hyperparathyroidism from patients with malignant hypercalcemia. Dr. Potts and his co-workers have contributed to pioneering work in the study of hypoparathyroidism, in the use of PTH (together with other agents) to reverse bone mineral loss in osteoporosis, and in the use of calcitonin to treat Paget's disease. The author or co-author of over 500 scientific publications, Dr. Potts has been elected to the National Academy of Sciences, the Institute of Medicine and the American Academy of Arts and Sciences.

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## **I FAMILY BACKGROUND AND EARLY YEARS**

Chappelle: Dr. Potts, please tell me a little bit about your family background, starting with your grandparents.

Potts: Oh, well, very interesting! My mother's parents were born in Ireland, and my father's parents were of English extraction but lived for a long time in the United States, back actually to Revolutionary War days. My paternal grandfather was a florist and a very distinguished grower of rare plants and had a very successful business in the little town I grew up in. They were Episcopalian. My mother's family were Irish Catholics, and they were born in Ireland and came here, probably in the early part of the last century. And the two clans, as it were, met--with quite harmonious results, at least as far as I was concerned. I had one sister, and we lived in the small town of Moorestown, New Jersey, which is a rather lovely little town in the orbit of Philadelphia.

Chappelle: What kind of education did your parents have?

Potts: Both my parents went to high school. My father went to a sort of abbreviated program in business school, and my mother, I think, did some work after high school, but neither had a college education. But, as with many recent immigrant families, they valued education and intellectual values and sort of pushed my sister and I along, as many families did in those days. So I went on to college and medical school, obviously.

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

Potts: Well, my father was also a florist and was quite successful; so when I went to college and medical school, they put me through, and I didn't have to work. I did work in the summers, but they supported me very well. The idea was that I should try to do well in school, and their job would be to support me: a pretty good bargain.

## **Life during the Great Depression and World War II**

Chappelle: What was it like growing up at the end of the Depression, during World War II, and in a town with a Quaker heritage?

Potts: Well, we knew about the Quaker heritage, but it didn't directly impact on us very much. There was a very good Friend's school there. I think that my father's family did quite well, despite the Depression; the florists were not as affected. So I think they were mindful of this, but I didn't feel any direct

impact of that in growing up. I was nine when World War II began and, of course, by that point the agony of the Depression--I was born in 1932--had already eased quite a bit, but I don't think we felt it as many people did living in cities. Small town was a lot easier, I think.

### **Early education**

Chappelle: Was education a priority in your family?

Potts: As I mentioned, it was very important. That's why they encouraged me to excel in school, and they would take care of supporting me. I didn't have to work nights and things like that. It was a very good bargain, I thought.

Chappelle: What kind of a student were you?

Potts: I did pretty well. I was at the top of my class all along.

### **Choosing a career in medicine**

Chappelle: Were you making any decisions at this point about what you might want to be doing when you were grown?

Potts: Well, somewhere along the way the idea of becoming a physician--I think probably reinforced by my mother--came in my mind. And I don't know when exactly that happened, but by the time I was in college I was definitely heading in the direction of medical school.

Chappelle: How did your mother encourage you?

Potts: I don't remember. I just remember thinking--I remember our talking about it--what it would be like to be a physician. I don't remember any eureka moment. It was just reinforced in the way that parents often do a good job.

## **II LASALLE COLLEGE (1949-1953)**

### **Choosing LaSalle College**

Chappelle: Then you went to LaSalle High School and College. Why did you choose LaSalle College?

Potts: Well, I think that my horizons weren't that broad. I would think it was a fine choice for me as it turned out, but I didn't think about going to the Ivy League schools and things like that. It wasn't--as I'd already mentioned--there wasn't a long tradition of family involvement with college education for *themselves*. So if you're busy trying to grow and learn, your orbit of awareness may be--not so great. And if you come from a background where many people have

gone to college--as my children, for example, one went to Brown and one went to Yale and one went to Harvard--they would think very differently about what their options might be. I was quite content with it and enjoyed LaSalle College. My greatest teacher that I ever had was at the college. And then for medical school, I knew the University of Pennsylvania was very distinguished, and that's where I wanted to go.

Chappelle: Are any of your children in science or medicine?

Potts: Yes. My daughter is a physician, and she is an assistant professor at Harvard, and she's at Children's Hospital in Boston, where she grew up. And my son-in-law, her husband, is a physician, also. That's how they met, through that mutual interest in medicine. She was much younger, and he was the head of cardiology at the MGH [Massachusetts General Hospital] and professor at Harvard. He now works as the head of worldwide research for Novartis. That's the only medical connection. My other son is interested in a lot of things. And my youngest son is an architect with a firm in Philadelphia.

### **Claude Koch: an early and most important mentor**

Chappelle: You mentioned that one of your greatest mentors was at LaSalle.

