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JOHN W. FUNDER, MD, PhD

Interview conducted by
Michael Chappelle
June 4, 2011

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INTRODUCTION

John W. Funder, MD, PhD is Professor of Medicine in the Department of Medicine at Monash University and Senior Fellow at Prince Henry's Institute of Medical Research. For over thirty years, Dr. Funder has been a leader in medical research in Australia. He has rewritten the pathophysiology of adrenal steroid action in the cardiovascular system, and he has been an innovator in publishing guidelines for the management of primary aldosteronism. Dr. Funder has also been a leader in translational research by leveraging off clinical studies to critically examine and recast what we believe about aldosterone, cortisol and mineralcorticol receptors. In addition, he has made very substantial contributions to research governance, representation, ethics, funding and translation nationally and internationally. He remains an intensely active thinker, passionately committed to medical research, its translation into healthcare, and to the importance of research and innovation to both Australian and global society.

BIOGRAPHICAL SKETCH

Dr. Funder was born the day after Christmas, 1940, in Adelaide, South Australia. He was educated at the University of Melbourne, where he was awarded both MD and PhD degrees in 1971. Dr. Funder was a medical officer at St. Vincent's Hospital in Melbourne, followed by a postgraduate period at the Howard Florey Laboratory of Experimental Physiology. He also spent postgraduate time in the Cardiovascular Research Institute in San Francisco, at the Necker Hospital in Paris, and at Prince Henry's Hospital in Melbourne. A number of positions of responsibility followed in quick succession: Associate Director of the Medical Research Center at Prince Henry's Hospital, Deputy Director of the Medical Research Center in 1983, and Director of the Baker Medical Research Institute in 1990. Dr. Funder's research began with a publication in 1968 on the "Effects of Adrenal Steroid Withdrawal on Chronic Renovascular Hypertension in Adrenalectomized Sheep," which examined the effects of glucocorticoids and mineralocorticoids on cardiovascular biology. Five hundred papers and thirty-four years later, he remains constant to this interest: his most recent paper examines "Experimental Cardiac Fibrosis, Differential Time Course of Responses to Mineralocorticoid-Salt Administration," exploring the role of glucocorticoid and mineralocorticoid on the cardiovascular biology. Between these papers is an investigative tour de force that explains the core concepts defining the physiology and molecular biology of steroid hormone action and the effects of the steroid hormone on the kidney and cardiovascular system. These studies span the animal kingdom from bacteria to man, and touch all aspects of adrenal steroid biology: synthesis, secretion, transport, binding, signal transduction, and biological effect. Dr. Funder is a council member of The Endocrine Society, has served on the advisory board of *Endocrine Reviews*, and has served on the editorial boards of *Circulation Research*, *Journal of Steroid Biochemistry*, *Endocrine Reviews*, *Steroids*, *Clinical Endocrinology*, *Endocrinology*, *Journal of Hypertension*, and *The Journal of Clinical Endocrinology & Metabolism*. He has been the president of the Australian Endocrine Society and president of the Australian Society for Medical Research. Dr. Funder received the Sidney H. Ingbar Award from The Endocrine Society in 2002, and chaired the Endocrine Society Task Force, which published the Guidelines for the Diagnosis and Management of Primary Aldosteronism in 2008.

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I. FAMILY BACKGROUND AND EARLY YEARS

Chappelle: Dr. Funder, would you please tell me a little bit about your family background?

Funder: Sure. My grandparents--if you'd like to go back as far as that--I remember all of them--one, my paternal grandfather, not very well. They're all in Adelaide [in South Australia]; they are Adelaide families. My father's family were--I think, originally--dirt poor. The name Funder is Danish, but the matriarch of the family was Florence O'Brien--that's not Danish, that's Irish. He had a little shop down in Port Adelaide, and I suspect ran an off-license betting shop or something, but they really did really very well and amassed, relatively, a lot of money. All four children--my father and his siblings--went to the University in Adelaide, and when they turned sixteen were given a car to drive to the University, and so on. This was *really* fairly special in the late twenties, 1930s. There were two doctors, a pharmacist, and a dentist among my father and his three siblings. On the other side, my maternal grandfather was the man who built the piers from which the Australian and New Zealand and British troops were evacuated from Gallipoli; they were Watson's piers--I'm John Watson Funder. He was an engineer--to be in the Army and be building piers--but wound up, in a sense, running the railways in South Australia. He lived to be one hundred. I inherited his dinner suit--his tuxedo--when he died, so he was a man of rather large proportions. At the end of the Second World War--my father had spent the early '40s in Melbourne as a pathologist--we moved to Melbourne from Adelaide, and that's where I grew up, where I went to school, the University, and so on.

[Interruption]

I was the eldest of a large family of seven offspring. Father was a hospital pathologist. Mother was a botanist; she has done her master's in botany in the '30s in Adelaide. I found out after my father died that she had actually been offered a place to do a doctorate in Oxford. I'm glad she didn't go because I think the war would have intervened and I might not be here had she gone to Oxford--but whatever. She was essentially a homemaker with seven kids. An intelligent woman, she is still alive. She is ninety-seven--that long-lived strain in the family is something I'm counting on--put it like that. We grew up in suburban Melbourne, went to the local Jesuit school--which was a terrific education, looking back on it. I did Latin and Greek--they were very classical things--and math, English literature, and so on, and physics and chemistry, also. And then went into medicine.

II. MEDICAL AND SCIENTIFIC TRAINING (1958-1974)

Funder: There was only one university in Victoria at that time, which was the University of Melbourne, which had been started one-hundred years before; they were still waiting for Monash, which was set up around the time I went off to the University, but didn't have a medical course when I started. I started medicine and was *very* active in student politics. I thought first-year medicine was extremely boring, and second-year medicine was worse. It was anatomy to the max; it was terrible. So I was on the student representative council, and I was in drama productions, and I was in residential college, and I did everything except medicine. I got honors in first-year and passed in second-year, but after one week of third-year medicine--it was a six-year course, straight out of school back then--I went and changed and did an honors arts degree in history and politics and philosophy. And then told my parents, who were horrified, of course.

