Developing a Drug to Treat Alzheimer's Disease

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A Vertical Climb

By

Jay Wright

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This book first published 2024

Cambridge Scholars Publishing

Lady Stephenson Library, Newcastle upon Tyne, NE6 2PA, UK

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

ISBN (10): 1-0364-0605-9
ISBN (13): 978-1-0364-0605-9

To my wonderful wife Donna, my best friend, who allowed me time to think and write. I love you so very much.

To my daughter Shonna who read these chapters and helped me translate technical information into understandable real-world English. Thank you daughter.

To my son Tim. Thank you for the many discussions about dementia, depression and life.

To Joe. We faced many difficult challenges over the years but you were always optimistic and ready to do battle with me, back-to-back, with our heads up. A true friend and brother.

To my students. So many shared moments of discovery and excitement. You taught me so much more than I taught you. Thanks to each of you.

To Amanda my Type Setting Manager, and Courtney my Cover Designer. Thank you for your insight, attention to detail and professionalism. Your encouragement along the way is much appreciated.

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INTRODUCTION

The development of a new drug requires that the candidate molecule be taken from the laboratory through clinical trials and FDA approval. This turns out to be a very long and challenging path. The most important reason to take this path centers on the need to find a cure for a disease, a clinical condition or a technical procedure for which a cure is presently unavailable or that lacks a satisfactory solution. Although years ago, large pharmaceutical companies were responsible for initiating such efforts, more recently academic researchers have been increasingly involved in drug development. These efforts include the search for a small molecule compound or biological therapeutic designed to interact with a target disease in such a way as to improve the condition. As mentioned below, the huge majority of these efforts fail to deliver a drug or therapeutic procedure to market. In most instances these failures occur because the drug does not deliver the desired clinical outcome and/or it causes undesirable side effects (Hughes et al., 2011). As you will see a third likely possibility is that the start-up company founded by the academic researcher simply runs out of money and dies. During the past 25+ years the time required, expense and effort have all increased while the probability of success has decreased. It is estimated that only one in 1,000 (0.1 %) pre-clinical trial drugs will ultimately be evaluated in human patients and of those that do make it into clinical trials only one in five (20%) are FDA approved (Moore, 2022). This is consistent with other experts' evaluation indicating that for each new successful drug making it to market between 5,000 and 10,0000 compounds fail (Moridani and Harirforoosh, 2014). In addition, the cost to achieve success has escalated from approximately $1.9 billion in 2011 to 3+ billion today (Liotta and Painter 2018: Schlander et al., 2021), and requires upwards of 12 to 14 years to complete (Qureshi et al., 2023; Moore, 2022). Nor will things improve in the future given that developmental costs double every 9 years (Yildirim et al., 2016). A number of suggestions for change have been proposed, some worth considering, others unrealistic and reasonably unlikely to be implemented. Most focus on ways to shorten development time and thus reduce cost. It must be acknowledged that the FDA has also made changes designed to provide feedback earlier in the internal review process and shorten the time for decision in the form of "expedited review, approved tracks and special review programs." Even so

the process continues to be exceedingly costly and slow (Olivencia and Sasangohar, 2021).

The major topic of this book concerns the role of the academic researcher/entrepreneur in drug development and whether it is prudent or advisable for the scientist to venture into this arena. The academic researcher's role in commercializing intellectual property owned by his/her university is fraught with difficulties, often beginning with their university's support system, or a lack there of. These problems include few available individuals with experience in drug development available to guide academic researchers. There is seldom a mentor or knowledgeable personnel to ask questions, interact with, or provide guidance. This was certainly my experience and it guarantees mistakes and a trial-and-error approach that is exceedingly inefficient and time wasting. Add to this the duties and requirements of the faculty position that typically include teaching, office hours, faculty and university committee meetings, community service and the added responsibilities of advancing commercially promising research findings, it may become overwhelming. There are also potential difficulties with the universities polices and regulations regarding intellectual property. This requires meetings to stipulate the financial and time line expectations for the sublicensee/faculty member including guidelines for the start-up company. There may be expectations by the university for money up front and/or a certain percentage of company stock. These details must be worked out and it goes without saying that the academic researcher is at a serious disadvantage having had little experience negotiating such contracts. The university often retains the right/option to license/sell the intellectual property to a commercial partner if satisfactory progress is not being made. This is often the case since funding the research will be problematic particularly while the start-up company is attempting to gain traction. Thus, the full potential of the commercially valuable research findings may never be realized or the financial rewards to the inventor(s) will be minimal. And a particularly troubling problem that plagues many early-stage companies is a lack of business experience on the leadership team (Liotta and Painter, 2018). Where does one find top flight business people willing to devote time to a brand-new company? This is a critical issue because business folks are not scientists and lack the knowledge to accurately evaluate the commercial potential of the intellectual property. As a result, they must decide whether to trust the enthusiasm of the academic scientist. This is also true of potential investors who often rely on scientific advisors for advice about the commercial potential of new findings. As it turns out, the members of the leadership team are the key to success. It has been demonstrated many times that outstanding research findings are only the beginning. Technically based