Potts: Yes. There was a teacher, Claude Koch, who was an ex-marine, but a very sensitive soul, a wonderful poet, and just a born teacher. We became so excited by his style of teaching and his introduction to great literature of the late 19th century and early 20th century that--there were four of us, who all were heading to medical school, and we spent a lot of time in special classes that he held. In fact, after I went to medical school at the University of Pennsylvania, we used to go back to his home, which was in Germantown in Philadelphia, and there would be discussions about literature. And that went on right through almost all of my time at medical school. There's a little sketch that he made of me with--it's very interesting--"Dr. John"--at the bottom--"1956." That's the year before I graduated, so I know we must have been going back there pretty often. He was very inspiring, with a very low-key style and a depth of knowledge and excitement about great concepts in literature, and [he was] also trying to relate literature of the time to what was going on in other fields in the arts--in painting, in sculpture, and in music. He was a very cultured person.

Chappelle: Were science and medicine a part of that?

Potts: No, no. He wasn't interested in that at all. [laughs] He knew we were going there, and he thought that was wonderful. But he wanted to humanize us with his effort, I think.

### III UNIVERSITY OF PENNSYLVANIA MEDICAL SCHOOL (1953-1957)

#### Deciding on the University of Pennsylvania

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

Potts: Well, from the point of view of anyone living in the Philadelphia area, at least to my mind, it was the most distinguished--with the old lineage. At that time there were several other medical schools, but none were part of a formal university. So I really very much wanted to go there. I didn't know what the competition would be like and whether I would be successful in getting in there or not. I had done very well in college, and along with another friend of mine who also went to the University of Pennsylvania--we were the two that were at the top of our class by grade point average. It was complicated because you were supposed to apply to various medical schools, and you don't know who's going to accept you, and they had many applicants. It's always been the case with medical schools; it's a complex process. So I didn't know whether to apply to the other schools--because if they gave you an acceptance you had to take it or drop it. The University of Pennsylvania was always the last one to do this. So I had my interview--I remember--with the dean of the medical school there, and we had a nice chat. At the end, I explained this dilemma to him, and I said, "I haven't applied to the other schools yet because I don't want to be losing my other options." And he said, "Oh, you haven't applied anywhere else. Well, if I were you, I wouldn't." [laughs] Which is as close as one would get to acknowledge that it was going to be fine. I followed his advice. It was very kind of him.

#### Choosing to be a physician-scientist

Chappelle: What feature or features mark your medical school training?

Potts: Well, that's the time when I became very interested in science--not at the beginning--I mentioned that I was still going back to LaSalle College and the teacher that I had, and we enjoyed him very much. And I worked reasonably hard, but I thought I was going into the practice of medicine, maybe back in my hometown. It wasn't that difficult to work at a reasonable but not a blistering pace, so to speak. And I knew I wasn't in the top one or two of the class academically, but I was enjoying medicine, found it very interesting. And then, when I got to the third year of medicine--when you begin to see patients as a student--I became very interested in the science that lay beneath the problems that we saw in patients. And I became very interested in science at that point, having seen others who were in my medical school class who'd been interested in science from an earlier time and had done work as high school or college students: I hadn't. But then, I suddenly wanted to. And I knew there was a way to get into that--to go to a good academic residency-training program where medicine and science were both important values let's

say, like the Massachusetts General Hospital, which I learned about in those days.

**Getting started in endocrinology and parathyroid hormone research with Brook Roberts; applying to the MGH**

Potts: I was disappointed because I thought, Well, you've been cruising along here, you have another barrier or hurdle to overcome, and you haven't been running fast enough. But to my great surprise I hadn't done as badly in school as I thought. And when I applied the following year to the Massachusetts General Hospital (MGH), they actually accepted me, which was very exciting for me. And part of that drive in that direction was reinforced by another wonderful supporter and mentor, a surgeon called Brook Roberts, who was a very distinguished Philadelphian from a long lineage. He had a gift for encouraging young people, and he was interested in parathyroid hormone--well, he was interested in metabolic problems and particularly parathyroid disorders. I actually wrote a little paper with him about that. I'd been interested in parathyroid hormone for some reason, thinking about science, endocrinology, and the idea that there would be a servo system, like a beautifully modulated thermostat that would keep a particularly regulated variable at a constant level by turning on and off to raise or lower it. It was fascinating to me, and so I became interested in parathyroid hormone. And maybe the fact that I had spent a bit more time and written a small clinical paper and so on--I did it because it was exciting, but it turned out to have probably been helpful in getting into the next step--into the residency that I went to.

Chappelle: So it was your relationship with Dr. Roberts that sparked your interest in endocrinology--

Potts: In part. Partly, it was an intrinsic reading about things, taking classes at that time, and partly reinforced by him.

Chappelle: And before that, your idea of the type of physician you were going to be --

Potts: Would be a practitioner in the town--like the people that I knew that had been my physicians. So that third year really changed my course.

**Parathyroid hormone: state-of-the-art 1950s**

Chappelle: What was the dominant paradigm or model of the parathyroid when you began thinking about it?

Potts: Well, it was known, as I think I've just described it, as a--obviously--a very subtly, beautifully regulated servo system that would turn on and off. It was known that there were glands, and they produced a hormone, and the blood calcium is what they regulated. And they would keep the calcium constant. No

matter whether you were eating calcium or deprived of calcium, it always stayed absolutely steady, which we knew was important to health: low or high levels of calcium could be destructive; in fact, very low calcium could be fatal. So we knew *that*, but the nature of the hormone--it was known by then that it was probably--it was a polypeptide. It was not like a steroid hormone: it was made of amino acids together in a peptide chain. But it wasn't purified, and it was very hard to know exactly what to do next--to be able to measure it in blood, et cetera. And I became interested in that.

