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10 lessons learned by a misguided physician

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Abstract

It was a great and humbling honor to receive the 2016 Distinguished Career Award from my SSIB colleagues. This paper summarizes the major points of my DCA talk at the 2016 annual meeting. It is a reflection on my 50 year medical and research career and 10 lessons I have learned over those years which might be of help to young investigators near the beginning of their own research careers. These lessons include: the value of being receptive to the opportunities provided you; how clinician-scientists can serve as critical role models for young investigators like me and a history of how my career developed as a result of their influence; the importance of carefully examining your own data, particularly when it doesn't agree with your preconceived ideas; the critical role that students, postdocs and PhD (and even veterinarian) colleagues can play in developing one's career; the likelihood that your career path will have many interesting twists and turns determined by changes in your own scientific interests and how rewarding various areas of research focus are to you; the importance of building a close-knit laboratory staff family; the fact that science and romance can mix. Finally, I offer 3 somewhat self-evident free pieces of advice for building and maintaining a rewarding career.

Keywords

diet-induced obesity; metabolic sensing neurons; diabetes; energy homeostasis; glucose homeostasis; neural development; gene-environment interactions

Introduction

Little did I realize when I first approached two new faculty members in the Pathology Department at Emory University School of Medicine with the “crazy idea” that they sponsor me to do some extracurricular research, that it would lead to a life-long passion and an actual career. Not only wasn't I quite sure why I had chosen medicine as a career path, but I had no idea why the thought of doing research sounded so interesting to me. Maybe it was that Experimental Psych class I took as an undergraduate at Emory. I certainly had had no other exposure to anything remotely “experimental” prior to that time. Although that research project (trying to create a new Goldblatt kidney model to study renal hypertension)

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fell squarely on its face, it somehow cemented in me a passion for asking and trying to answer interesting questions about how the body works. In those days, the term “molecular biology” even didn’t exist. The closest we came in our medical training was learning about Mendel and his peas. However, what medical school and my career in medicine did teach me was systems biology and physiology. After a long career in medicine and research, I still consider myself to be primarily a whole animal physiologist who happens to focus on the brain as my organ of interest. My attraction to research has always been because it was fun and never in my wildest dreams did I expect that it would lead to the incredible honor of receiving the SSIB Distinguished Career Award (DCA). Nothing means more to a scientist, and to me, than being recognized by their peers for their contributions, no matter how small, to the ever growing body of scientific knowledge. This award is truly a great highlight of my career. Preparing to give the DCA lecture at the 2016 annual SSIB meeting led me to reflect back over my years as a physician and scientist and prompted me to think about some of the guiding principles and lessons that I have learned. I have distilled these down into 10 lessons and a few truisms that I will relate here.

Lesson 1: Diligence is the mother of good luck, Anon, late 16th century; my adaptation: Luck helps if you’re receptive to what it brings you

This is probably the most important of all my lessons. To paraphrase, the harder I worked, the luckier I got. That “work” is as much mental as physical and includes recognizing where your talents lie and what your weaknesses are. My “talents” tend to be as an intellectual counterpuncher. I’m more a synthesizer of the works and ideas of others than as someone who comes up with totally new and original ideas. So, reading and discussing science with my peers, students and postdocs has been the stimulus for the hard work and subsequent good luck that allowed me to carry out the research of my choice. But, in the end, it really didn’t seem like hard work. I can truly say that I looked forward every day to going to my laboratory with the chance that I would discover something novel, something never before seen in the world of science. We are incredibly lucky to have the opportunity to contribute to such findings, even if they aren’t necessarily earth shaking.

Lesson 2: Clinical medicine is fun, but research is even more fun and Lesson 3: You can be a good scientist even if you’re only a “lowly” MD

When I was in the throes of medical training, my role models were all MDs who carried out basic and clinical research. Many also were excellent clinicians. In those days, it was unusual for such physician-scientists to obtain a PhD. In fact, all of my early mentors were MDs who carried out research but had no PhD. Despite the fact that medical training emphasizes memorization of facts and clinical algorithms, my heroes had somehow overcome that mind-numbing approach and had learned to think about hypothesis-driven ways to ask and answer questions about the basic functions of the body and brain. My first exposure to such an individual came when I was an intern in Internal Medicine at Cornell Affiliated Hospitals on a 1 month rotation through Neurology, a field for which I had a strong attraction. My ward attending was none other than Paul McHugh, MD, a then young physician who was doubly boarded in Neurology and Psychiatry. His endless enthusiasm and sheer joy in seeing patients with neurologic problems cemented my desire to become a neurologist. Before that month was out, I applied to, and was accepted into, the Cornell

Neurology residency program. Only later, during that residency, would I meet Paul again, this time as an exceptional clinical psychiatrist and a skilled clinical researcher. Paul would later receive the 2009 SSIB DCA.