small companies must have people with business and marketing experience to succeed, and this guidance must occur early on (Ricci, 2011). These team members can advise researchers concerning what investors are looking for and how to pitch presentations. Regarding presentations, enthusiasm is not enough. Key questions include: how will this technology solve a need or important problem? How much money will it take to get the product to market, and what is the time line? What is the ratio of invested dollar to predicted recovery value? Who will keep the project on course and be responsible for the careful and prudent use of investors' monies? And, who will deal with questions and complaints over the course of the project?

These issues can certainly discourage drug development efforts by academic researchers. On the other hand, there is the question of responsibility. Do we have an obligation and duty to follow through with efforts to commercialize the research findings from our laboratories for the good of patients in need of help? Should this be our role as cutting edge researchers? In my opinion, only the researchers who finds themselves in this position can or should answer this very personal question. As you will see, my research colleague and best friend, Dr. Joseph Harding and I decided to take the risk, pay the personal and financial price in order to move our drug into clinical trials, and we do not regret our decision.

This book describes the ups and downs of a research program initially focused on developing a drug to treat hypertension, but later made an abrupt shift toward understanding those mechanisms controlling memory. Joe and I met by chance and began a collaboration that lasted many years. He was trained as a neurochemist and medicinal chemist from the Atlantic Northeast and I was trained in physiology and neuroscience from the Pacific Northwest. Our experiences were in areas that had little to do with diseases that predispose dementia; however, a chance discovery pushed us into a race to discover a drug to treat Alzheimer's disease. This was a very serious challenge given that many scientists, properly trained and focused on this disease, had failed to develop an effective drug. Our lack of training in neurodegenerative diseases turned out to be fortunate because we were free of the preformed hypotheses and biases that often plague such researchers. This can occur when new findings do not agree with those published by close colleagues and mentors. It is perplexing to publish results that are different from, or contrary to, findings by those researchers you trained under and admire. Initially we were not interested in small proteins called peptides. This was also important in that we had to acquire the tools and skills to work with these compounds without the potential baggage that occurs when trained at universities that have research groups dedicated to understanding their functions. Early on in our research program we were

generally ignored or only marginally paid attention to by prominent scientists around the world. In fact, as we published our results and gave presentations at national and international meetings, people often asked "Where is Washington State University located? It's in Seattle, right?" Although this was discouraging, we soon realized that it was an advantage since we were afforded time to get ahead of our competition with patent applications, and later efforts to raise funds for our start-up company. As a result, we developed a "first-in-class drug" to treat patients with Alzheimer's disease and other dementia-inducing diseases, as well as a drug to treat pancreatic cancer.

Our collaboration stretched over forty years with the last thirty years devoted to understanding neurodegenerative diseases. Many of our research questions were hypothesis driven while others were initiated by gut feelings. We learned from our successes, but we learned much more from our many failures. During these years we remained focused on understanding the causes of Alzheimer's disease. This required the use of newly available instruments, techniques and animal model testing protocols that we were not familiar with. Thus, we faced many new learning experiences in order to continue our research program. We were required to learn how to use amino acid peptide synthesizers, elevate our knowledge of high-pressure liquid chromatography, tissue radiolabeling techniques, preparation of cell cultures, and modification of radioimmunoassay. And with regard to animal models, we had to learn how to use the circular water maze test of spatial memory, laser Doppler blood flowmetry, hippocampal slice preparation and electrophysiological recording from slices, cytotoxicity testing and enzyme-linked immunosorbent assay (ELISA). Each of these tasks required time to set up and practice in order to perfect a high degree of efficiency and accuracy. We were fortunate to have colleagues willing to share their knowledge and expertise concerning information, techniques and tools valuable to our understanding of the brain renin-angiotensin system as related to memory, blood pressure and blood flow. We were also very fortunate to have outstanding undergraduate, graduate and postdoctoral students working in our laboratories. These students made significant contributions to our understanding of the brain renin-angiotensin system and taught us much more than we taught them. At this point in time, we have moved our technology as far up the cliff as we can go. It is now up to those at our company, Athira Pharma, to take our drugs to the summit. The incline is now very steep and there are no safety ropes to protect against a fall. Only two possible outcomes lie ahead, success or joining a long list of failed companies. Joe and I will hold our breaths until we learn which one it will be. As he said to me when we began our collaboration, "No crumbs,