Chappelle: You told them after the fact?

Funder: I told them after the fact. But I had a scholarship, and I changed it from medicine to arts medicine, so, you know, my fees were paid. That was okay; I wasn't totally--but I was hoiked out of the residential college and taken home and told "knuckle down." So in my fourth year at the university, I met my future, now late first wife, and I thought, Oh, God! You can't possibly give her--think about getting married. It was back in the days when, in your early twenties, you thought about getting married, not like today. On an arts degree, what am I going to do, be a librarian or something? I'm not cut out for that. So I went back to medicine, completed the arts degree part-time, and graduated in 1965--which seems like yesterday, but in fact was quite a long time back--did residence, and then wanted to do research. I said to one of my mentors when I was a hospital resident, I noticed that all the young women--who were my friends, the nurses--they all get nosebleeds at the same time. And I'd learned during my course that women in institutions--nuns, and so on--they tend to cycle at the same time, so they get their period at the same time. I said, "Is there some estrogen or progesterone sensitive mucosa in the nose, so that these women who brush their nose would all get nosebleeds at the same time?" He said, "I don't know, but if you are going to do research, do it properly. Don't do some half-ass project like that, while you're going on doing clinical stuff. I'll arrange for you to meet the people at the Howard Florey Institute." So he did--God bless him--and they took me to lunch, which went until six o'clock. It was Panzee Wright, who was the professor of physiology; Derek Denton, the director of the Florey; and John Coghlan, who was really, I think, much of the scientific drive--in the biochemical sense--at the Howard Florey Institute. Now imagine that now: you've got a PhD student--the professor, the institute director, and in a sense the head scientist takes this person to lunch; it goes till six o'clock; God knows how many bottles of wine were drunk, and in the end he is signed up. I was the second PhD student at the Florey. I was PhD student

number 467 at Melbourne University. No university in Australia had granted a doctorate until after the war. Compared with the floods of kids, now, who are enrolling in PhDs, doing good PhDs, doing good work, et cetera; you were a rare bird back then. By then I was married, and by then I had one, then two children, and my late wife Kathleen was working as a student counselor in school. She was a psychologist and doing a part-time master's. So we were busy. And at the end of my PhD, which was in hormones and high blood pressure--I've been very constant, perhaps too constant, too focused--I got a National Heart Foundation of Australia fellowship and went off to San Francisco.

Chappelle: Let me interrupt you for a second. What led to your interest in hormones and hypertension?

Funder: That was [because] they said, We've got these sheep; we want to know if we take their adrenal glands out, or if we do other *stuff* with regard to the adrenal glands--and we have models of hypertension by constricting the renal artery--will that affect that? Are they able to be hypertensive with this hormone or with that hormone? That was chosen for me--it had nothing to do with nosebleeds or anything like that. So I sort of just fell into that area. And then at the end of 1969, I applied for and got a National Heart Foundation of Australia four-year traveling fellowship: two years away and then two years back to set yourself up. The choice of San Francisco--where I worked in Professor Edelman's lab, Dr. Izzy Edelman, a wonderful man--was made for me by John Coghlan, who met Izzy at a meeting in Japan. And Coghlan says, "I've got this young fellow; we want to send him somewhere, and you do, 'how does aldosterone work on its target tissues,' and we are very interested in what controls aldosterone secretion. Can he come and work with you?" Izzy said, "Fine, if he gets some money." I've got some money from this fellowship and went to San Francisco. And that was terrific; it was really terrific. I was told, Oh, you've got to be careful--these Americans--they work all this time, and it's publish or perish, and it's desperate, and dangerous to go out after dark, and so on. I had two kids, and by the time we left I had three kids, so I didn't do much going out after dark. I'd get to work at half-past 8:00 or 9:00 in the morning, and I'd leave at 5:30 to come home to help with the kids, and we'd go traveling on the weekend and do stuff. Everybody was very welcoming in the Cardiovascular Research Institute (CVRI) because Iz was the associate director of that. It was really terrific. It had an equal number of postdocs, which I was one of--fellows--from America and what were termed aliens, which is a bit, you know, spice wars, but still--that was the policy: half and half. So I met people from all over the world in the Cardiovascular Research Institute and remained good friends with some of them and with some of my American colleagues. I worked with, very closely with David Feldman, who is now down at Stanford, a distinguished endocrinologist, who went off into vitamin D, which is now having an extraordinary renaissance. Whereas, I have stuck with hormones and high blood pressure and hearts, and stuff like that. But Kathleen,

my wife, who is marooned with these three kids up in the fog, and she said, “I would love to go to Europe, can’t you?” So I went off to a meeting in Munich, met people there, and they said, Come and work in Paris. We do angiotensin receptors; you do aldosterone receptors. Let’s see if we can do something useful.

Chappelle: Let me take you back a little bit to the CVRI when you were there.

Funder: Sure.

Chappelle: Would you say a little bit more about Isidore Edelman and his scientific stature?

Funder: Sure. He was a wonderful *thinker*. He had trained as a nephrologist, as a kidney doctor. He had a stint in the Army trying to find out ways of rehydrating people who were dehydrated and stuff like that. So he was interested in fluid and electrolyte balance. And aldosterone is what determines how much sodium we retain in the kidney, and with the sodium comes water, so that took him into that. But he’d done biochemistry before he did medicine as his undergraduate career, and he was a very rigorous thinker, and I profited enormously from the training. In *thinking*, yes, but in biochemistry, really. I mean I’ve done undergraduate medical biochemistry, but never a proper biochemistry course, like the four years he had done before he went off to medical school and the University of Indiana--because back then, being Jewish, he was--there were effectively quotas in New York, where he grew up. So he was a graduate of the University of Indiana--medical graduate--from there. I remember celebrating with him his fortieth birthday. He used to make sure [that] if we wanted to do a particular experiment, we did it first on the white board. You know, what’s this, what’s that, what do you think the outcomes are going to be--very good training for a scientist-in-training. I got eleven papers out of two years there. That was a terrific outcome. I’d had a lot of experience writing--put it like that--with that very varied degree in student politics and arts and philosophy, and stuff like that.