During the next year, as a first year resident in Internal Medicine, I approached the department chair about doing a research project. Even though I was already signed up to start a Neurology residency the next year, the only place he could find for me to work was in the laboratory of Jules Hirsch, MD, the chief of the Rockefeller University Hospital. At that time, Jules was already established as one of the leaders in the emerging field of obesity research. My job was to tend to the medical needs of his 300–400 pound patients who were admitted to his service for 6 months on a 600 kcal/day starvation weight loss regimen. In fact, I was given no defined research project. But, as luck would have it, his laboratory was populated with nascent scientists like Judy Stern, Marci Greenwood and Joel Grinker who would go on to become major players in the field of obesity research and would be my entrée to that field later in my career. That rotation in Jules' lab also led to co-authorship on my first clinical research paper which focused on the affective responses of our obese patients during their six month weight loss ordeal [1].

After 2 years in Internal Medicine, I began a 3 year neurology residency where I rotated through New York Hospital and Memorial Sloan Kettering Cancer Hospital. During this residency, Donald Reis, MD, a neurologist who carried out research on hypertension and the role of the brain in regulating blood pressure, gave us several lectures on the biochemistry and pharmacology of monoamines. It was through these lectures that I developed a life-long passion for these critical little molecules that would become a major focus of my research. Through Don, I was introduced to Gerard Smith, MD who ran the Bourne Laboratory at the White Plains division of New York Hospital. In those days, we neurology residents were allowed 4 months of research and I was lucky enough to have Gerry accept me into his lab. Gerry, another MD without a PhD, and the 2004 SSIB DCA awardee, was already a leader in the study of ingestive behavior. Jim Gibbs (another MD scientist who was also a DCA awardee), Paul McHugh and Tim Moran (then a research assistant) all worked in the lab at that time. At the time I joined the lab, Gerry had developed an interest in the role of ascending dopamine pathways as mediators of ingestive behavior. From Gerry I learned to do stereotaxic surgery and behavioral assessment of rats and how to think “scientifically”. Those 4 months resulted in my first platform presentation at the American Academy of Neurology and my first basic research publication [2].

Also during my neurology residency, I was exposed to another extraordinary clinician-scientist, Jerome B. Posner, MD. Jerry was then a young neurologist who was head of the Neurology Service at Memorial Hospital. No matter how early in the morning I arrived, Jerry was already in his office ... 5AM was his usual starting time. He used that time well and it was through him that I acquired most of my clinical neurology skills. He had an encyclopedic knowledge of the neurological and medical literature and could apply that knowledge and we residents were the lucky recipients of his imparted wisdom. There were times when I spent hours going over a patient's history and physical and was still confused about what was going on, only to have Jerry spend 5 minutes at the bedside to localize the patient's lesion, make a diagnosis and formulate a treatment plan. But Jerry was much more

than a skilled clinician. Over the ensuing years he became one of the founding fathers of the field of paraneoplastic diseases of the nervous system. He was the first to identify antibodies that appeared to cross react with various tumors and specific cells in the brain to cause devastating disabilities [3]. Over his long career, Jerry was a role model as a superb clinician, teacher and scientist for many of us who rotated through the Cornell Neurology residency program. He was the ultimate example of what was known as the “triple threat” physician; one who could move effortlessly from bedside patient care and teaching of residents and students to clinical research.