let's go for a home run." I hope you enjoy reading about our journey and gain an understanding concerning the many challenges we faced.

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PART I

RETURN TO THE PACIFIC NORTHWEST

CHAPTER 1

OUR MOVE WEST

My first academic job was at Fordham University in the Bronx. A good Jesuit university! They needed someone in neuroscience and I needed a job to feed my family. This was a big change from the Pacific Northwest and Michigan and not what I expected. The Bronx is one of five boroughs that include Brooklyn, Manhattan, Queens, and Staten Island. These five make up New York City. Each borough has its own charms and problems. The word borough comes from an Old English word "burg or burh", meaning a fortified settlement. The Bronx consists of many small shops located in old buildings, elevated trains and subways beneath the streets. And of course, Yankee Stadium, the home of the famous New York baseball team. As a kid I followed the Yankees when Mickey Mantle, Roger Maris, Yogi Berra, Whitey Ford and my favorite, their shortstop Tony Kubek, were in World Series play every year it seemed. The Fordham campus is surrounded by cyclone fencing with guards positioned at the entrances. Cars are required to have passes in order to enter. The surrounding area is clustered with apartment buildings, most of them very old. The students are predominantly from well to do families and often evidence a bit of entitlement that may interfere with taking responsibility for a poor score on a quiz or examination. I was among three new faculty members hired at the beginning of that academic year. The nonclergy faculty members, approximately two-thirds of the department, were referred to as "lay faculty." As new first year members we were allowed to attend but not participate in discussions at the faculty meetings. In addition, the three of us were positioned at the very far end of a long table with the chairperson at the head and more senior faculty closest to her, followed by a progression of less senior faculty down the length of the table, ending with us newbies. Of course, this "no speak" policy did not go well with my sense of fairness so by the third meeting I was no longer able to control myself and spoke up during a discussion about course content. As I expressed my view all eyes were directed down the table toward me. Once I finished my comments everyone refocused toward the chairperson's end of the table and the discussion picked up precisely where it had left off. Thus, my input was not acknowledged in any way. My two colleagues very subtly moved their chairs a bit away from me, not

wanting to be accused of approving my maverick behavior. From that meeting on I made a point of commenting on as many topics as I possibly could. Toward the end of that first month Father Zagers, an amiable and kind clergy, took me aside and explained that the Chairperson, Professor Anne Anastasi, was especially irritated with my "persistent interruptions of the department's discussions and I should make an effort to inhibit my comments." I explained to Father Zagers that I was equally annoyed with the format of the meetings and intended to continue presenting my views. I added, "Isn't the University paying me to contribute ideas designed to better configure courses in order to provide content that educate and engage our students?." His response was a smile and a wink followed by: "I will say a prayer for you Jay." We became very good friends soon after that chat.

Professor Anastasi and I never did "click" as best illustrated by one particular demand, her insistence that all of "her faculty" join the American Psychological Association (APA). Since I was not a member she asked the head secretary, Claire, to schedule a meeting with me. I said that I would be happy to meet with Anne. I began calling her "Anne" once I discovered that no faculty members, except a chosen few, were permitted to do so. Anne explained to me that she had been nominated for the Presidency of the APA and it would improve her chances of receiving the position if all of "her faculty" were members of this organization. I first congratulated her on the nomination and then explained that I was a member of three other professional organizations and I did not send manuscripts to any APA journals. The department, after all, hired me as a "neuroscientist" thus my scientific articles were most appropriate to be included in journals concerned with physiology and neuroscience. Thus, there was no advantage for me to be a member of the APA. As a compromise I asked "Is the department willing to pay my membership fee to join and the yearly dues?" She never answered this question. Clearly Anne was not accustomed to being challenged in this way by any one, let alone a first-year assistant professor.