#### **IV MASSACHUSETTS GENERAL HOSPITAL: INTERNSHIP AND RESIDENCY (1957-1959)**

##### **Learning how to be a good doctor; early interest in the NIH**

Chappelle: Did you have a particular research goal in mind at this point?

Potts: No, I think I was young and didn't have a lot of background. I just thought that would be an interesting area to work on if I have an opportunity to do so. But as an intern and resident in medicine at the Massachusetts General, where I had gone by then in Boston, my job was to take care of patients and learn how to be a good doctor.

I did learn, early on, that there was then the opportunity of going to the National Institutes of Health (NIH), which was becoming a great beacon for people: if they were interested in medicine and science and biomedical research, if they went in a strong academic residency program, on the one hand, then they might have a chance to go to the NIH where they could learn science in a way that would allow you to begin to formulate a plan about what you might like to do.

#### **V NATIONAL INSTITUTES OF HEALTH (1959-1968)**

Chappelle: What got you your position at the NIH?

Potts: Well, I think the people that I worked with at the MGH took a kindly attitude toward me, and I suspect that Brook Roberts wrote letters. Alex Leaf, who was later to become the chief of medicine, felt that I was interested in science. I think he wrote a strong letter; several other people--I don't know since you never see those letters. All I knew is that I was very excited one day to be called and be told that I was accepted in the National Heart Institute.

##### **Protein Chemistry with Christian Anfinsen at the National Heart Institute**

Chappelle: Who was your mentor at the NIH?

Potts: Well, when I went there, you had a few months to pick the investigator you wanted to work with. And I learned that there was a fine protein chemist named Christian B. Anfinsen who was at that time applying the techniques of protein chemistry at a stage when it was still a very young field. I'd heard that he was very receptive to physicians with very little training but who were enthusiastic and supposedly reasonably bright, and he would bring them in and show them how to work in science. So I applied to him, and he took me. It was very nice. The NIH had a system where you would have--six residents, chosen from different institutions around the country, would go into the Heart Institute; other institutes had similar tracks. There was something called the research associate: if you'd done a lot of research, you might have gone directly into research; if you looked like you had potential for it, you would do one year of a sort of residency, helping to take care of the patients that were admitted to the clinical center but then would go on and do your research. So I applied to him, and he was gracious enough to take me in. And then I plunged into the world of protein chemistry, which was very exciting.

Chappelle: What research were you doing in protein chemistry?

Potts: He was working then on the structure of an enzyme called pancreatic ribonuclease. It was an enzyme that for today isn't that important. But it was available in large amounts and could be purified. And the techniques for doing the structure of a protein were still very laborious--required lots of material--and the methods had not been developed in a sophisticated way that came later. So you had to have something that was in large quantity. The first molecule that structure was done was insulin by Frederick Sanger who was in the MRC (Medical Research Council) in England, and he had laboriously worked out the structure of insulin. Ribonuclease was one of the next important ones being worked on. Anfinsen was a real pioneer in the field, and he adapted the techniques of protein chemistry and also a lot of ideas about how a protein organizes itself. Because ribonuclease--bovine pancreatic ribonuclease--was a highly organized enzyme: the chain was folded back on itself and stabilized with disulfide bonds, and that's what made it what it was. And part of the reason he later won the Noble Prize was he not only did the structure of this, along with two people from the Rockefeller, who were independent--really competitors--but he also inaugurated the concept that the primary structure of a protein determines how it folds itself, which was a very important concept. So I worked on that and wrote three or four papers in that area.

### **Beginning a collaboration with Gerald Aurbach on parathyroid hormone**

Chappelle: How did this relate to your interest in the parathyroid?

Potts: Well, it meant that I learned now the tools of how to do it. If I could get my hands on parathyroid hormone--and I felt that was a rather formidable task--and I hadn't done very much reading then. I went to visit Howard Rasmussen,

who I knew had already started some work in this area. He didn't really encourage me very much, I would say--he was then at the Rockefeller. But then I learned from another colleague--just as I was in the middle of my early phase at the NIH--that Gerald Aurbach, whom I'd heard of, had also come, like me, to the NIH from Tufts, and he was a person who I knew had just recently developed a new technique for purifying parathyroid hormone. We met at lunch and decided to collaborate, and that began a wonderful collaboration that lasted for over a decade, even after I subsequently left NIH. I was there from '59 to '68, and beginning in around 1960, began to work hard on it with Aurbach--on parathyroid hormone. Donald Fredrickson who was the head of one of the laboratories gave me an opportunity to have my own laboratory--to stay on. You didn't necessarily have that opportunity--they were there for two years, and then you would leave. So I stayed there altogether for eight years and had a little section on polypeptide hormone.

Chappelle: What was Donald Fredrickson's style as a leader?