Chappelle: What research did you do with him?

Funder: We did some of the very earliest stuff of the receptors, the keyholes into which the aldosterone goes to turn on what it does in the kidney, but also in other tissues, too, like the salivary gland, because aldosterone affects the amount of salt and water that comes out, not so much in us, but in ruminants. Back at the Florey--back in Australia--I worked quite a lot with a preparation in the sheep of externalizing the parotid duct: so drip, drip, drip. And a good dripper--a sheep that was really chewing its cud all the time and dripping out of one side and wetting the cud with the other one--could lose, oh, two, three, four liters of saline a day of quite sodium rich fluid and would become quite sodium deficient very quickly without diuretics or messing about. So we’d use that a

lot as an experimental model, back there. We were interested in a bunch of stuff, but it was about aldosterone, mineralocorticoid receptors, and a bit about glucocorticoid receptors, and they were very early days, *very* early days.

Chappelle: You were able to publish a lot of that.

Funder: I got eleven papers out of that.

Chappelle: And how did that experience affect your career?

Funder: Well, I think it sort of set it in stone. There is a limerick: “There once was a man who said, ‘Damn!’ It is borne upon me that I am an engine that moves in predestinate grooves. I’m not even a bus; I’m a tram.” I think I was a tram, in a sense, from then on. Now, I’ve had excursions into other areas of science and of scientific side issues from neuroendocrinology to medical ethics to some cancer stuff, and so on and so on, but it’s always been--the train tracks have always been there. It’s always been cardiovascular endocrinology.

III. PRINCE HENRY’S HOSPITAL (1974-1990)

Chappelle: After completing two fellowships, why did you choose to return to Prince Henry’s Hospital?

Funder: Well, it’s complicated. I’d done a year in Paris at the behest/request of my wife, and it was terrific. All three of my children--one was tiny then--we went back for a year, a few years later. I was a visiting professor. All my children speak fluent French. One of them--the oldest--I’m told by my French friends, without any accent; he can be mistaken as French, because they went to a local school and then four years later went back to the local school. I went back to Prince Henry’s, rather than the Florey, because at that stage the Florey had very tight, rigid notions about who did what. And if I went back to the Florey, my role was to be the scribe. I wasn’t going to do any experiments; I wasn’t going to plan any experiments; I was just going to give everybody else’s results and write them up. They had a way of publishing, which was alphabetical. And that’s insupportable, frankly. If you do the experiments, if you plan the experiments, if you do the work as a young postdoc or aspiring, you want to be first author. Later on, you want to be last author--have *your* students or fellows taking the front position. That’s absolutely normal. I mean there are big papers with one hundred authors where the authorship doesn’t particularly matter because it’s all been put in from everywhere. But basically they are the rules, and the Florey was still batting under some archaic English system of alphabetical authorship. So I said, No, I didn’t want to do that. I wanted to plan my own experiments. And someone said, Oh, no, that’s not possible. “Good day.” So I went to Prince Henry’s.

Chappelle: And what were your responsibilities at Prince Henry’s?

Funder: Oh! I set up a lab, wrote grants, got students, got postdocs, just did the normal sorts of growth things that you do. I also set up--because I'd had these experiences of doing mineralocorticoid and glucocorticoid receptors--studies on them in San Francisco and in Paris for a year--I set up a service to measure estrogen and progesterone receptors in breast cancer specimens as a guide to subsequent treatment by the oncologists, and that's a compensable thing. People can get it off--we have a national health system in Australia, so it doesn't come out of their pockets. Thus, I was able to generate some money, which went into a very good, what was called a special purposes fund. The wonderful thing about that was that it paid for books, journals, but also, if you were prepared to go coach, an immense amount of travel. Some of the senior specialists--contributors to that fund--would only travel first class with their wives; they would exhaust their travel fund in one splurge a year going to London. I used to get about five trips a year out of that fund, which for a young investigator was fantastic in terms of being able to network--largely here, but also in Europe, less actually in the U.K. than in continental Europe, but mainly here and in the States. That was really an immensely important part. I mean Henry Burger, my boss at Prince Henry's, was also part of that. His consulting fees as an endocrinologist went into that fund. That was very important. In the mid-seventies and the eighties when I was at Prince Henry's, the ability to do that--the people who made a lot of money, the clinical chemists, and the images, and so on, put it in. And the people who didn't make very--I actually did all right. But other people who did mostly private patients once a week would put in, and they'd get more than they put in. And the big people--chemists, the pathologists, and so on--they'd take out less than they put in. Those days are gone. It's now everybody for himself, but it was a wonderful way to be able to become international.

Studying aldosterone

Chappelle: What were your overarching research goals when you got there?

Funder: I think it was always to work at--there were enigmas--questions that came up from stuff we did in San Francisco: how does this thing work? How does aldosterone work? It circulates at one *thousandth* the concentration of another hormone, cortisol, which fits equally well into the receptor, into the keyhole. On probability grounds, aldosterone is never going to--what, one time in a thousand--going to get in. So that was really a very important driver of what we were doing. I mean there was a lot of what I'd call bread and butter stuff: you do things; you measure aldosterone and receptors in any tissue you can think of--in any animal you can think of--that gives you your sort of turn of the wheel papers. But [the enigma] that was a driver, and that came through over the next ten, fifteen years. The answers--they are not all in yet--but the answers started to come through. Bits that are now in the textbooks started to come out of the work that students, fellows, postdocs did in the lab. And that was terrific.