Short background: Anne grew up in a wealthy Manhattan family and upon joining the faculty at Fordham continued to live in a brownstone downtown. She was home schooled by tutors through grade school and high school, attended Barnard College and whizzed through graduate work at Columbia University completing here a PhD in advanced statistical methods in two years at the age of 21! A truly amazing accomplishment. She wrote several well received statistical textbooks and was widely known as a pioneer in psychometrics. The rumor was that she earned more income from her books each year than she received in salary. She also received the National Medal of Science in 1987 for her work concerning measurement

techniques in heredity and environment. And something I very much liked about her, she used the subway to travel up to the Bronx each day despite the real possibility of being mugged or worse. On this point during my first-year I asked members of my graduate class if any of them had been mugged on the subways. It turned out that most had been confronted for money by muggers more than once. The students explained that if you gave the mugger $10 this usually prevented a hit to the stomach or a hard slap to the head. Apparently, the muggers believed in repeat customers so they didn't intend to badly injure anyone. I later learned from Claire that Professor Anastasi carried a cane with her on the subway and had never been mugged.

Returning to the episode in Anne's office, once she learned that I was not interested in joining the APA she became very angry and began grabbing pencils from a jar on her desk, breaking them in two and throwing them in the air. Upon seeing the pencil fragments flying here and there I could not help myself and began laughing. This behavior by an intelligent well-respected professional, who had published excellent textbooks on advanced statistical inference, caught me by surprise. Claire heard the commotion and came in with the idea of "rescuing me", but more importantly getting me out of Professor Anastasi's sight as soon as possible. Once outside the office Claire explained that she would deliver my mail to my office each day for a week so I would not have to come into the main office and risk being seen by Professor Anastasi. I explained to Claire that I would in fact pick up my mail each day as usual. At that point I had two powerful women in the department wanting my head on a stick! Lucky me! Turned out that Anne Anastasi was elected President of the APA in 1972, even without my membership in the APA. We were all proud of her. A truly important accomplishment and well deserved. Professor Anastasi and I never became friends but we did share a mutual respect for each other.

After several years at Fordham, and despite occasional minor confrontations with Professor Anastasi, I was about to be promoted to associate professor and tenured. However, my wife Donna and I were not happy. My commute each day from Monsey east over the Hudson River via the Tappan Zee bridge and then south on the New York freeway to the Bronx initially took about 45 minutes but over time increased to well over an hour and much longer on Friday afternoons. My record time getting home during rush hour was three hours and twenty minutes. During one of these trips, I was in the "fast lane" traveling along at 3 mph and noticed an empty beer bottle positioned on the fog line. In another mile a second empty bottle turned up. The driver emptied the bottle, opened the driver's door and placed it on the line. As we rolled slowly along, he managed to drink a six pack, no high-speed traffic to worry about that day. Also, the cost of living and housing

prices were high, and it was doubtful that we could get together a down payment for a home. In addition, if I stayed and was promoted to associate professor, the possibility of finding another academic job was low. Universities at the time were much more likely to hire at the assistant professor level. So, I applied for jobs out West since both Donna and I grew up in the State of Washington. I was offered a half-time appointment at Western Washington University where I had received my undergraduate and master's degrees. I had also applied for, and received, an NIH funded two-year post-doctoral position to work with Dr. Robert Lockard at the University of Washington in Seattle. Speaking of the University of Washington, the year before I lost out on a tenure track job there to a friend, Dr. John Simpson, who had completed a post-doc at the University of Pennsylvania.

Our plan was to travel from New York by car to Olympia, to stay with Donna's folks, accept the post-doc and find a place to live in Seattle. We also decided that it was best to put our children, Tim and Shonna, on a plane for SeaTac Airport. Just before leaving I received a call from a search committee at Washington State University (WSU). I had applied for a job there just in case something was open. They had a one-year temporary job for much less salary than I had received at Fordham and no guarantee of a tenure track position. Even so I agreed to be interviewed by conference call while we traveled west. As it turned out I called on the agreed upon day and time from a laundromat in Omaha Nebraska during a thunderstorm. It was difficult for me to hear the questions asked by the committee members so I came away with no idea if I had answered any of their questions. Once Donna, Tim, Shonna and I arrived at Donna's parents' house we waited for our few possessions to arrive via the moving company. While there I received another call from the WSU committee asking me to travel to Pullman to complete a formal interview.