After finishing my neurology residency, I was lucky enough to be selected as a Clinical Associate in the neuromuscular program at the National Institute of Neurologic Diseases and Stroke. This was the Vietnam era and, since these NIH appointments were under the Public Health Service and kept us out of the military, we were known as the “Yellow Berets”. I had one obligatory, but rewarding year of clinical service taking care of neuromuscular patients. But the second year was all mine to do with as I pleased, as long as it had a research focus. Stimulated by Reis and Smith, I was able to pursue my interest in brain catecholamines. Again, I was lucky enough to come in contact with 3 contemporaries, MD Clinical Associates in the laboratories of the prominent catecholamine pharmacologists, Irving J. Kopin, MD and the Nobel Laureate, Julius Axelrod, PhD. These colleagues helped me set up my own laboratory and learn, through trial and error, how to purify 1mg of dopamine- β -hydroxylase from 50 cow adrenal glands and then make antibodies in rabbits to use for immunocytochemistry studies, a field which was then in its infancy. Without going into details, this endeavor was the real beginning of my basic research career even though I never did get to publish any results using those precious antibodies. Together with my clinical training, my early research results helped me obtain my first academic position as an Assistant Professor of Neurology at Dartmouth Medical School and as the neurologist at the White River Junction Vermont VA Medical Center. It was the \$15,000 of VA funding for new physicians that allowed me to set up a small lab, hire a technician (at slave wages!) and begin my research career. None of this would have happened had it not been for the long list of MD-scientists who stimulated my interest in research and encouraged me along the way. Although I love clinical neurology, and continue my clinical practice after having closed my research lab, it is basic research that has truly sustained and nourished me throughout my career.

Lesson 4: Go where your data lead you

My clinical duties were quite heavy at Dartmouth and left me little time for my research. When I was offered an Associate Professor position at New Jersey Medical School and the East Orange VA Medical Center which provided me with protected time to do my research, I eagerly accepted. My VA-sponsored research involved axonal transport of catecholamines in the brain [4], the role of norepinephrine in mediating the plasticity in the somatosensory cortex [5], traumatic brain injury [6] and brain transplantation [7]. But it was my interest in autonomic nervous system function that first drew me into the field of neural regulation of body weight in obesity. Through Judy Stern, who I first met in Jules Hirsch’s lab at Rockefeller, I met Ann Sullivan, PhD who was then head of the nascent obesity program at Hoffmann-La Roche Pharmaceuticals. Ann was using the early colonies of Zucker fatty rats

from Marci Greenwood and Pat Johnson's lab at Vassar. Little was known about these rats except that they ate voraciously, became massively obese and had a severe cold intolerance. Much later, after leptin's discovery, they were found to have a defect in their leptin receptor function which underlay most of these abnormalities [8]. But it was the cold-induced hypothermia that first piqued my interest since I knew that thermogenesis required sympathetic nervous system activation and I had developed assays for norepinephrine and its synthetic enzymes to study sympathetic function in humans and rats. So, I set about examining brain catecholamine metabolism and peripheral sympathetic function in the rats in the Roche Zucker colony and found that both were markedly abnormal [9–12]. During those years, brown adipose tissue as a major producer of thermogenesis was a major focus of research in obesity. We found that Zucker rats had markedly abnormal brown adipose sympathetic activity, structure and function [13, 14]. But there were no known obese human homologues of the Zucker pathology at that time so Ann's group developed one of the first models of diet-induced obesity (DIO) using a defined moderate fat diet (as opposed to the cafeteria diet of Tony Sclafani [15]) in outbred Sprague-Dawley rats as a better model for human obesity. Given the sympathetic abnormalities in the Zucker rat, we began to examine sympathetic activity and brown adipose function in the DIO model. However, there was a problem. No matter how careful I was, there was always a huge variance in almost all outcome variables in these animals. This included a wide spread of body weight gain on a moderate fat diet. It was after assessing several hundred of these rats that I finally looked at my cumulative data. It became obvious that the variability I was seeing was due to the fact that there were two groups of weight gainers on that moderate fat diet among these outbred rats; about half overate and developed and maintained DIO while the other half were diet-resistant (DR). Sympathetic activity in several organs reflected this dichotomy [16, 17].). While most investigators assessed animals and humans who were already obese, I felt it was more important to be able to determine those factors that predisposed an individual to become obese. Thus, I developed methods to prospectively predict which of the outbred rats would become DIO and DR before they were exposed to a high calorie diet [18, 19]. But these methods were cumbersome and, after several years of trying to get someone else to do it, I finally bit the bullet and, together with my colleagues, selectively bred the highest and lowest weight gainers on our "high energy", 32% fat, 25% sucrose diet to develop separate strains of DIO and DR rats [20]. Having gone where my data led me, the selectively bred DIO/DR model became the basis for most of my research studies and much of my NIH funding over the rest of my career. Had I not looked at my data carefully, it is likely that I would never have pursued this avenue of research.