So I think it would be--it sounds a bit grandiose--but it would be fair to say that what drove it was wonder, just wonder of how all this worked, how all this fitted together. I think to do science--this sort of science, biological science--without a sense of wonder, it must be like what cats' vision is like: everything is gray. Whereas if you have got a sense of wonder, if you can look at a result coming out of a beta counter or a gamma counter, and say nobody else in the world has ever actually learned this before--oh, that's a big charge, a really big charge. That's lovely.

Chappelle: Would you talk about your discovery of the mineralocorticoid receptors in non-epithelial tissues, and its significance?

Funder: Okay. It's been a long and unfolding, and still incomplete, story. Classically, it was thought [that] there was a hormone, aldosterone, and what it did was maintain sodium balance, and with it potassium went the other way and water came with the sodium. So it was pretty heretical to say, Hey, but they are in the heart, and they are in the brain, and all sorts of places. Then the question came up, what's aldosterone doing there because it goes up in response to sodium deficiency, goes down in response to sodium repletion, but that's not something that--the hippocampus of the brain, which is concerned with affect, cognition, and all sorts of stuff; it's not linked into that in any sort of loop. And I must say that, in many tissues, it's still not clear. In the heart, for example, we've got *very* good evidence of what happens to those receptors--what's driving them *pathophysiologically* in heart failure and high blood pressure, and so on like that. That's not universally agreed on mechanisms, but it's there, and clearly it's happening. And whether it is aldosterone or--in the context of tissue damage--cortisol, which I think there's a lot of evidence for. But the brain is still terra nullius; it's terra incognita. It really doesn't belong to anybody in this domain. Big things are happening in neuroscience--that's not to say that's not the case--and in a host of other tissues. We've really got very little idea what they are doing. In macrophages, white blood cells, there is all sorts of stuff happening around. If you knock them out in macrophages, blood pressure doesn't go up in response to salt and exogenous aldosterone. Hey! What's all this about? So for every answer, there are two more questions. So that wonder really comes good.

Chappelle: When you made that discovery and found those receptors in the heart and in the brain, what did that do to the field?

Funder: Well, the important thing was to show--and we did--that what had been called corticosterone-*preferring* receptors in the brain--distinct from the regular glucocorticoid receptors, were actually identical with the mineralocorticoid receptors in the kidney. So that opened up a field of asking questions: what the hell are these things doing in the brain? And a lot of people have worked on that. I think it's fair to say that there's still more heat than light in answering those questions. A parallel thing--and probably even more of a driver--was

still, how does aldosterone *ever* work--in the *kidney*--where we know it works? I mean the proof of pudding is in the eating; it *works*. That came in the late-eighties with the demonstration in my lab and in Chris Edwards' lab in Edinburgh of an enzyme that protects the receptor--that metabolizes the cortisol to an inactive steroid. In the process, that's probably not enough by itself because of that thousandth of a difference. But it sets the thing intracellularly, so that what cortisol does get into the receptor, can't act. So it makes an aldosterone selective tissue.

Chappelle: Which enzyme?

Funder: It's called 11 beta hydroxysteroid dehydrogenized--11 β -HSD2 is the enzyme. I once wrote an editorial in *Science*, the journal *Science*, entitled, "All Really Great Lies are Half True." We thought we had the answer then, and we only had half the answer. I'm convinced of that. The rest of it is now just starting to come out, gradually being accepted, more or less grudgingly--less grudgingly in Japan than anywhere else. They are doing really a lot of stuff in aldosterone, particularly clinical stuff at the moment.

Chappelle: Would you sum up what you thought you had, or what the field thought it had, at the end of the 1980s?

Funder: End of the 1980s. Well, Ron Evans, who is a friend, a very good friend, had cloned the human mineralocorticoid receptor, and so that was there. He had shown at the molecular biological level that it was expressed in the brain and in the heart and those other non-epithelial places. We thought at the end of the 1990s that, clinically, aldosterone wasn't terribly important; that autonomous aldosterone secretion--that's primary aldosteronism--was maybe one percent, if that, of all hypertension and was pretty benign. And we had drugs that would affect the renin-angiotensin-aldosterone system--ACE inhibitors and the early angiotensin receptor blockers. They were fine in hypertension; they were fine in heart failure. We didn't need much else. It was the lull before the storm.

IV. THE BAKER MEDICAL RESEARCH INSTITUTE (1990-2000)

Chappelle: How did you feel in that lull about your career as a researcher?

Funder: Ah! Well, I could keep on doing stuff; that wasn't the issue. I'd spent much of the nineties trying to run a research institute, the Baker Institute in Melbourne, with a lot of administrative and managerial and fund raising and stuff to do. Some of which I enjoyed, and some of which I didn't. In fact, in 2001, I resigned or retired from there. Being an institute director used to be a life sentence, but increasingly it's not.

Chappelle: How did you get to the Baker?

Funder: I applied to be director and was appointed director in 1989. Oh, you know, because it was up the tree. I was forty-nine, and I thought, Well, this is the way to finish off a career--to be the director of an institute--a well-established--started in 1926--research institute and probably the second biggest of the teaching hospitals. It's the Brigham's and Women's--rather than the Mass General--equivalent in Melbourne, the Alfred Hospital. I did a small amount of stuff [research]. I had some very good Japanese postdocs and some very good technicians while I was at the Baker, but I was really pretty distracted by having to administer. I think I've done more proper thinking and parsing of areas and issues, since not having a fulltime day job. I mean being very, very busy doing a whole bunch of stuff, but not having those responsibilities, not having a lab, not having fellows, not having students--lots of collaborations--than I was in the Baker. I was notionally, at least, the master of all that I surveyed--[but] I didn't have any time to do anything. People had their own programs, and that was terrific in the place. I couldn't tell this one to do this and this one to do that. It might not work like that.