We set out for Pullman and were making good time when we arrived in Royal City. Donna asked how much farther, and I said, "Maybe twenty minutes." I was off by a lot. Turns out Pullman is located up against the Idaho border and next to a second University town, Moscow, where the University of Idaho is located. Once in Pullman I called Dr. Mary Kintzle, the head of the search committee and she invited us to her home. Dr. Kintzle turned out to be very welcoming and insisted that we stay with her making use of her spare bedroom. The next day she took me on campus, I gave my colloquium presentation explaining my research and teaching interests and future plans. Only a few faculty members and students showed up. I was then scheduled for several interviews with faculty members in their offices. This seemed to go well. Before we left Pullman, I was offered the temporary

position but it had been reduced to three-quarter time, not full time. Mary explained that a member of the Psychology faculty, Dr. Dudley Klopfer, had accepted the position of campus Ombudsman and now decided to keep a quarter of his position in the department. This was a surprise and required that Donna and I make a choice between the post-doc at nearly the same pay as I had received at Fordham, or the WSU position with even less salary than originally listed. Two things figured into our decision. First, Mary Kintzle treated us so very well during our stay in Pullman and, during the interview, one of the tenure track faculty members shared with me that he was currently teaching the neuroscience classes and planned to leave at the end of the coming academic year in order to re-train in clinical psychology. Thus, there would be an open tenure track position available in the department. So, despite major concerns, Donna and I decided to take a chance on WSU. As with so many difficult decisions, this turned out to be both good and bad!

CHAPTER 2

MY FIRST YEAR AT WASHINGTON STATE UNIVERSITY

During my first meeting with the department Chairperson, Dr. Roger Davis, he told me that I was hired for one year on a temporary basis. But then I did not hear from him concerning my teaching assignments. Following that meeting I made several attempts to find out about my assignments for the fall semester. Margaret, the department's head secretary, kept telling me that the Chairperson had not made a decision and to check with her later. Finally, it was the morning of the first day of classes and I was in our two-bedroom rented house having a cup of tea at the kitchen table. The house was in poor condition all around with questionable electrical wiring and in need of a new roof, but it was the best we could find on a one-year lease. Margaret called and was very angry with me because I was not at my "assigned section of Introductory Psychology." She told me to get to that class immediately! In the meantime, Professor Davis would "entertain my students." I rushed up to campus and found the correct building and room. As I entered Professor Davis simply said to me "It's about time" and left the room. He did not bother to introduce me to the approximately 200 students enrolled in the class and apparently had not even shared my name as he talked with them for 20 minutes before I arrived. It hit me hard when a student in the front row asked, "Who are you? Isn't Dr. Davis our teacher?" That was my first day at WSU! I decided not to share the details of this day with Donna, but at that time I wondered if we had made a colossal mistake in coming to Pullman. It also occurred to me that my luck with chairpersons was truly bad!

During this first year I was assigned a small office, no windows and one small empty room in the basement as a lab. By the time I left Fordham, I occupied a corner office with large windows permitting a view onto the beautiful campus and a suite of well-equipped laboratory rooms. During that first year at WSU the faculty member who was teaching the neuroscience classes did indeed leave, so toward the end of the academic year I applied for the open tenure position, along with nearly 80 other applicants from

around the U.S. and Canada. The departmental search committee interviewed three other applicants plus me. Eventually Margaret called to say that Professor Davis wanted to meet with me. Dr. Davis explained that the psychology faculty had given me a positive vote for the position. However, I was not his top pick. I learned later that one of his former students had applied and Roger had campaigned for him among the senior faculty, not for me. Once I learned this from a faculty member, I figured I had nothing to lose so I pressured Roger for more lab space. Professor Davis did eventually assign me a larger lab but again empty of any equipment. The equipment would have to come from successful grant applications. Eventually over the years Roger and I become good friends and colleagues and we were awarded NIH grants to do behavioral research with his aging rhesus monkey colony. Roger's animals were very old and displayed some of the same memory issues as seen in aging humans. Although I was not aware at the time, this experience would be especially important later when I moved toward research on Alzheimer's disease. Roger and I worked well together and thought along similar research lines. Years later the sad day came when Donna and I attended Roger's funeral. Margaret, whom he had married years before, asked me to give the eulogy. I had only fifteen minutes to prepare and then found myself standing in front of Roger's family, friends and members of the department and college.