Potts: Well, he was a very charismatic and interesting person who took a lot of interest in the residents, and we used to meet with him periodically, and he would talk about what was going on in the broad area of metabolic disease, which was his interest. He was interested in lipoproteins. And he, like a lot of the early mentors--Bob Berliner was the director of intramural research, Fredrickson was the clinical director in the Heart Institute, and Anfinsen was head of one of the laboratories--they all were very supportive of the young residents that were around. It was great of him to give me this opportunity.

Chappelle: And what were your most significant contributions to the field at this time--in your NIH days?

Potts: Well, we'd learned how to isolate the material in high yield; we learned how to do the structure. We were moving very well in the late 1960s when I was there. We had part of the structure worked out, but it was still very laborious and difficult: the amount of material available was very tiny compared to the amount of material you could get, say, with pancreatic ribonuclease, which was a byproduct of pancreas extracts from cattle. And that's where the parathyroid hormone came from, too, but there's much less of it in the body than there would be of pancreatic ribonuclease, which is a large enzyme dumped into the intestines to do its job. So it went slowly. Hugh Niall was a wonderful young scientist--younger than me--came from the laboratory of Dr. Pier Edman in Australia who'd just developed an automated technique for sequentially breaking off one amino acid after another in order to determine the order of the amino acids, which was, in the end, the structure. He joined us and we began to use his techniques. We diverted because at that time the molecule, calcitonin, which seemed to be the yang of the yin and yang of parathyroid hormone and calcitonin, became available. And we worked on the



structure of several of those while we were building up a stockpile of parathyroid hormone.

## **VI MASSACHUSETTS GENERAL HOSPITAL AND HARVARD MEDICAL SCHOOL (1968-PRESENT)**

### **Achieving the structure of parathyroid hormone**

Potts: Then MGH invited me to come back as the Chief of Endocrinology. So we took the partially completed structure of the parathyroid hormone, continued to work with Aurbach, who remained in the Arthritis Institute--a different institute than I was in--and we continued to work on the material and exchange it. By 1971, we had a good portion of the structure determined, at least at the business-, or amino-terminal end of the molecule. And there we again had the problem--if the structure was correct--the only way to prove a structure is to synthesize it. And another Australian had joined me, Geoff Tregear--

Chappelle: This is at the MGH?

Potts: The MGH. So the continuity of work went from the NIH to the MGH. And at MGH, we did do solid-base synthesis--Tregear did--and the material was active in a bioassay that had been developed by Aurbach, and we were all very excited. We had achieved the structure. We must have been correct because it was biologically active.

### **Building a network**

Chappelle: I meant to ask you--before we left the NIH--about developing your career and building a network. Would you talk a little bit about building a network within the biomedical enterprise? What did you learn in this regard at the NIH?

Potts: Well, it's a very interesting question, how you build a network. I think it has to do with many different features, probably has to do with personality, good fortune, and other young people that want to advance themselves. But I found myself building up a very nice group of associates, and I enjoyed them all and felt that this was a real opportunity to solve the problems, the research problems that I wanted to work on. By that time I had quite a few young people that had been working with me over the many years that I'd been there. They seemed to enjoy working together, and we could accomplish a lot as a group. When I went from NIH to MGH, I invited them to come with me, and we put in research grants and made it possible for them to go. So there was a sense that the laboratory had a certain harmonious interaction. I mean, everybody is worried about their own recognition whether it be the leader of the lab or the youngest person in the laboratory. But if you can understand how to trade off those sensitivities so that everyone gets their moment in the sun relative to their experience and feels supported by one another, it can be a

beautiful thing. It's one of the--it happens in other fields, too--but in biomedical research it's a beautiful thing when you see a lab that works together well. And the leader has to appreciate what that's all about and nurture it and sometimes resolve conflicts or swallow his own reservations about something, in order to keep the group going well.

Chappelle: When you mentioned "moment in the sun" and "nurturing," it made me think of your family as growers.

Potts: Ah, yes! [laughs] Well, I don't know that it--it would be a very nice analogy to draw out, but it might be a little forced. It was more the psychological aspects of it, I think. Some people are brilliant and great leaders of laboratories, and their sheer intellect is awesome, and sometimes they aren't the most supportive mentors, but they often develop very good laboratories because of the force of their intelligence and their drive and their position. And people go there and work because they will learn a great deal. Others groups are a little more--built on mutual support, a sense of helping everybody to work together. I mean there are many ways to do this. But the one that I liked was the one that we did. Maybe it was because the sheer force of my intellect was not as great as some of the others: I better be nice to people. I don't think that was a conscious decision. Rather, I think the point was that I felt very fortunate to be in this position and to be able to be making the progress that I could see toward the goal of understanding parathyroid hormone and producing the chemical side of the biology of the problem. And I could see that many people were contributing to this, and we could do things as a unit and a group that we couldn't do by ourselves. I think that was what I actually felt about it. I don't believe you do these things because if you don't keep the people loyal to you, you know the work won't get done. That doesn't quite make sense. It's really that as you rush for the goal, and you have people working with you--if you have enough sensitivity to see *their* needs and how to nurture *their* career development--the thing becomes a harmonious gelled-achievement of organization.

### **The Endocrine Unit**

Chappelle: Your original position at MGH was Chief of Endocrinology in the Endocrine Unit.