Paradigm shifts: the RALES trial and primary aldosteronism

Chappelle: What was happening to the consensus?

Funder: Well, the consensus was broken. And it was broken in a number of ways in the first decade of this millennium--a little earlier than that, in the last decade.

Chappelle: When?

Funder: I'm talking in the late 1990s, lets say. It was broken in two ways. One was the publication of what is known as the RALES trial, which is the Randomized Aldactone Evaluation Study, and it was to give spironolactone, a mineralocorticoid receptor antagonist, on top of standard of care, to patients who were in New York (Heart Association) Class III heart failure. These are patients who have got about--even with treatment--about two years to live on average. A low dose of spironolactone--the average dose was actually 26 milligrams a day, the smallest tablet is 25 milligrams--on top of standard of care--gave an astonishing thirty percent improvement in survival and thirty-five percent fewer hospitalizations. I mean, Whoa! Thirty-five percent fewer hospitalizations, even the health economists get interested. So that told the cardiologists that something was happening here. Now, they all thought it was aldosterone; I think, increasingly, evidence is not. It is mineralocorticoid receptor activation, but it's activation by another hormone in damaged tissue, whatever. The second paradigm shift--to use that, perhaps, fairly hackneyed phrase--was the demonstration that primary aldosteronism, autonomous aldosterone secretion, was *not* a minor, benign player in elevated blood pressure. I think there is now, around the world, international consensus that it is probably ten percent of all hypertension; that it is much more dangerous than essential hypertension--by studies on age-, sex-, and blood pressure-matched

controls. If you've got primary aldosteronism, you are four times more likely to have a heart attack, up to twelve times more likely to have atrial fibrillation--which you know flicks off things, and you have strokes--it's not a good disease to have. And that made people think. So, in the last decade and a bit, aldosterone has really come sort of back into prominence. It has been enthusiastically adopted by the cardiologists, who before that never even thought about it. There are ten times more cardiologists than endocrinologist in most countries. They tend to be terrific in many ways. I mean if I need a stent, I'm going to go and see a cardiologist. But they are sort of the orthopedic surgeons of medicine; you know, fix it and forget it, "bum, bum, bum." And they work on the principle that if a little bit is good, a lot will be better--many of them. It's not been necessarily totally plain sailing since then, given that this large group--of sort of half--accepted that it's probably good to use a mineralocorticoid receptor antagonist in heart failure.

Chappelle: So the RALES trial--how did it cause the consensus to be realigned or was it just a temporary--

Funder: No, no, no. It's not been temporary at all. It's been followed by two other trials, one called EPHEsus [Eplerenone Post-acute myocardial infarction Heart failure Efficacy and SURvival Study] which is using--what RALES did was to say, Hey, we need a new mineralocorticoid receptor antagonist. Spironolactone was patented more than fifty years ago, and it's a very effective drug with nasty side effects. In addition to being a mineralocorticoid receptor antagonist, it's an androgen receptor antagonist, so if you antagonize androgens you get erectile dysfunction--can get--and gynecomastia, which is enlargement of the male breast. It's also a progesterone mimic, so that in women who are cycling, it throws their cycles off. It's a dirty drug. That sparked the industry, in particular G. D. Searle, which was then taken over [by an other company and then another, et cetera] to develop a second-generation antagonist, which is called eplerenone. They did, and then there have been trials with eplerenone--EMPHASIS--you *never* put eplerenone head to head with spironolactone. Spironolactone is better except it's got those dreadful side effects. So they did it in heart failure post-myocardial infarction. And it was good; it worked. It improved survival and with fewer hospitalizations. More recently, it's been done in New York (Heart Association) Class II heart failure, a trial called EMPHASIS. Again, it's been shown to be very useful. It's been constantly shown--*in* the province of the cardiologists, which is heart failure. It's not that they set out to deny anybody else. The point is that outcomes are easy, relatively: people die or don't die, and you can compare curves diverging in terms of mortality--body bags. The big use for these drugs, clearly, is not in heart failure, but in high blood pressure--people in their forties and fifties and sixties with high blood pressure. I have turned into rather a crusader for putting in low dose spironolactone or eplerenone into first-up treatment. Somebody comes in with high blood pressure, make sure it's not white coat hypertension, or that they are nervous, and so on. Okay. They've got hypertension; put them

on an ACE inhibitor and very low dose spironolactone, very protective of blood vessels. Nine hundred and ninety nine people with primary aldosteronism never get screened, let alone diagnosed, let alone treated. And it's magic for them, and so on. So I've turned into a crusader for that.

[Interruption]

Chappelle: Would you say a little bit more about the RALES trial and the initial hypothesis that was based on it?

Funder: The initial hypothesis was that--it was based on animal studies--that if you gave aldosterone in excess to animals--and you needed to give them a bit more salt as well--they got high blood pressure and their hearts got bigger and, ultimately, they went into heart failure. On the basis of that trial, RALES was set up in patients with heart failure, progressive severe heart failure: half of them dead in under two years or under three years. And the results of the RALES trial were fantastic, thirty percent improvement in mortality survival, better survival, and thirty-five percent fewer hospitalizations. It's wonderful. There are two enigmas: the first is that the dose of spironolactone added to conventional therapy that caused this wonderful result was very low. The average dose was 26 milligrams a day and the smallest tablet 25 milligrams. And the second thing is [that] the aldosterone levels were low-normal, and if it's blocking aldosterone, what's happening here? And there is nothing abnormal about the sodium--that was all fine. And that proved important in the next--almost ten years--dissecting just what's happening here. The second of those, which is, how can this happen when aldosterone levels are low-normal? I think it's now accepted that in the context of tissue damage and, of course, that's part of heart failure--the cardiomyocytes, the muscle is under a lot of stress. Those mineralocorticoid receptors in the heart muscle cells would be filled with cortisol and somehow--we don't know the mechanism; we can make suggestions--somehow under *those* conditions, cortisol mimics aldosterone: you get the same sort of effect as you got experimentally with rats and so on when you gave them lots of aldosterone. I think that's pretty well accepted. What's been longer coming is an answer to the question of, why was such a low dose of aldosterone effective--I'm sorry--why was such a low dose of *spironolactone* effective?