In my eulogy, I did my best to summarize Roger's extremely distinguished career. He had completed all his degrees at the University of Wisconsin working with a very famous psychologist named Dr. Harry Harlow. He also published many scholarly papers in excellent scientific journals along with three books focusing on what he had learned from working with his rhesus monkeys. I also talked about how Roger, a rather small man, had been the coxswain on the rowing crew at the University of Wisconsin for all four years while an undergraduate student. Roger had told me how he loved bossing around those big strong guys, hollering orders at them as he steered the shell. He also explained that there were drawbacks to being the coxswain. If the team lost, he was blamed, chased down, tackled and thrown into the water. And if the team won, he was cheered, chased down, tackled and thrown into the water. When my eulogy was over, I was relieved because it seemed to have gone well. My mind flashed back to that horrible first day of classes when I had dashed across campus because he had failed to tell me about my teaching assignments. At that moment it occurred to me that my relationship with Roger had ended just as it began. I was placed in an uncomfortable situation, unprepared and in something of a panic. Roger would not have wanted it any other way.

CHAPTER 3

A CHANCE MEETING

The first time I saw Dr. Joseph Harding was on the doorstep of our rental home in Pullman Washington. I had walked home from work to find Donna talking with a guy on the front porch. As I approached it was clear that they were in a serious discussion comparing lease agreements for the house we had lived in for the past year and were soon to vacate. Donna introduced me to "Joe" and explained that our leases overlapped by one week. Joe introduced me to his wife Barbara who sat in their U-Haul truck from Delaware holding their two-month-old baby girl, Erin. They had just driven across the country with an infant and though I knew she must be tired, Barbara joked and chatted with Donna as if she had just ridden across town. I had mentioned to the realtor that we **might** move to a three-bedroom house a week before our lease was up, and of course this did not happen. So as fate would have it, we were all booked to live in the same house for a week. I said to Joe, "let's unload your things from the truck into the basement so you can return it. Then we can have a talk with the realtor." Once confronted with the situation, the realtor agreed to pay the Harding's motel costs for the week. Everything was settled and we parted, returning to our respective busy lives.

Several months later I ran into Joe while walking across campus. Winter had arrived and the ground was covered with snow. We said hello and laughed a bit about the lease debacle. I asked him if he wanted to get out of the cold and have something to drink in the Student Union. Turned out we were both tea drinkers. This was his first time in the Student Union cafeteria, and he commented that it seemed pricey for a "do it yourself" cup of tea. "Might as well buy a cup of hot water and bring along your own tea bag." As we sat down at a table, I asked him about his research interests. He said he wanted to continue the work he had started in New Jersey. His project concerned olfactory nerve regeneration in mice and he explained that this entailed surgically severing the olfactory nerve and then allowing recovery time for neural regeneration to occur. The challenge was to know when the recovery was complete. We kicked around some ideas and agreed that one way to determine recovery time was to let the mice tell him. I explained that

I knew how to do this since I had trained using animal behavior techniques. We discussed offering small cocktail sugar cubes that have little or no odor, and placing a drop of scent on them such as anise or orange. The cubes could be hidden in non-odorous bedding at various locations in an open field box. After being placed on a restricted diet the mouse could search through the chips to find the cube. Testing could occur daily until the mice reliably found the cube. This would be an excellent indicator that olfactory nerve recovery had taken place. A histological examination could then be conducted to determine the degree of nerve recovery.

By this time, we were both on our second cup of tea and Joe asked me about my research. I explained that I was interested in the physiology and neural circuitry of body water balance and blood pressure. I was especially focused on the role of angiotensin peptides but had no way to measure the level of these peptides in animals. Joe paused and then said, "why not use an RIA?" I told him that I was not familiar with the technique, and he explained that RIA stands for radioimmunoassay. I learned later that this was a technique originally developed by Rosalyn Yalow and Solomon Berson in the early 1960s. Joe had learned how to do this assay at the Roche Institute of Molecular Biology in Nutley, New Jersey, while on post-doctoral appointment. A senior researcher named Dr. Sidney Spector had recently modified the RIA to make it more sensitive to just about any molecule that an antibody could be prepared against. I asked Joe if it could be used to measure the levels of peptides in plasma and he assured me that it probably could. This meeting was a pivotal moment when things first began to fall into place between the two of us.

The mountains were the main reason that Joe came West. He is a first-class mountain climber and had previously climbed Mt. Rainer. Over the next years he continued to climb Mt. Rainer and other mountains in Washington, Oregon and British Columbia, nearly always taking the most challenging approach. Joe and Barbara are also excellent down-hill skiers and that was another attraction for them coming to the Pacific Northwest.