Lessons 5: Even PhDs can teach you something, and Lesson 6: Your students, postdocs and scientific colleagues are the lifeblood of your career; treasure them-you never know where these associations will lead you

Although most of my early research heroes and role models were MDs who had never undergone the rigors of PhD training, the remainder of my career has been influenced largely by PhD students, postdocs and colleagues. These scientists have become my friends and, in many cases, long-time collaborators. To mention a few:

Stephen C. Woods, PhD: Steve is known to all of us who study ingestive behavior and the regulation of energy homeostasis. He was the 2012 SSIB DCA awardee. As a VA employee, I was allowed only one 5 month sabbatical during my career. Steve, then in the Psychology Department at the University of Washington, was kind enough to be my sponsor and to actually give me his office to work in (he was then a Dean). During my time at UW, I spent many hours talking science and life, eating good food and drinking even better wine with Steve. Before coming to UW, I had been familiar with his and Dan Porte's (another MD scientist) writings on autonomic control of the pancreas. But, over the course of my 5 months in his lab, I developed an abiding respect for the depth of Steve's knowledge and way of thinking about scientific issues. He remains one of my scientific heroes and, several years later, we even co-authored a paper together [21].

Ambrose A. Dunn-Meynell, PhD entered my lab as a postdoc in 1990 and stayed on to become my partner in (scientific) crime for the rest of my research career. While I have been the "front man" for presentation of many of our research findings at meetings, Ambrose was the real mover of all technical aspects of our lab. He is a master of research techniques and educated himself in molecular, biochemical and surgical procedures which became the backbone of our joint scientific endeavors. My research success is inextricably linked to him in all our ventures into the various scientific efforts we have undertaken over the years. Without him, it is likely that I would never have been awarded the SSIB DCA [6, 22–26].

Vanessa H. Routh, PhD joined my lab as a postdoc with an interest in learning to do patch clamp electrophysiology. Having no experience of my own in this field, I placed her in a colleague's lab at New Jersey Medical School and was also able to send her for some advanced training in the lab of Michael Ashford in Scotland. Vanessa's interest was, and continues to be, in hypothalamic neurons that "sense" glucose by altering their firing rate as ambient brain glucose levels rise and fall. Based on her careful studies, we were the first to emphasize the need to assess such neurons in vitro at the glucose levels to which they were exposed in vivo, i.e. 10–25% of blood levels [27]. We also first coined the terms "glucose-excited" and "glucose-inhibited" to describe those neurons which were activated and inhibited at high glucose levels, respectively [27]. Vanessa obtained a faculty position at NJ Med School where she has risen through the ranks to become a Professor. She is a pioneer in the study of these glucosensing neurons, especially glucose-inhibited neurons and the mechanisms by which they sense glucose and their effects on physiologic functions in the behaving animal [27, 28].

Ling Kang, PhD did a research rotation during her first year as a PhD student in our Department of Neurology and Neuroscience graduate program and decided to stay to complete her PhD studies. A native Chinese speaker, Ling struggled at first with both the language barrier and her mentor's strict and sometimes overly "direct" ways of "guiding" her in her studies. After several hysterical crying bouts, she learned to live with this new, frightening environment and we settled into an easy working relationship. Ling became incredibly productive over the course of her PhD studies and an additional year as a postdoc in my lab. She "wrote the book" on the characteristics of glucose-excited neurons with regard to glucokinase as a rate-limiting step in glucosensing and the many transporters and receptors expressed in these neurons using single cell PCR [29, 30].