[Interruption]

And the answer to that question--why was such a low dose of *spironolactone* effective seems to have come from studies--again, on rats--on an isolated rat heart preparation. It's called a Langendorff beating rat heart--it looks awful, hanging down, blood going through. And if you tie off one of the big coronary arteries, the rat has a heart attack. You tie it off for half an hour, and then let it reperfuse with the saline-buffered solution, and you get an area of a myocardial infarct of dead tissue, and where the cells are undergoing apoptosis, they die.

Other people have shown that if you put aldosterone into the perfusing fluid the infarct got bigger and the apoptosis got more pronounced, and you could block that with spironolactone. We showed that if you put cortisol in at very low doses exactly the same thing happened: the infarct got bigger. So that supports the interpretation that, Hey, in the RALES trial, it's cortisol or aldosterone, and you could block that with spironolactone. And then just to be sort of ultra careful, we took hearts and just put in spironolactone. What happened then was the infarcts got smaller, and the apoptosis got less. So the spironolactone was having an effect *on its own*--of its own accord. We thought, Maybe there's some aldosterone or glucocorticoids hanging around. So we adrenalectomized animals--took out their adrenal glands, the source of all this--and a week later, did it again. Spironolactone is *protective* by doing things in its own right. At the meeting here in Boston [The annual meeting of the Endocrine Society was held at the Boston Convention and Exhibition Center in June of 2011], it's the beginnings of unraveling that that are going to be presented, and were presented yesterday at the aldosterone meeting [The Aldosterone Conference meeting was also held in Boston in June of 2011]. And it's wonderful because what spironolactone does is to induce the synthesis of protective proteins and repress the synthesis of pro-apoptotic proteins. The pharmacologists call that an inverse agonist. It's actually doing stuff. It's not just sitting there like the key to the *trunk* of the car in the *ignition*; it's doing stuff of its own accord. And it does it at very low concentrations, experimentally. If we extrapolate that to the clinic, we can say that is maybe why you only needed 26 milligrams of spironolactone to get that effect. Because it doesn't have to block out every last molecule--just has to get a few of its own in, and then, Hey! Suddenly it's changing the balance. So that's been wonderful. Now, that's yet really to--it's only I think ____ (??). It's a bit like turning around the Queen Mary. And there needs to be a lot more studies. I mean it's an *initial* study. But it's unequivocal what it tells us, which is spironolactone isn't just a *blocker*, it's doing stuff of its own accord, which is very protective. So RALES has been--I think probably a good word is "prismatic." It's actually sort of opened up a white light into a series of different spectra and allowed us to ask different questions. It's been good.

V. PRINCE HENRY'S INSTITUTE OF MEDICAL RESEARCH (2001-present)

Chappelle: Why did you leave the Baker Institute?

Funder: Oh, I left the Baker Institute because--

Chappelle: This is in 2001?

Funder: End of 2001. Well, a number of reasons. My wife died in the middle of 1998, and that was really hard time, very hard time. I'd been there since 1990. And I think it was probably just time to go. I'm not a very good manager. I hate taking file notes--when people come and see me--in case, you know, something

happens and lawyers get involved, all that. I mean that really drives me mad. I was sixty-one at the end of that year, and I thought, Well, I'll do some other stuff. So I did. I decided in about twenty-four hours. I thought, Oh, I'll pack it--you know, I'll get a life. It's no great fun, often, for some people--I think it was for me and I know other people who have been in the same situation--to spend probably forty or fifty hours a week administering when what you really want to be doing is thinking and testing and wondering and writing. I quite like writing and sending stuff off and talking about it, and so on. And I've done that much more since I've been not having had a day job. I've actually been busier in many senses, but I can choose what I want to do. It's wonderful.

Chappelle: So you're based at Prince Henry's. You left the Baker for Prince Henry's?

Funder: Well, I'd been at Prince Henry's until I went to the Baker. Prince Henry's moved and then as soon as I left the Baker, various ones said, Will you come to Prince Henry's? Will you come to Melbourne University, and so on.

Chappelle: But you don't consider that a day job?

Funder: Well, no. It is a day-job but it's not an 8:00 till 6:00, five days a week, day-job. It's not a consuming day-job. I can choose what to do, whom to collaborate with, where to go. I've still had a number of jobs since then, but none of them have been fulltime. I was director of research strategy at the hospital for two and a half years, which was not terribly successful because the powers that be in the hospital are research naïve and ignorant, I mean that's not true of all hospitals in Melbourne, but this one: never mind the quality, just feel--hopeless, absolutely hopeless. Talk about turning around the Queen Mary; this is like turning around the Titanic. So I finished that at the end of 2010. I've now got--notionally one day a week--and well paid for one day a week--a job as executive director of *Obesity Australia*--on the basis that I think that it takes one to know one. That's actually terrific. It's a very interesting area. You know the tsunami of obesity that's hit America, Australia, and so on in the last twenty-five years: multifactorial--everybody thinks it's the fault of the obese person. In many instances, that is not necessarily the case because there is now wonderful evidence for preconception, intrauterine, and early life programming of set points of hunger and satiety and particular tastes for foods in the early post-weaning life. But there is a lot of high-energy dense foods, and people are doing sedentary jobs rather than working in steel mills, et cetera, et cetera, et cetera. So, very complex: it needs to be addressed both globally here in America and in developing countries. In China and Shanghai, there are a lot of very obese people, almost half of whom will develop diabetes, perhaps more in Shanghai than in America or Australia; it's probably closer to forty percent. But even apart from the diabetes, the lost productivity, the medical costs are going to be crippling. We've got to do something about it. And the administrators--at least in my country--know about this and are worried stiff about this. The politicians are very short term--so next electoral cycle. At least

the Australias--a lot of people are not necessarily invested in it. They are not diabetic carer's, or they are not scientists working there--a lot of sort of high profile people, who have come together, and have been animated by this. And it's a wonderful thing to do when you're getting old and gray. And it's a source of constant wonder: How are we going to juggle all this? How are we going to do it?