After this first meeting, one of many hundreds that would occur over tea during the next forty years, Joe and I decided to begin working together. We tested mice with olfactory nerve cuts in the open field and these animals told us when recovery occurred. We also prepared antibodies against the small peptide angiotensin II (AngII) and radiolabeled this ligand to create the very first RIA for an angiotensin peptide. This RIA and radiolabel binding of brain tissues soon became essential in our efforts to locate and quantify endogenous levels of AngII in plasma and brain tissues. Years later this resulted in our ability to determine the importance of brain angiotensins

acting at specific brain binding sites related to the acquisition, encoding and retrieval of memories.

Looking back, it is amazing that Joe and I ever crossed paths. Long before our first meeting on the steps of our rented house we both experienced major health challenges. Joe was born two months premature, Rh+. He had his entire blood volume replaced and was not expected to live. He was the first born in his family and his parents were overwhelmed watching their new baby battle for his life. When I was twelve, I suffered a ruptured appendix. My mom thought I had the flu and it was three days following the rupture before she took me to the clinic. By then I had developed peritonitis. I remember Mom helping me out of the car and mostly carrying me to the door of the clinic where I fell. She helped me back on my feet and I shuffled along as best I could. At the far end of the hall a surgeon, Dr. Hazelrigg, happened to be coming out of an office. He spotted mom and me and came running. He helped me back into the car and told mom to take me up the hill to St. Peters Hospital for surgery. He had immediately recognized my problem, called ahead, and rushed up to the hospital to perform the surgery. Following surgery, I was in a coma for seven days. During that time Dr. Hazelrigg prepared my family for the very real possibility of my death. Luckily, I woke up on the eighth day with two IVs and a stomach pump tube in place. Even today approximately 75,000 children in the U.S. develop severe sepsis each year and about 10% die. The number of sepsis childhood cases is increasing by about 7,000 each year and it is not clear exactly why.[1] During sepsis, the immune system often overreacts and attacks the body's organs, thus damaging the heart, lungs, kidneys, and brain. Penicillin saved my life; a drug, I might add, that was discovered by accident in 1928. Dr. Alexander Fleming, a Scottish researcher and bacteriologist, returned from vacation to a messy lab at St. Mary's Hospital, London. In his sink he noticed that a tenacious mold had invaded one of his petri dishes containing staphylococcus bacteria. He subsequently discovered that this mold reliably killed bacteria. Lucky for me, and so many others, he later made use of this chance observation to develop penicillin.

Given these events, the possibility of Joe and I meeting seemed nearly impossible. Our brushes with death in early childhood, both of us coming to WSU and renting the same house, and months later running into each other on campus and having a cup of tea together. The odds are in line with getting attacked by great white sharks, or maybe slightly less unlikely considering that Washington State University is eight hours from the ocean. This book is about an ongoing effort to beat the odds and our long journey

[1] www.sepsis.org

to develop drugs to treat Alzheimer's and Parkinson's diseases. Our path has had many dead ends and required frequent reevaluation and changes in direction. As you will see, this is often the way research progresses, with successes punctuated by major failures, followed by reevaluation of the hypothesis. Perhaps Dr. James D. Watson (1968) said it best in his book about the discovery of the double helix.

> "As I hope this book will show, science seldom proceeds in the straightforward logical manner imagined by outsiders. Instead, its steps forward (and sometimes backward) are often very human events in which personalities and cultural traditions play major roles. To this end I have attempted to re-create my first impressions of the relevant events and personalities rather than present an assessment which takes into account the many facts I have learned since the structure was found. Although the latter approach might be more objective, it would fail to convey the spirit of an adventure characterized both by youthful arrogance and by the belief that the truth, once found, would be simple as well as pretty. Thus, many of the comments may seem one-sided and unfair, but this is often the case and horrified way in which human beings frequently decide to like or dislike a new idea or acquaintance. In any event, this account represents the way I saw things then, in 1951-1953: the ideas, the people, and myself."