Nicole M. Sanders, PhD—Several years ago, as I wandered through the thousands of posters at a Society for Neuroscience meeting, I met Nicole who was a first year graduate student of Sue Ritter's. Nicole had used her insatiable curiosity to ferret out a little known (to most neuroscientists and this neurologist) phenomenon known as hypoglycemia-associated autonomic failure. In her typical single-minded way, Nicole had developed a research project based on this fascinating phenomenon, i.e. repeated bouts of hypoglycemia blunt both the awareness of, and the sympathoadrenal, glucagon and glucocorticoid responses to subsequent hypoglycemic bouts [31–33]. This is a major clinical problem for insulin-dependent diabetics since it leads to episodes of hypoglycemic coma and death in a substantial number of individuals [34]. It was my good fortune to lure Nicole to my lab for a 3 year stint, leaving behind her husband at Washington State University to finish his veterinary neurology residency. Over this stimulating 3 year period, we had many discussions and amiable arguments that greatly advanced my understanding of this research area and launched me into this field which would provide me with a great deal of fun, intellectual stimulation and an additional source of long-time NIH funding [25, 35–39].

Christophe Magnan, PhD came to my lab to do a sabbatical from his position at the Universite Paris VII. His interest was in lipo-gluco-toxicity and he had a deep knowledge and long experience with the effects of lipids on brain function. It was through the many hours of discussions and side trips to jazz clubs with him that I developed my nascent interest in neuronal fatty acid sensing. This initial visit led to a long-standing collaboration which has resulted in several publications [40–42]. He was also responsible for my introduction to a young French PhD student, Christelle Le Foll, who would soon become my postdoc and close collaborator.

Christelle Le Foll, PhD came from the field of adipose biology. She was convinced by Christophe Magnan and me to come to my lab to begin a study of the mechanisms underlying the ability of hypothalamic neurons to sense fatty acids. Christelle became spectacularly successful at this. Her contributions include the discovery of CD36 as a major regulator of neuronal fatty acid sensing [43–45] and the first demonstration that hypothalamic astrocytes are a major regulator of food intake inhibition after ingestion of high fat diets [46, 47]. She also was a major player in our foray into our explorations of the mechanisms by which amylin enhances leptin signaling in the hypothalamus [26, 48, 49].

Matthew R. Ricci, PhD came to the lab as a postdoc after completing his studies with Susan Fried, then at Rutgers University. Matt initiated what was to be the first of many studies of the ontogeny and developmental aspects of obesity in our selectively bred rats DIO and DR rats [50]. Matt's findings led me into the field of gene-environment interactions and their influence on neuronal development, obesity and diabetes. These studies were subsequently carried forward by **Judith Gorski, PhD** [51–53] and **Christa M. Patterson, PhD** [53–56], graduate students in lab. They also led to my long-time, fruitful collaborations with **Sebastien B. Bouret, PhD** in our studies of how genes and the maternal and postnatal environment interact to influence development of hypothalamic pathways, leptin and amylin signaling [53, 56–60].

Lesson 7: Even a veterinarian can teach you something

I remember hearing **Thomas Lutz, DVM, PhD** give the SSIB Epstein Award lecture at our annual meeting in 2006. Although I was vaguely aware of amylin's effects on food intake, his lecture piqued my interest. It also made me aware of Thomas as a first rate researcher. However, it was the findings of Roth and colleagues showing that amylin acted in the ventromedial hypothalamus to increase leptin signaling in leptin-resistant individuals [61–63] which led me to begin studying amylin-leptin interactions in collaborations with Thomas. More importantly, over this time, Thomas and I became good friends, ski and hiking buddies, pursuits which made our scientific collaboration all the sweeter. It was through his insights that we discovered that amylin increases hypothalamic leptin signaling and sensitivity by stimulating microglial production of IL-6 [48, 49] and that hypothalamic amylin signaling is required for full leptin signaling. Our collaboration continues to this day [26].

Wolfgang Langhans, DVM - although Wolfgang and I have never published together, our long-time interactions at scientific meetings and social gatherings have greatly influenced and informed my thinking about the physiology of gut-brain interactions, an area that I know little about. He has had a distinguished career as both a leading scientist in this area and as an effective administrator in his home institution, ETH. We first became friends at the bar at a SSIB meeting in Florida over drinks with little umbrellas in them. I don't remember much about what we talked about at that bar but it must have been important. To this day, we maintain our friendship, bad drinking habits and mutual scientific interests. I hold my friendship with him and Thomas as important examples of how science and friendship can go hand in hand to further both.