Potts: Yes, I was chief. Traditionally at the MGH, there were several--two major units: the Thyroid Unit and the Endocrine Unit. There was a great man, who I never met because he was disabled by surgery, Fuller Albright, one of the great and imaginative investigators of the entire twentieth century. Albright achieved many things despite severe physical disability from Parkinson's disease, which he acquired because of the influenza epidemic of 1918 when he volunteered when underage to get into the service. He contracted influenza, and about ten or fifteen years later, the disease began to manifest itself, but he continued to

be creative right up until this accident--[the result of a surgical attempt] to try to correct [his disability]. His surgical difficulty in 1957 left him totally paralytic and unable to speak. Anyway, after he had become disabled, it was necessary to find the next chief of endocrinology. And by that time, the man who had been the chief of the Renal Unit, Alexander Leaf decided--he was very interested in science and people who were doing things that would bring science as well as medicine to bear--was the one who invited me to become the chief of the Endocrine Unit, which was a very big responsibility.

Chappelle: Would you sketch out the Endocrine Unit?

Potts: Well, it turned out that I had to write my own grant to come; they didn't have a lot of funds to support me. There was partial salary support for *me*, so we had to produce the resources. Research space is always a critical thing in an institution related to biomedical research: if you get some space, then you can build a group; if you don't have any space, it doesn't matter how many people would like to work with you or how good you are as a leader, you won't have much of a group because you can't work in closets. So we did have the space, but we didn't have very much resources; we had to build that up on our own. I had to learn how to do that. I once waggishly said to one of my colleagues, a few years after I'd been there, now I knew what it meant to become chief of the Endocrine Unit: you were given an empty hotdog concession stand, *but* it was in Yankee Stadium. So if you knew what you were doing, you could begin to produce the resources. And so we had good luck with NIH: they liked what we were going to do, and they gave us a grant. And we got some support from industry and from another private foundation. So over a few years--which all leaders of laboratories know--you have to find money in different ways that will allow you to build up the support that you need. Because you have young people working there with you, and they are depending on you: if you don't have a salary for them, you've failed them.

### **Advancing the field of parathyroid hormone research**

Chappelle: The research you were doing at this point, this was a continuation--

Potts: Of what I'd done at NIH.

Chappelle: And you're still operating within the --

Potts: Parathyroid hormone.

Chappelle: And the same paradigm?

Potts: Yes, in fact, I've stayed working on the parathyroid hormone my entire career because the field of interest has magnified underneath the concept of parathyroid hormone--and we can talk about that later--but the level of interest,

its application in medicine, what you want to understand, how it works, is probably somewhat analogous to other biologic systems. You begin with a limited set of questions: can I get the structure of the hormone, can I develop an assay to measure it, can I learn more about how it works. Then gradually, as success comes, the complexity of the system in which it operates becomes more apparent, so the breath of the question constantly grows. And if it's an important question, other people are working on it. For example, when we did the structure of the parathyroid hormone, a younger colleague who'd been with me at NIH, but didn't come with us to Boston, also worked independently on the structure, having learned methodology that Niall brought to us. So he also did the structure of the hormone and continued to work on it, independently. That was Bryan Brewer. He then later went into the lipid work with Don Fredrickson and didn't stay in the parathyroid hormone field, as we did when we went to Boston. We could get to that later. But the areas that we wanted to understand about parathyroid hormone kept growing: we had the hormone, the impact of molecular biology became apparent, and we wanted to apply it. Henry Kronenberg, who's now the chief of the unit, and others came to the unit--Joel Habener and a group of other very talented younger people--they learned the techniques of molecular biology, not from me, but from other colleagues they went to under the fellowship support that we had. They went to MIT in the laboratory of Alex Rich and other people and learned the molecular biology it takes. They then came back, and they were able to work on applying molecular biology [inaudible]. We then cloned the receptor. Now we had the lock and the key. The hormone is the key and the lock is the receptor and we worked on that. Then later--I think I mentioned to you, perhaps I didn't--John Parsons, a pharmacologist, came and we turned to a different direction. We'll get to that later, probably.

### **A new paradigm and treatment for osteoporosis**

Chappelle: Well no, this is what I'm asking you. Up *until* John Parson's arrived, would you say you were working *within* the dominant paradigm?

Potts: Ah, yes! I see what you're getting at. The point was that parathyroid hormone was thought of as the regulator of calcium metabolism: it would preserve calcium egress in the kidney; it would take calcium--if you were in a period of starvation, it would take excess calcium from the bone; it would help vitamin D to absorb all the calcium that was available in the intestine, if any; and it was the servo system whose job was to control the blood level of calcium. Period. If it did anything to the bone, it was best understood by seeing what happened when you had a small tumor of the parathyroid glands: overactive parathyroids, called *hyperparathyroidism*. In that case, the bones had holes in them because it took too much calcium out of the bone. In fact, one of the early things we did was to develop a radioimmunoassay based on the purified hormone--we did that with Berson and Yalow, other great figures in endocrinology, who won the Nobel Prize for the wonderful things they did.

One of the things they did was to collaborate with Aurbach and me when I was still at NIH--going backwards a minute in time--to develop the first assay: so that if a patient had a high blood calcium, you could measure whether the hormone was high; if it was, it meant that they had a hyperparathyroidism. That was the paradigm at the time. That would have been, say, in the very late '60s, early '70s.