Some years ago, I attended my high school reunion and was talking with a good friend from that time in my life. Pat was a successful insurance salesperson at the time and we had grown up together beginning in the first grade through elementary school and high school. His family had the perfect hill for sledding and whenever it snowed our gang headed to his house. On one snowy day Pat and I waxed the runners on our sleds so well that we screamed down the hill making record distances. On one run Pat did so well that he had to duck under the barbed wire fence at the base of the hill. Unfortunately, the wire caught the left side of his face, producing a 2-inches-long scratch. Pat has proudly worn that scar all of these years. He once told me that it gave him something to talk about with potential clients when they first met. Pat knew that I taught at a university but not much beyond that. He asked me, "Jay, what do you do?" A simple question. During the next ten minutes I did my best to explain my job. He listened patiently and when I stopped, he said, "Jay, you are a scientist, aren't you?" I paused and said, "Yes Pat, that is what I do." This illustrated to me that I must work harder at communicating what scientists do in more understandable ways. So, I promised myself that someday I would try to do a better job of explaining how I spent my life. This is one such attempt.

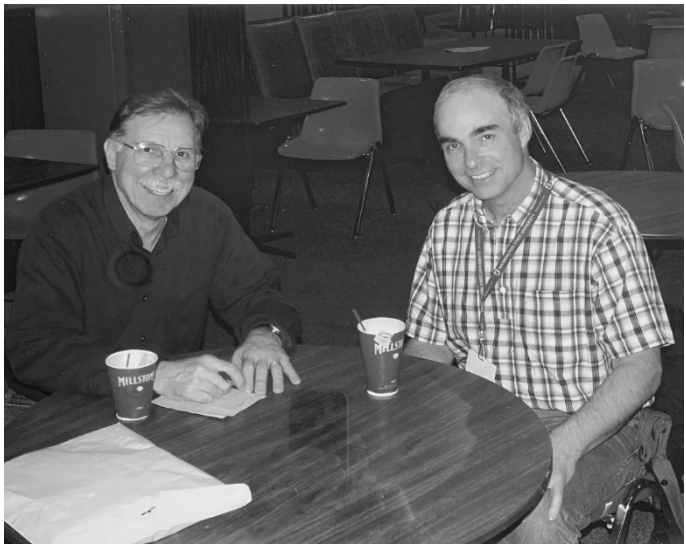

Figure 3.1 Joe and Jay (taking notes) having afternoon tea discussing hypotheses and research design at the Washington State University student union. I always brought the tea bags and Joe ordered two cups of hot water! I once complained to the Director of the student union about the cost of a cup of tea. He listened but did not reduce the cost so Joe and I continued to bring our own bags and buy two cups of hot water.

Reference

Watson, James D. "The Double Helix. A Personal account of the Discovery of the Structure of DNA: Touchstone Book." Simon & Schuster, New York (1968). Preface, page xi.

CHAPTER 4

EARLY YEARS OF OUR COLLABORATION

During the initial years of our collaboration, Joe and I continued conducting research in our specialized areas of interest. Joe had perfected a surgical procedure with mice that severed the olfactory nerves without any blood loss and minimal collateral tissue trauma. As mentioned, I used an open field finding task to determine the latency to olfactory nerve recovery. It turned out that this behavioral measure was far more sensitive and predictive of recovery than any chemical assays that we used. The animal's nose was superior to any lab bench chemical measurement concoction we could come up with. This pleased me. I continued my interest regarding the brain's control of thirst, body dehydration and systemic blood pressure in rodents. This work included the investigation of desert adapted rodents. We initially focused on blood concentration, known as osmolality. However, I was excited about utilizing Joe's expertise related to the use of radioimmunoassay to measure plasma levels of angiotensin II. The RIA method required radiolabeling AngII with iodine^{125} and preparing antibodies against AngII. We managed to accomplish this without much difficulty. The basic principle is that radiolabeled antigen competes with a non-radiolabeled antigen in plasma taken from the animal for a fixed number of antibody binding sites. Thus, it is often called a "competitive binding" or "displacement binding" assay. To our knowledge this was the first AngII RIA in the world. Now there are commercial kits available for measuring levels of many drugs, peptides and hormones. These kits are being used in all hospitals and clinics around the world. Looking back, this was a very useful technology that we could have commercialized but at the time we focused on our basic research questions.

My working hypothesis suggested that when water is difficult to find in the environment, the animal's body dehydrates and blood concentration (osmolality) elevates. This results in an increased synthesis of AngII that drives up systemic blood pressure. This is because AngII is a very powerful vasoconstrictor of blood vessels. Such systemic changes are designed to heighten and focus the animal's attention on behaviors that increase the probability of locating water. This theory led to the identification of AngII