Lesson 8: Your research focus is likely to change many times during your career-fun, funding and fashions

I began my scientific career primarily focused on catecholamines and autonomic nervous system function. That was what got me into the lab every day. Over the years, changes in my personal research interests, and to a lesser extent, current research funding and fashions, have led me into a wide variety of differing clinical and basic research areas. Those studies have covered areas as diverse as iatrogenic muscle fibrosis [64], biorhythms [65], dorsal spinal column stimulation [66], axonal transport [4], neural plasticity [5], brain transplantation [67], traumatic brain injury [68], autonomic function [10], neural regulation of energy and glucose homeostasis in obesity and diabetes [69], neuronal metabolic sensing [70, 71], neural development and gene-environment interactions [59]. Although I have always suffered from a degree of attention deficit hyperactivity disorder, these diverse areas of research focus over a more than 50 year career are not really that unusual in our world. It is all part of the guiding principle that you must continue to grow during your career to maintain freshness and continued contributions. Most of all, it should be fun. For those who are really interested, here is the web site that includes the entire record of the various areas of research I have pursued during my career: http://www.ncbi.nlm.nih.gov/sites/myncbi/1H_6dztg3zKQZ/bibliography/45719445/public/?sort=date&direction=ascending)

Lesson 9: Your lab associates, students and postdocs are your family...they are the real drivers of you career and your scientific legacy

When I first opened my laboratory, our Department of Neurology and Neuroscience at the New Jersey Medical School had no graduate program. For that reason, research studies in my first years were carried out primarily by research assistants and the occasional postdoc. Along with Ambrose Dunn-Meynell who came as a postdoc, Charlie Salter and Antoinette Moralishvili were dedicated research associates in my lab, all of whom worked with me for more than 25 years. Even my most junior research assistant, Sunny Lee, was with me for more than 5 years. Those of you lucky enough to have worked with such dedicated and skilled associates know their value and the critical glue for research continuity they provide. Most importantly, they, along with my students and postdocs, have been my scientific family for many of my formative years in research and are the ones ultimately responsible for my success.

Lesson 10: Science and romance can mix

More than 20 years ago, I met a postdoctoral fellow of Mary Dallman's in a coffee line at a scientific meeting. Over the next few years, we ran into each other at other meetings and gradually became friends. When she moved to New Jersey to take a job in the obesity program in the Pharmacology Department at Merck, our relationship strengthened. Although shared scientific interests were part of the attraction, we found that we shared many other non-science interests. This sort of relationship is not uncommon among our community of scientists who, by nature of our abundant curiosity, develop many other interests outside of science. Today, **Alison M. Strack, PhD** and I are husband and wife and continue our pursuit of love, science and the natural world together. We have even published together. Science is a great place to find a soul mate [72].

So, as I conclude these recollections of a long career and some of the lessons learned over that career, I have some parting free advice. These are all old tropes and many would say they are, therefore, worth every penny that you pay for them. But, here they are:

1. *Be science, not technique driven.* The temptation to jump onboard the latest technological trend, and to find experiments to fit those technologies, can be overwhelming. Study section critiques don't help dampen this temptation. But, technology is there to help answer a question, not to be the question.
2. *It's much more fun when your hypothesis is wrong*-I have learned much more from being wrong than from being right. Don't sweep contrary findings under your intellectual rug.
3. *If it's not fun, you probably should be doing something else*-even in your darkest days doing science, it should still have more positives than negatives. If it doesn't find a new career.

So, it is with a great deal of nostalgia that I reflect on my career in research and clinical medicine. Although I will no longer carry out active research, I do expect to keep abreast of new findings in the science of ingestive behavior and the neural regulation of energy and glucose homeostasis that I spent so many years studying. Most of all, I fully expect to

continue to follow the careers and scientific output of all of my SSIB friends and colleagues with great interest. You have been my scientific family and I hope to keep up with you for years to come. Thank you so much for the wonderful honor of awarding me the SSIB Distinguished Career Award.

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HIGHLIGHTS

- Career Development Award
- Lessons learned during a long career in medicine and research
- Overview of research career and topics
- Individuals critical to career advancement
- Free Advice