Osteoporosis was known to be a very troublesome disease that many patients, if they lived to be older--over sixty, particularly women--would get this loss of bone mass and lead to the state where the bones were no longer strong enough to support their weight. They would have what was called fragility fractures: their vertebral bodies would collapse and break, crush a bit, or they'd have a minor fall and break their hip. And it was often--particularly a hip fracture--it was a life-changing event for many elderly people; they never recovered from it. But there weren't any treatments for it. And there weren't any techniques for measuring bone mass that were really very accurate, so that you didn't know you had osteoporosis, necessarily, until you began to break bones, and then they all would break pretty quickly, one after the other.

Parsons had noted that Albright, who had been the chief of the Unit so many years earlier that I came to at MGH, had done a study in rats and showed that a daily injection of parathyroid hormone--instead of having it come up high, as you would in the period of challenge of low calcium, it would come up and stay much higher than the basal level and bring the calcium up with it. But if you did just a little squirty injection [pulsing parathyroid hormone] for a few hours--that Albright noted in rats that he was studying for another reason we didn't get into--that it *built* bone; it didn't break it down. And he said, "You know we should try parathyroid hormone as an agent for osteoporosis." Well then, since there wasn't anything around for that, we tried it, and that story went on for many years, but it proves to be a paradigm-shifting development in which it builds bone--for reasons that are paradoxical when you understand its role in biology but which may be explained in other ways. We now have some insight into it. It was a wonderful development. So parathyroid hormone moved from the calcium thermostat to a critical agent in bone health. And that's been the dominant paradigm now.

### **The new paradigm advances the field**

Chappelle: And how did that switch of paradigms affect the field of endocrinology as a whole?

Potts: Well, I think that the realization that a hormone could be used in a powerful way to stabilize bone and build it back up linked two different fields. The bone field was not much of a field back then. In fact, the American Society for Bone and Mineral Research, which is a sort of sometimes cooperating sister institution to the Endocrine Society, didn't even exist until--it's just celebrated

its twenty-fifth anniversary. And it came into being because the success--and it wasn't just what we were doing, but others were learning how to measure bone mass non-invasively. They isolated bone cells, found out how the bone cells talked to each other in vitro, and then how to follow how that communication occurred in vivo. And as people were aging at the time, you could learn how you might be able to prevent or reverse osteoporosis, which was very important. And there were other great figures in the field: Herbert Fleisch in Switzerland and Gideon Rodan who was first at the laboratories here and then went to Merck where he teamed up with Michael Rosenblatt and others. And they all developed the anti-resorptive agents, which would help bone to build back up by blocking its loss; parathyroid hormone would build bone up by directly driving new bone formation.

All these entities drifted together. And so now, even at the Endocrine Society, there are several sessions on bone and the interplay between endocrine agents and the bone. So the field has just moved on--as happens when the field gets lively and that which wasn't appreciated before suddenly becomes the new paradigm. And then there'll be a change; we'll find out something else about parathyroid hormone or about bone, and it'll take another change. Good scientists are alert to that and excited by changes. Those that are a little bit too wedded to their own traditional way of thinking even sometimes resent these paradigm shifts and are slow to accept them. It's not wise, but that's what happens.

### **Therapeutic results of treating osteoporosis with PTH**

Chappelle: What were the therapeutic results?

Potts: The therapeutic results were very, very striking. Parathyroid hormone--we learned early on--when given to patients with osteoporosis would build bone back up. We didn't, in the early days, know quite how to measure this as well as we do today; now we have methods of non-invasively measuring bone mass, and you can see the increase in the bone mass, two and three percent per year. In fact, parathyroid hormone will build up bone as much as twelve to fourteen percent in eighteen months time, which is very powerful and moves you away from the fracture threshold. That's what we can say today. But we could sense that we were getting the positive result, back then, by bone biopsies and by measuring total calcium balance--rather crude techniques compared to today. But we knew we were in the right direction, and our patients, who had nothing else to help them, were pleased to have this opportunity.

## **Patenting, the Harvard rule, and initial hesitation of the pharmaceutical industry regarding the development of PTH**

Potts: Now, when we did the structure and the synthesis of the molecule, it was the Harvard rule that it had to be dedicated to the public domain: one of the things that delayed the pharmaceutical companies picking up the idea. Other investigators, some of who are members of the Endocrine Society and here [at the Society's annual meeting], also picked up the theme begun by Parsons and our group; it happened in England, and it happened here. Others began to study it and be excited by it, and the methods were then getting better and better to evaluate what was happening. And so there were a number of clinical investigator-initiated studies, and finally Eli Lilly Company said, We can handle this without a patent, and they came in, developed the drug, and its been approved since 2001. It's now about a little under a billion-dollar-a-year drug internationally, and it's been very, very helpful in treating patients with osteoporosis. It had some problems during its development; some things happened that slowed it down. For example, there was a toxicology study that was probably much too--I would say ill conceived. There was some osteosarcoma that showed up in the cancer-prone rat strain that the toxicologist chose to study and pour parathyroid hormone into, and the FDA almost didn't approve the drug, but then when they saw the great clinical benefit, they did. It still carries a black box warning, but now everyone realizes, I think, and is comfortable with the view that to treat patients with osteoporosis the risk/benefit ratio is very, very favorable, and the likelihood that they are going to develop an osteosarcoma is very low. That's another topic. Anyway, it goes on, and it's been very exciting to watch it, and it's been gratifying to me.