Medical Research Politics

Chappelle: You mentioned politics, research representation--

Funder: Oh, okay.

Chappelle: I would like you to get a chance to talk about that.

Funder: I don't know where it began really. I was a keen debater at school. I won the Victorian impromptu speech in my last year of high school, which is not a great accomplishment, but I was a university debater--college, university in the varsity, in fact, some international debates, too. So that was one thing. But in residential college I was in at Melbourne, I was on what was called the "general committee," the student body and then was elected president of the student body. And I was on the student representative council as a *freshman* at the university. I mean, "Woo, boo, go." What is this? And I liked doing stuff--writing stuff--for the student newspaper, and so on. And that continued. When I was a PhD student, I used to write opinion pieces for one of the local sort of semi-intellectual journals--monthlies. I was also the wine correspondent, slightly after that, for a fairly scabrous--a bit like the *Berkeley Barb*--scabrous weekly. I guess I got really into medical research politics--we had a crisis in funding in 1976. I mean the figures are now ludicrous. There had been a glitch in the budget allocations or something, and we were suddenly faced with 850,000 dollars to fund six months of the medical research being done in Australia. It wasn't very well funded, and that's thirty-five years ago, but, Hang about. That's not very much money. So four of us--John Coghlan, who had been my mentor at the Florey; John Chalmers who is a wonderful charismatic, spiky, cardiovascular physician; Tony Basten, who is an immunologist--the four of us became known as "the Melbourne mafia," even though John Chalmers was in Adelaide and Tony Basten was in Sydney. And we use to go up to Canberra and talk to politicians. Back then they weren't all the spin-doctors and the minders and the barriers, and God knows what. So we got that turned around, and from that stemmed a continuing interest in medical politics. I was president of the Australian Society of Medical Research in 1979--which was the young Turks--you had to be under forty to hold office, and you had to write a one pager to go in the annual meeting thing about what you thought about stuff. I wrote this thing called "All Really Great Lies are Half True," which is being asked for evidenced-based outcomes of what your research *would* do--I mean you couldn't know until you got the results of the

research--it was sort of crazy. And I was so pleased with this I thought, I'll send that off to *Science*. So I did. And for the first time in my life, I got back the galley proofs as acknowledgement; it was wonderful. It's called "All Really Great Lies are Half True," and I wouldn't change a word of it, now, I think.

VI. THE ENDOCRINE SOCIETY

Funder: I was on the council of the Australian Endocrine Society and then was president, and became more and more involved in the affairs of the Endocrine Society--our Endocrine Society, the one in Washington--and was on journal editorial boards, but then particularly on the working groups, and then the committee to deal with international things, and was immensely honored to be the first non-North American to be elected to the council of the Society in 2002. And I regard this society as my intellectual home. It's got fantastic--"collegiality" is the word. Scott Hunt, who I think is terrific, uses the word--the word of approbation he uses of the Society is "nimble." And that's true: I think it is in many ways--occasionally lumbers, but it's usually nimble. But it's somewhere where, from the practitioners to the physician-scientist to the basic scientists working in the lab--even though there have been tensions in the past--it's a totally collegial, wonderful group of people. These are my peers; these are my friends. Walking around this morning in the hall in Boston, I've seen and greeted a hundred people. And most of the people under fifty I don't know, for heaven's sake. You know these are the old stages. It's an extraordinary organization. I've never been in an organization--except perhaps those early days in the Australian Society for Medical Research when we were going up to Canberra, knocking on doors, and taking the treasurer--*the treasurer of Australia*--to dinner, just him and me. And he said, "Why are we here, John?" I said, "I need your help. I need you to tell me who I should contact to make sure we don't have another fiasco in the budget." "Oh," he said, "that's easy. Start writing down the names." Of course, I've *got* him. And in the archives of the Australian Society of Medical Research--this is after this 1976 nonsense a couple of years before--there is a telegram--this is before, when telegrams were still in: "Dear John, medical research budget has gone from fourteen million to eighteen million dollars. Now are you happy? Phillip." It was Phillip Lynch, the commonwealth treasurer. I telegrammed back, "Phillip, happy, yes; satisfied never, John." That's been lost, that part. So it's been a long involvement in medical politics. In fact, this *Obesity Australia* thing I was speaking about, that's essentially political. I mean we need to change community attitudes, which will allow our politicians to do stuff, which they need to do. And we have to change community attitudes on the basis of the best evidence there is, the best wisdom there is. So it's really a political organization that I'm chairing, in fact, executive chairing, I wish there were a CEO, but we can't afford one yet, but we'll get one.

Endocrine Society Guidelines for Primary Aldosteronism

Chappelle: Would you talk about the Endocrine Society's Guidelines for Primary Aldosteronism?

Funder: This has been interesting because--

Chappelle: Would you explain your role in getting the guidelines started?

Funder: It was terrific because--I'm an aldosterone physiologist--I'm a rat doctor, really. I do stuff with rats and mice and sheep--historically--and so on. It's been a long time since I've seen patients. But the vagaries of treatment, of the way people handle patients with primary aldosteronism, it seemed to me right that--we needed to try and get a little bit of consensus into this--not to shoehorn people into [following a cookbook]. So we set a council meeting in Sonoma, of all places. Each winter in January, there is a meeting of council and committee chairs. And I proposed this--I think to the then chair of the clinical guidelines committee, Bob Utiger. He said, "We've got a full dance card for next year, but I'll see what the committee thinks." And the committee says, "We ought to do that; the time is right."