### **PTH: from bench to bedside**

Chappelle: Aside from your early contribution, did you have an active role in shepherding it through from bench to bedside?

Potts: Well, that's a very good question. Many people played roles there. Robert Neer is one of the lead investigators in our group--who was there when I first came--so he and I and other people, David Slovik and others, worked on this together as a group through the 80s and published several papers showing that it would work both in men and in women. The methods were getting better. He and I worked with Eli Lilly to get them to pick up the opportunity, encouraged them to do so. And then there was a clinical advisory group that Eli Lilly put together, and I was the chair of that and tried to help them as they were facing the practical problems, for example, encouraging them to stay the distance when osteosarcoma appeared and the trials were halted. I went with them to the FDA, along with others, and gave testimony about the fact that this was a beneficial drug. So I guess I've been with it all the way, playing different roles at different times.

## VII CURRENT RESEARCH: MAKING A BETTER PARATHYROID HORMONE; PARATHYROID HORMONE AND ITS DEVELOPMENT OVER EVOLUTIONARY TIME

### Parathyroid hormone-related protein as a possible treatment for osteoporosis and hypoparathyroidism

Chappelle: And are you still actively involved with parathyroid hormone therapy?

Potts: Yes, yes. I'm very interested in making a better parathyroid hormone at the basic science level, one that might work even better than the one that we now use.

Chappelle: For osteoporosis?

Potts: For osteoporosis. And there are some theoretical reasons why we might be able to make a better one. We think it may be that parathyroid hormone works the way it does because it imitates a companion molecule called parathyroid hormone-related protein (PTHrP) that we now know, through the power of molecular biology, goes back in time--both of them go back to fish, parathyroid hormone and parathyroid hormone-related protein and the receptor [PTH/PTHrP-related receptor 1 (PTHr1 or PPR)]--very early in evolution--which tells us there's more to parathyroid hormone's role than we now know because the glands first appear in vertebrates when they move to land and had the challenge of calcium metabolism. But to come back to the point you're making, we think that a quick "on and off" interaction between the lock and key would be the way to make an even more effective parathyroid hormone. Because what limits its effectiveness is that after about twelve to eighteen months bone resorption begins to pick up. So what you want is to build bone and not break it down--parathyroid hormone first builds it up. My colleague John Bilezikian, who's done a great deal of work in this field, calls it the "anabolic window". If you imagine bone formation going up like this [gestures]--bone resorption doesn't, and then begins to come up. So the gap between the two is maybe responsible for most of the gain. That's probably oversimplified; the story's much more complicated. Some people feel you need some resorption to get optimum formation; it's part of the great questions being currently addressed. But we have reason to believe that you might be able to design a molecule that wouldn't have that rise in resorption. Andrew Stewart, who is speaking tomorrow or the next day here giving the Aurbach Memorial Lecture, is going to talk about PTHrP. He's introduced it into therapy of osteoporosis and shows that it--some preliminary data that suggests that it might be more effective even than parathyroid hormone, which to me makes sense because it may be what parathyroid hormone is imitating. Parathyroid hormone-related protein may be being made in the bone--and [has a] quick "on and off" mechanism, quicker than PTH, which really has another function. So PTH may have been imitating what PTHrP does. Given that, we



think we can make a molecule that will be more like PTHrP or even better than PTHrP in this regard. And then we've learned--this is work that Tom Gardella, Makoto Okazaki, and others in our group at the moment have gotten into--we've learned that you can go the other way; you can make a parathyroid hormone that *locks*: the key goes in the lock, and the whole operation goes through the door, into the room, and continues to work. We think *that* molecule, that direction, might lead to a treatment for *hypoparathyroidism*, a condition that affects only a small number of patients, maybe less than two-hundred thousand in the United States. But my colleagues and I went to a meeting at the Hypoparathyroidism Association of the United States, and we were all deeply moved--this was just last week--to hear about the problems they suffer and the difficulties that are often seen when you try to treat these patients with vitamin D and high calcium intake--because parathyroid hormone has never been used in any systematic way for hypoparathyroidism. Normally in endocrinology, if you have too much of a hormone, you take out the gland that's overactive; if you have too little, you replace it with a hormone. Parathyroid hormone has never been long-acting enough to have it as a practical treatment for hypoparathyroidism, but I think it might be a good treatment, and I think we may be seeing--in our very basic research--a way to go that might provide a treatment for hypoparathyroidism, which of course would make my colleagues and me very, very happy if we made another medical contribution. We're working very hard on that, now.

## VIII THE ENDOCRINE SOCIETY

### Networking at the annual meetings

Chappelle: And in terms of that aspect of your research, what opportunities do you get at the [Endocrine Society's] annual meeting this year to network about this? How does the meeting help you advance your work?

Potts: Well, I think it's an excellent question. These meetings--like that of the Endocrine Society or this so-called sister institution, the American Society for Bone and Mineral Research--are great meeting places where people from all over the country, from abroad, and from both Asia and from Europe come together. And there's a set agenda where people are invited for the program committee--who has to prepare all this some time in advance. They give research talks--formal and informal and different formats--and there's great intellectual stimulation. People ask questions and you can see a vast sea of intellectual effort being stimulated by this meeting, and there are many sessions in this meeting on the bone field. But of course, I like to go also and listen to things that my colleagues are doing in other areas, in steroids and in reproductive endocrinology. So you get stimulation by listening to what's happening in your own field and what's happening in fields that might be not directly related, but in which you may sense another paradigm shift or a way in which people think differently about things. So it's a tremendous stimulation.

This Endocrine Society has so many topics that bone is only one of them, but we will hear a lot about bone and talk a lot with our colleagues about it. I've already talked with some of my colleagues here about this idea about the long-acting parathyroid hormone. They're interested.

## **IX TEACHING PARADOX**

### **On paradox, paradigm shifts, and the scientific method**

Chappelle: How do you teach paradox? How do you teach an appreciation of paradox?

Potts: Now, that's an excellent question. Maybe best by example, more than anything else. If something new turns up that doesn't make sense, how do you react to it? It may cause the pathway that you were thinking of going in to be turned on its head. Does that make you annoyed, and you feel maybe you didn't do the experiment right: do it over again, it's wrong. Or do you say, Hey! maybe there's something here we don't understand. A certain humility toward our understanding in biology, in my mind, is important. A scientist has to be skeptical about his own findings and reproduce them very carefully, and only when he can't prove himself wrong, can he think he's right. That's sort of one aspect of the scientific method. But often times we're off with much broader concepts, and all of a sudden something goes the way we didn't imagine. I love paradigm shifts and paradox; it makes one think. And I think the sort of group that we have drawn together at the Endocrine Unit of the MGH--of which now I am a senior member because Henry Kronenberg is the chief; but Harald Jüppner, who went with me to this parathyroid conference of patients with hypoparathyroid--when we see new things, I think, with this sort of general attitude in the group, Hmm, maybe we don't understand something; that could be very interesting. And it's much more interesting to discover something that's the opposite or different than what you expected because it often signals a sudden new burst in understanding. I think that's the only way you can teach it. You can't give a lecture about how--you can show by example, when you're talking about what you're doing; you can show by anecdote or by responses what's happening; but you can't teach it in a didactic way, I don't think.

## **X THE ENDOCRINE SOCIETY: HELPING EMERGING SCIENTISTS**

### **Keeping institutions strong through the nurturing of young scientists**

Chappelle: In a period of tight funding, what can the Endocrine Society do to help the new, emerging scientists establish their careers?

Potts: It's an excellent question and one that the senior members of the Endocrine Society worry about a great deal. What can we do, those who've been fortunate enough to move through our careers and are now in senior positions? Sometimes they're holders of chairs; or, as in my case, I'm still on full-time

academic salary because it's the policy of the hospital [MGH]: for years of service given, there's support. So I don't depend on grants for my salary support; years ago, I did. So what we are doing is using some of the resources--the Endocrine Society is really doing a remarkably good job of using the resources that it generates. It has an annual budget of about twenty-three million dollars or twenty-five million dollars, I believe. And it has reserves of about eighteen to twenty million that have been invested. It's very aggressively using that money--and very wisely--to encourage young people to enter the field, to provide fellowships to make it possible for them to come to the meeting and see what's going on here, travel grants. The current president, Margaret Shupnik, at this luncheon we just came from, was telling us about the large number of young people that had been gathered in pediatric endocrinology, in clinical endocrinology, and basic endocrinology--because there are people who are not physicians who are members of the Endocrine Society, there are PhDs. So you have streams of basic science, clinical science, and people in between, who might be physicians or PhDs. And so trying to stimulate them to not be discouraged--to support them with grants is very important. The other thing the Endocrine Society does is lobby with Congress, with the NIH, to keep the support level for younger people coming. And there are a lot of things that happen in NIH now. Sometimes a first award is given a better hearing; if this is your first grant, you'll get it funded even though your priority score is lower. We want to encourage people to come into the field. And you have to look for other means of support. For example, if you can get unrestricted money from industry, if you can get philanthropy in your institution to give money, then you can use it to stabilize the young people. It's a constant problem. The feeding and nurture of the young is a major challenge. The institutions like the Endocrine Society, or my own hospital, or the Harvard Medical School--that really pay attention to that--are doing the right thing most of all; but secondly, they're keeping themselves stronger because by bringing the younger people on is how the institution renews itself, and they understand that, I think.

Chappelle: Well, thank you.

Potts: It's been pleasant talking with you. Thank you very much.

**END OF INTERVIEW**

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#### INTERVIEW HISTORY—John Potts

Dr. Potts was interviewed by Michael Chappelle on June 15, 2008, during the Endocrine Society's Annual Meeting held at the Moscone Center in San Francisco. The interview took place in a conference room at the Marriott Hotel and lasted 57 minutes. The transcript was audit-edited by Mr. Chappelle and reviewed by Dr. Potts 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 one (1) 60-minute videotape, 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.