Chappelle: And which committee is this?

Funder: There is an overarching committee within the Endocrine Society called, I think, the Clinical Guidelines Committee. What I was then chair of was the particular task force to develop clinical guidelines for case detection, diagnosis, and management of primary aldosteronism. Money was tight--it's always tight--so we could only have six people on that task force. I wanted it to be international. Two of the outstanding people are Bill Young at Mayo Clinic, who is the incoming president of the Society, which is terrific, and Michael Stowasser from Brisbane. So there were *two Australians* on it; I mean this is mad.

[Interruption]

Chappelle: Who else was on the committee?

Funder: Carlos Fardella from Chile, Franco Mantero from Italy--from Padua, Celso Gomez-Sanchez from Mississippi: and that was our compliment, except I managed to persuade the powers-that-be that we should add Bob Carey. Bob Carey was then the president of the Council of High Blood Pressure Research, deep in the toils of the political machinations of American Heart Association, and was incoming president of the Endocrine Society, so he was the bridge man. So we worked for a couple of years--teleconferences, e-mails back and forth, a couple of face-to-face meetings--developing, thrashing out a consensus. I mean [regarding the consensus] it's not what all those people do necessarily--they do variations--but, in a sense, guidelines. I'm the person with

far the least experience--hands on experience--in that process. I learned a lot from those people. And now that I've been able to stand back a bit and say, "But we are missing the wood for the trees." If ten percent of the people with high blood pressure have got primary aldosteronism--if you take America, twenty percent of the people in America have got high blood pressure, so two percent of the American population--we're talking six and a half million people. In Dallas/Fort Worth--which means six and a half million *patients*--they've done 250 operations for primary aldosteronism in the last ten years. We are *missing* the wood for the trees. I have no personal investment--in a sense--in it, but I've become a crusader for looking at hypertension differently because we are missing all the people with primary aldosteronism. The guidelines, I think, have been useful. They are work in progress; they have to be. They are not set in concrete. Already there have been things that people--I have edited a journal volume, *Quarterly Reviews in Endocrinology and Metabolic Disease* with a whole lot of people who weren't on that committee. There was nobody from Japan, which is now really the epicenter of studies here. So I have two Japanese and Germans, and so on. It's a work in progress.

VII. CURRENT VIEWS ON ENDOCRINOLOGY

Chappelle: What are your current views of the field?

Funder: Well, there are always beaut(??) new things to do. I was privileged to review a very good paper in *Science*, which is published in *Science* in January. And I was then asked to write an editorial commentary about it, showing that [in] about thirty-five, forty percent of primary aldosteronism there is these little benign tumors, adenomas--they don't metastasize and they don't spread--they can cause a lot of trouble. They are due to a mutation, a particular potassium channel, KCNJ5. I wrote the commentary and pointed out that there were things that would flow from this and so on, and so on, and so on. At the current meeting of the Endocrine Society and at the meeting of the Aldosterone Conference that just precedes the Endocrine Society, there are papers describing a total, I think, of about eight hundred of these tumors, showing the same sorts of proportions. Two papers have been submitted to a journal, from two different groups, studies from all over the world. I mean this is heady, heady stuff. The most recent paper I've published in collaboration with a spectacular postdoc called Karin Kassahn from Brisbane--where I have an honorary appointment--is I think probably the definitive work on the evolution of the mineralocorticoid receptor. Nothing is definitive in evolution, really, because we weren't there, but there's been a back and forth about which is the oldest of the family members of the four closely related mineralocorticoid receptor, glucocorticoid receptor, androgen receptor, progesterone receptor? The argument has gone back and forth, but I think we've nailed it. "Plunk." Which is good fun. I think aldosterone is here to stay. I think the mineralocorticoid receptor has still got a lot of things that we need to find out about it. We're really not terribly across what it does in the brain. We don't

know if it has a physiology--as opposed to a pathophysiology--for instance in the heart. We don't know what it's doing in your healthy heart or hopefully my healthy heart. We *do* know what that receptor is doing and how we can ameliorate what it does in heart failure or in high blood pressure. So there's a lot of stuff to do there. Aldosterone itself, probably less, because the drivers to aldosterone secretion--the main ones--tend to be changes in sodium and potassium, which is what it affects in the kidney, and changes in intravascular volume--if you lose a lot of blood you really need to hang on to water and sodium to bring back your blood volume. That physiology is well ensconced, well accepted. Everybody knows that; there is no question about that. So I think aldosterone is here to stay. The future is with the mineralocorticoid receptor and what else it sees and what else it listens to and where that happens and what that means. And if there is no physiology, what's the *pathophysiology*? I mean why have we got it to make things worse in heart failure? Why is the receptor in the heart muscle if it doesn't have a normal role? Well, it probably *does* have a normal role. [In] evolution you tend to get rid of things that you don't really need. I'm not sure why we need sinuses or vermiform appendix but the C-peptide that joins the two active bits of an insulin molecule has got ten times more mutations in it than the insulin itself, because it's important that that insulin stays as insulin, it doesn't matter what happens to the belt as it's read off--holds them together. Stuff like that. So the receptor will see me out. [laughs]

Chappelle: Thank you.

[End of Interview]

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Interview History—John W. Funder, MD, PhD

Dr. Funder was interviewed by Michael Chappelle on June 4, 2011, during the Endocrine Society's Annual Meeting held at the Boston Convention and Exhibition Center in Boston, MA. The interview took place in a conference room at the Westin Hotel and lasted sixty-eight minutes. The transcript was audit-edited by Mr. Chappelle and reviewed by Dr. Funder 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.